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:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from AbbVie
2. **Company summary of information for patients (SIP)** from AbbVie
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. Parkinson's UK
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5. **External Assessment Report** prepared by BMJ Technology Assessment Group
   a. External Assessment Report
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Post-technical engagement documents

7. **Technical engagement response** from AbbVie
   a. Technical engagement response
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8. **Technical engagement responses and statements from experts:**
   a. Dr Camille Carroll – clinical expert, nominated by AbbVie
   b. Dr Pathikonda Uma Nath – clinical expert, nominated by the Association of British Neurologists
   c. Patient expert, nominated by Parkinson's UK
   d. Marc van Grieken – patient expert, nominated by Cure Parkinson's
9. **Technical engagement responses from stakeholders:**
   a. Parkinson's UK

10. External Assessment Report critique of company response to technical engagement prepared by BMJ Technology Assessment Group

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

August 2022

File name	Version	Contains confidential information	Date
ID3876_Foslevodopa-Foscarbidopa_NICE_Doc B_Final_25APR_23 [ACIC]	Final	Yes	25th April 2023

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Abbreviations

Abbreviation	Definition
3-OMD	3-O-methyldopa
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AWMSG	All Wales Medicines Strategy Group
BK50	Median bradykinesia score
BK75-BK25	Interquartile range of bradykinesia score
BL	Baseline
BMI	Body mass index
BMT	Best medical therapy
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost-benefit analyses
CDP	Carbidopa monophosphate
CEM	Cost-effectiveness model
CI	Confidence interval
CLES	Carbidopa-levodopa enteral suspension
COMT	Catechol-o-methyl-transferase
CR	Controlled release
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSAI	Continuous subcutaneous apomorphine infusion
CSCI	Continuous subcutaneous infusion
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CUA	Cost-utility analyses
DAT	Device-aided therapy
DBS	Deep brain stimulation
DIC	Deviance information criterion
DK50	Median dyskinesia score
DK75-DK25	Interquartile range of dyskinesia score
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
ECG	Electrocardiogram
FAS	Full analysis set
FE	Fixed effect
fMRI	Functional magnetic resonance imaging
GP	General practitioner

HCRU	Healthcare resource use
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPG	Implantable pulse generator
IR	Immediate release
IRT	Interactive response technology
ITT	Intention-to-treat
J2R	Jump-to-reference
LCIG	Levodopa-carbidopa intestinal gel
LDP	Levodopa monophosphate
LECIG	Lecigon
LED	Levodopa equivalent dose
LOCF	Last observation carried forward
LS	Least squares
LYG	Life years gained
MAO	Monoamine oxidase
MCMC	Monte Carlo Markov Chain
MDS-UPDRS	Movement Disorders Society-Unified PD Rating Scale
M-EDL	Motor aspects of experiences of daily living
MHRA	Medicine and Healthcare Products Regulatory Agency
MMRM	Mixed model for repeated measured
MRI	Magnetic resonance imaging
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
ONS	Office for National Statistics
PAS	Patient access scheme
PBO	Placebo
PD	Parkinson's disease
PDQ-39	39-item PD Questionnaire
PDSS-2	Parkinson's Disease Sleep Scale-2
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PICOS	Population, Intervention, Comparison, Outcomes and Study
PKG	Personal KinetiGraph™
PM-PDSC	Phillips-Medisize Parkinson's Disease Subcutaneous
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial

RE	Random effects
REML	Restricted maximum likelihood
RR	Relative risk
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SPECT	Single Photon Emission Computed Tomography
SUCRA	Surface under the cumulative ranking curve
SW	South-west
TEAE	Treatment emergent adverse event
TLR	Targeted literature review
TNAS	Treatment-Naïve Analysis Set
VAS	Visual Analogue Scale
VAT	Value-added tax
WTP	Willingness-to-pay

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

B.1.1 *Decision problem*

This submission focusses on part of the technology's marketing authorisation for this indication. Foslevodopa-foscarbidopa is anticipated to be licensed for the "treatment of advanced levodopa-responsive PD with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results". The proposed position is for patients with PD that is responsive to levodopa, with symptoms not adequately controlled by their current medical therapy (i.e., best medical therapy [BMT]) and for whom apomorphine or deep brain stimulation (DBS) are unsuitable or no longer providing adequate symptom control. Although this is narrower than the marketing authorisation, it reflects the population in which foslevodopa-foscarbidopa offers best value for money.

The decision problem addressed in this submission is outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with PD that is responsive to levodopa, with motor symptoms uncontrolled by standard therapy.	Adults with PD that is responsive to levodopa, with symptoms not adequately controlled by their current medical therapy (i.e. BMT) and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control.	The population addressed in the submission is narrower than the full anticipated license population as it reflects the population in which foslevodopa-foscarbidopa offers best value for money.
Intervention	Foslevodopa-foscarbidopa	Foslevodopa-foscarbidopa	N/A – in line with the NICE final scope
Comparator(s)	• BMT for treating PD, including: o Levodopa plus the following adjunctive treatments: ▪ Dopamine agonist ▪ MAO-B inhibitors ▪ COMT inhibitors o Amantadine • Apomorphine, with or without standard	• LCIG • BMT	Throughout all stages of PD, treatment choice is highly individualised and based on patient and clinician preference. As an advancement of continuous levodopa-carbidopa based therapies, it is anticipated that foslevodopa-foscarbidopa would be used in a patient population similar to LCIG rather than other advanced therapies, providing patients with greater

	oral medication • DBS • LCIG		convenience and improved 24-hour dosing. As patients progress to advanced PD, some advanced treatment options may be unsuitable for some patients, or there can be a need to discontinue an advanced therapy. Patients unsuitable for or discontinued from advanced therapies will remain on BMT, despite the insufficient control of their symptoms. Additionally, some patients may not have access to advanced therapies or may choose not to take them for individual reasons and remain on BMT; apomorphine is not available locally in every clinical commissioning group and DBS and LCIG are only available to patients at tertiary centres. Introduction of foslevodopa-foscarbidopa would increase the available treatment choices for patients and clinicians. LCIG and BMT therefore represent the two relevant comparators for this evaluation.
Outcomes	The outcome measures to be considered include: • 'On'/'Off' time • dyskinesia • motor complications • cognitive functioning • mortality • adverse effects of treatment • HRQoL	The outcome measures used in this submission include: • 'On'/'Off' time • dyskinesia • motor complications • cognitive functioning • mortality • adverse effects of treatment • HRQoL	N/A – in line with the NICE final scope. All outcome measures included in the scope are either captured in the pivotal trials and/or the economic analysis

Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Subgroups based on the proportion of time spent in the 'Off' state • People for whom apomorphine is not suitable • People for whom DBS is not suitable	N/A – no subgroups were considered as part of the cost-effectiveness evidence presented in this submission	A scarcity of available evidence for comparisons based on the proportion of time spent in the 'Off' state meant that such a comparison would lack robustness and be associated with a high level of uncertainty. Based on the anticipated positioning of foslevodopa-foscarbidopa (i.e. for patients with advanced PD who are unsuitable for apomorphine and DBS), subgroups of patients for whom apomorphine or DBS are not suitable are no longer of relevance for this evaluation. These patients are covered within the main population given this anticipated positioning.

Abbreviations: AE: adverse events; BMT: best medical therapy; COMT: catechol-o-methyl-transferase; DBS: deep brain stimulation; HRQoL: health-related quality of life; LCIG: levodopa-carbidopa intestinal gel; MAO-B: monoamine oxidase type B; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PD: Parkinson's disease; PSS: Personal Social Services; SAE: serious adverse event; UK: United Kingdom.
Source: NICE (ID3876 final scope).[1]

B.1.2 *Description of the technology being appraised*

A description of the technology being appraised (foslevodopa-foscarbidopa) is summarised in Table 2. The summary of product characteristics (SmPC) is provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Foslevodopa-foscarbidopa (Produodopa®)
Mechanism of action	Foslevodopa-foscarbidopa is a novel combination of levodopa monophosphate and carbidopa monophosphate. These are water soluble phosphate ester pro-drugs of levodopa and carbidopa,[2] in which the phosphate group is rapidly cleaved off in the endothelial capillary system before reaching the brain. As such, they have identical modes of action to conventional levodopa and carbidopa, but are suitable for subcutaneous dosing. Levodopa relieves symptoms of PD following decarboxylation to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits the extracerebral decarboxylation of levodopa to dopamine, which means that a larger amount of levodopa becomes available for transportation to the brain and transformation into dopamine.
Marketing authorisation/CE mark status	• MHRA marketing authorisation for foslevodopa-foscarbidopa is anticipated in November 2022 • Approval for the delivery pump is expected in [redacted]

Indications and any restriction(s) as described in the SmPC	The license wording is currently anticipated to be for the "treatment of advanced levodopa-responsive PD with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of PD medicinal products have not given satisfactory results".
	
	Foslevodopa-foscarbidopa is anticipated to be contraindicated in people with:
	• Hypersensitivity to the active substances or to any of the following excipients:
	  o Sodium hydroxide
	  o Hydrochloric acid
	  o Water for injections
	• Narrow-angle glaucoma
	• Severe heart failure
	• Acute stroke
	• Severe cardiac arrhythmia
	• Non-selective MAO inhibitors and selective MAO type A inhibitors are contraindicated for use with foslevodopa-foscarbidopa. These inhibitors must be discontinued at least two weeks prior to initiating therapy with foslevodopa-foscarbidopa. Foslevodopa-foscarbidopa may be administered concomitantly with the manufacturer's recommended dose of a MAO inhibitor with selectivity for MAO type B (e.g. selegiline HCl)
	• Conditions in which medication with adrenergic activity are contraindicated (e.g. pheochromocytoma, hyperthyroidism and Cushing's syndrome)
	• Suspicious undiagnosed skin lesions or a history of melanoma

<table>
<tr><td>Method of administration and dosage</td><td>Foslevodopa-foscarbidopa is administered as a continuous subcutaneous infusion, 24 hours/day.

The recommended starting infusion rate of foslevodopa-foscarbidopa is determined by converting the daytime levodopa intake to levodopa equivalents and then increasing it to account for a 24-hour administration. The dose may be adjusted to reach a clinical response that maximises the functional ‘On’ time and minimises the number and duration of ‘Off’ episodes and ‘On’ episodes with troublesome dyskinesia. Full details on calculating the initial dose are provided in the draft SmPC.

The dose may be adjusted to reach a clinical response that maximises the functional ‘On’ time and minimises the number and duration of ‘Off’ episodes and ‘On’ episodes with troublesome dyskinesia. The maximum recommended daily dose of foslevodopa is 6000 mg (or 25 mL of foslevodopa-foscarbidopa per day, equivalent to approximately 4260 mg of levodopa per day). If enabled by their healthcare professional, patients may self-administer an extra dose to manage acute ‘Off’ symptoms experienced during continuous infusion.</td></tr>
<tr><td>Additional tests or investigations</td><td>N/A – No additional tests or investigations are required prior to treatment with foslevodopa-foscarbidopa</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>The list price for foslevodopa-foscarbidopa is as follows (excluding VAT):
<table><tr><th>Pack</th><th>List price (£)</th></tr><tr><td>10 ml vial for infusion</td><td>84.70</td></tr></table></td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>[redacted]
<table><tr><th>Pack</th><th>Net price (£)</th></tr><tr><td>10 ml vial for infusion</td><td>[redacted]</td></tr></table></td></tr>
</table>

Abbreviations: MAO: monoamine oxidase; MHRA: Medicine and Healthcare Products Regulatory Agency; N/A: not available; PAS: patient access scheme; PD: Parkinson’s Disease; SmPC: Summary of Product Characteristics; UK: United Kingdom; VAT: value-added tax.
Source: AbbVie Data on File (draft SmPC), 2022.[3]

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

Parkinson's disease (PD) symptoms, both motor and non-motor, vary between patients and day-to-day, with fluctuations in symptom control becoming more frequent and unpredictable as the disease progresses to advanced PD.

- PD is a chronic neurodegenerative disease, affecting dopamine regulation in the brain.
- An estimated 120,000 people are living with PD in England,[4] with the disease most common in people over 60 years old and in males.[4-6]
- The symptoms of PD are varied and highly individualised. Patients can present with both motor symptoms, including tremors, rigidity, slowness or absence of movement, and non-motor symptoms, such as depression, sleeping disturbances and psychosis.[7-10]
- Both naturally-occurring and medication-related symptoms inevitably worsen over time.[11, 12] Fluctuating dopamine levels combined with a narrowing of patients' therapeutic window leads to motor fluctuations, a continuous switching between states of good and poor control of motor symptoms, as a result of both disease progression and oral medications taken to control PD.[11]
- PD progresses differently for each individual; the PD patient population is highly heterogeneous and defining stages of the disease when symptoms become more uncontrolled is non-trivial.[13]
- The variety of motor and non-motor symptoms substantially impacts the quality of life (QoL) of both patients with PD and their caregivers.[14-17]

No cure exists for PD with current treatment aimed at controlling symptoms, and providing more stable dopamine concentrations.

- To date, no treatments have been reviewed by NICE for PD through its technology assessment process. NICE's guideline NG71 provides recommendations on the management of PD.[18]
- Initially, people in the early stages of PD typically receive oral levodopa and carbidopa.[11, 18] As the disease progresses, various oral combinations are added as adjuvant medication to alleviate motor fluctuations and treatment-related side effects, including monoamine oxidase type B (MAO-B) inhibitors, dopamine receptor antagonists, catechol-o-methyl-transferase (COMT) inhibitors and amantadine.[18]
- PD is a progressive disease and over time, oral therapies no longer adequately control symptoms, leading to patients experiencing dyskinesia and motor fluctuations. People in this stage of PD (known as advanced PD) are offered device aided therapies (DATs) and surgical interventions. These include apomorphine as continuous subcutaneous infusion (CSCI) or as intermittent injection, DBS and levodopa-carbidopa intestinal gel (LCIG); the latter two requiring invasive surgery in order to be administered.[18]
- The treatment of advanced PD is highly individualised and based on patient and clinician choice, dependent on a range of factors including patient characteristics, suitability for treatment and lifestyle preferences. Lack of uniform access to DATs further restricts the choice of treatments available to patients and clinicians.

Foslevodopa-foscarbidopa is the first and only 24-hour, non-surgical, subcutaneous levodopa infusion, positioned for use in patients with symptoms not adequately controlled by their current medical therapy (i.e. BMT), and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control.

- Foslevodopa-foscarbidopa is a novel formulation combining two prodrugs of levodopa and carbidopa, for subcutaneous dosing.
- It is delivered via 24-hour non-invasive CSCI, providing constant and stable concentrations of levodopa, and eliminating fluctuations commonly associated with oral treatments.
- As an advancement of continuous levodopa-carbidopa based therapies, foslevodopa-foscarbidopa is anticipated to be used in patients with symptoms not adequately controlled by their current medical therapy, and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control, giving patients a novel, non-surgical treatment option.

B.1.3.1 Disease Overview

Parkinson's disease

PD is a chronic, progressive, neurodegenerative condition that affects dopamine regulation in the brain.[7] Pathologically, PD is characterised by the loss of dopaminergic neurons residing in the *substantia nigra pars compacta* and the presence of alpha-synuclein-positive cytoplasmic inclusions, termed Lewy bodies, in surviving neurons.[7] The aetiology of PD is not well understood, although common genetic drivers have been identified, and age and gender are well acknowledged risk factors.[19, 20] The incidence of PD in males has been shown to be more than 1.5 times higher than that in females in age-matched analyses,[5] and 90% of PD diagnoses are made in people over the age of 60, although PD can also occur in those under 50.[6, 11]

In England, it is estimated that around 120,000 people are living with PD.[4] Incidence and prevalence of PD in England have been estimated to be 28 and 218 cases, respectively, for every 100,000 people.[4] PD is the fastest growing neurological disorder in the world.[21] Due to the correlation between age and incidence of PD, the number of cases are expected to continue to increase with the UK's ageing population,[22] reaching 165,000 cases in the UK in 2026.[4]

Symptoms and disease progression

The symptomatology of PD is heterogenous and multifaceted. Patients with PD classically present with motor symptoms, including bradykinesia (slowness of movement), akinesia (absence of movement), tremors and rigidity.[7, 8] PD is also associated with numerous non-motor symptoms, some of which can precede the motor dysfunction by more than a decade.[9] These non-motor symptoms span a wide spectrum, and can include physical symptoms such as loss of the sense of smell and constipation, and psychological symptoms, such as rapid eye movement sleep behaviour disorder, other sleep disorders, depression, anxiety, pain, cognitive impairment and psychosis.[10]

The gravity and complexity of symptoms vary between patients and from day-to-day. The progression of PD therefore does not follow a well-defined pattern and is non-linear, with symptoms inevitably worsening over time.[12] Due to symptoms being specific to each individual patient, PD requires highly personalised management.[23]

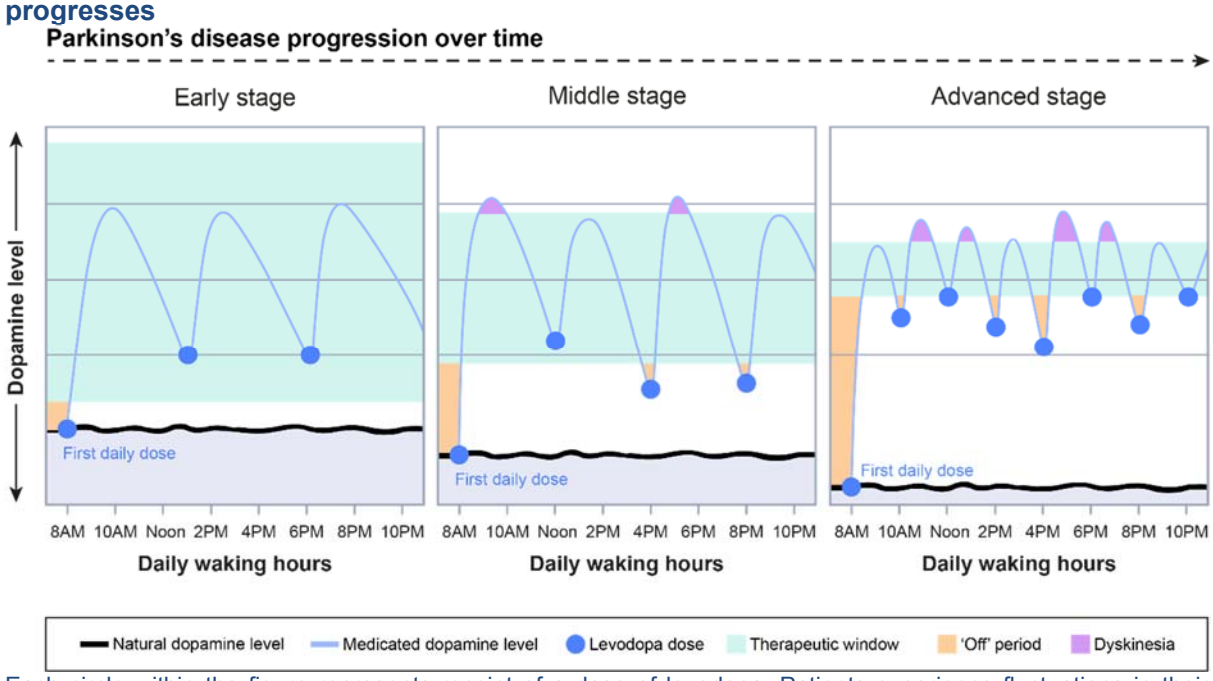
Since no curative or disease-modifying medicines currently exist for PD, treatment is primarily aimed at controlling symptoms.[11] The majority of patients will initially receive levodopa, a dopaminergic drug, as the first treatment option. Levodopa is considered the gold standard therapy to control motor symptoms, and is used to compensate for the loss of dopamine-secreting neurons.[13] However, as discussed in Section B.1.3.2, PD treatment is highly individualised and may initially include a number of oral treatment combination options.

Oral levodopa-based treatments are associated with fluctuating dopamine level profiles (Figure 1).[24] Patients at early stages of PD generally have good response to levodopa-based therapies, however PD symptoms reappear when the effect of treatment wears off, known as 'wearing Off'.[11] 'Off' time is defined as the time between doses when the efficacy of treatment reduces and PD symptoms become uncontrolled, posing a significant burden on patients. Reducing 'Off' time episodes is a key treatment goal in the clinical management of the disease.[25] However, managing 'Off' time with oral therapies becomes increasingly more difficult over time due to a

narrowing of the therapeutic window as the disease progresses (Figure 1). 'Off' time episodes during periods of 'wearing off' become more regular, longer-lasting and more unpredictable.[11]

Patients with PD therefore tend to experience motor fluctuations, namely cycling between 'On' states with good control of motor symptoms and 'Off' states. This is aggravated by uncontrollable and unpredictable movements (dyskinesia) associated with peak dopamine concentration following levodopa intake.[11] Higher and more frequent dosing of levodopa is therefore needed to better control symptoms.[11] The use of levodopa has been linked to the onset of motor fluctuations in 50% of people after 5 years and 80% of people after 10 years; it has also been estimated that 30–80% of people will develop dyskinesia with long-term levodopa use.[26, 27]

Figure 1: Narrowing of therapeutic window and increase in motor complications as disease progresses



Each circle within the figure represents receipt of a dose of levodopa. Patients experience fluctuations in their levodopa plasma levels between doses of oral treatment as their disease progresses and their therapeutic window narrows. 'Off' periods and periods of dyskinesia become more frequent and more unpredictable as the disease progresses into advanced PD.
Source: Armstrong et al. 2020.[11]

Advanced Parkinson's disease

As well as varying day-to-day for each patient, symptoms of PD progress differently between different individuals.[12] Not everyone will present the same symptoms at the same time, but both naturally-occurring and medication-induced symptoms worsen with disease duration.[12] The PD patient population is therefore highly heterogeneous and defining stages of the disease when symptoms become more uncontrolled is non-trivial.[13]

Indeed, the transition from earlier stages of PD to more advanced disease represents a continuum; the '5-2-1' motor criteria have been developed by AbbVie based on Delphi panel consensus to help support the identification of patients with advanced PD.[28] These describe advanced stages of PD as the presence of at least one hour of troublesome dyskinesia a day, at least two hours of 'Off' symptoms a day, or at least five oral levodopa doses a day.[28] Attempts to build on the 5-2-1 criteria to define advanced PD in European Delphi panels have resulted in the

identification of criteria which also consider non-motor symptoms and functional impairment, however, these definitions are not equally adopted across clinicians.[28-31]

Impact of Parkinson's disease on patients and their caregivers

As described above, PD symptoms can present in a number of different forms. Physical symptoms can impair basic tasks such as walking or handling objects, which get more difficult as the disease progresses and symptoms worsen and become uncontrolled by medication. Non-motor symptoms such as constipation, sleep disorders, cognitive impairment and drooling can also limit the wellbeing, independence and social life of people with PD.[10, 14]

Another important aspect of PD are the psychological symptoms experienced by patients, with depression and anxiety being commonly reported symptoms of PD, and which can have a significant impact on patients' mental health.[32] These can also further exacerbate the physical impact of PD. For example, patients with PD tend to get tired more easily due to the extra challenges in carrying out daily activities; sleep can also be interrupted by middle of the night motor episodes, as well as other sleep disorders, leaving them feeling less rested.[33] These complications are particularly heightened for patients receiving non-continuous PD medications, who therefore commonly experience early morning 'Off' times.[34]

The QoL of patients with PD is substantially inferior to that of the healthy population and is correlated with the complexity of the disease and comorbidities.[15] There is a strong correlation between deterioration in QoL and motor fluctuations due to the 'wearing off' of medications: the impact of 'Off' time is not just physical, but creates emotional distress, due to the fear that 'Off' time will appear at any time.[35] One particular study has identified that patients experiencing more than one hour of 'Off' time daily reported worse QoL outcomes compared with those experiencing less than one hour based on the 39-item PD Questionnaire (PDQ-39) summary index ($p<0.001$) and all sub-dimensions, as well as in the EuroQol-5 Dimensions 5-Level Questionnaire (EQ-5D-5L; mobility: odds ratio [OR] 2.1, 95% confidence interval [CI]: 1.3, 3.5; usual activities: OR 2.6, 95% CI: 1.8, 3.7; anxiety/depression: OR 1.6, 95% CI: 1.1, 2.2) sub-categories.[16] UK-based surveys identified that people with complex PD found the most troublesome symptoms to be fluctuating response to their medication, mood changes, drooling, sleep problems and tremor, and showed increased concerns around dyskinesia and motor fluctuations as PD becomes more advanced.[36, 37]

Complications exacerbated by non-continuous administration of PD medications can have a substantial additional impact on patients' QoL. Sleep problems in particular can have a large impact on patients' QoL, with a study finding sleep problems (as measured by PD Sleep Scale-2 [PDSS-2]) to be significantly correlated with PDQ-39 score.[38] Morning akinesia, or early morning 'Off' time, has also been found to significantly impact patients; studies have also found that the QoL of patients with early morning 'Off' time is reduced.[39, 40]

Moreover, the disability induced by motor complications, and the consequent need for around-the-clock assistance has a substantial effect on families and caregivers.[17] As well as requiring support with physical functions, patients with advanced PD may show increased cognitive and psychosocial limitations. Carers are needed to help with daily functions such as medication dosing, help with dressing, walking and eating. Day-long assistance is needed for people with advanced PD, and consequently their carers experience lower QoL than the general population, with high rates of depression, social isolation, and loneliness.[17, 41] Caring for patients with PD often disrupts caregivers' QoL and there is a correlation between patients' QoL and the burden perceived by the caregiver.[42] A 2017 report by Parkinson's UK found that households with a

member with PD would be £16,582 worse off per year,[43] adding to the direct and indirect costs of care for patients with PD.

Hospitalisation, visits to accident and emergency (for example due to falls) and routine consultations as well as indirect costs of care have been shown to pose a much larger financial burden as PD reaches an advanced stage.[44, 45]

Overall, PD is a highly debilitating disease for patients, which progressively and inevitably worsens over time. The complex and multifaceted symptoms of PD have a highly detrimental impact on patients' ability to perform day-to-day activities, their mental wellbeing, and overall quality of life. Patients with advanced PD face worsening symptoms, which cannot be controlled by standard therapies, and are therefore particularly impacted by the disease.

B.1.3.2 Clinical pathway of care

Current treatment options

To date, NICE has not reviewed any treatments for PD through its technology assessment (TA) process, however treatments are available for patients. NICE's guideline NG71 'Parkinson's disease in adults' provides recommendations on pharmacological management of motor symptoms in PD.[18]

Initial therapy

Pharmacological therapy is generally started when motor symptoms becoming disabling.[46] Patients are typically offered oral levodopa as initial treatment, with the aim of replenishing the natural reduced supply of dopamine in the brain.[47] In order to minimise conversion of dopamine in the bloodstream and maximise its absorption in the brain, levodopa is commonly administered with carbidopa, an inhibitor of aromatic amino acid decarboxylation, allowing for lower doses of levodopa to be administered and therefore fewer associated side effects.[13, 47] Dopamine agonists or MAO-B inhibitors can also be considered for patients in the early stages of PD whose motor symptoms do not impact on their QoL.[18]

When motor symptoms progress, and 'wearing off' and dyskinesia episodes appear, optimal levodopa oral therapy can be supplemented by adjuvant oral therapies, which include MAO-B inhibitors, dopamine receptor antagonists, COMT inhibitors and amantadine.[18]

Non-oral advanced therapies

For patients whose PD progresses to an advanced disease phase, both device-aided and surgical interventions may be considered when oral combinations become less suitable for maintaining good symptom control and stable plasma dopamine levels. This is due to the narrowing of the therapeutic window as shown in Figure 1, and due to irregular gastric emptying, which are typical symptoms of progressed PD.[26] At this stage, the primary goal of therapy is to reduce 'Off' time and increase 'On' time without troublesome dyskinesia.[48] Continuous treatment methods are the preferred treatment options for patients with advanced PD. Whilst patients uncontrolled by standard therapies face limited treatment options, the choice of treatment at this stage of the disease remains highly individualised,[23] with patient choice and preference being key to clinical decision making.

According to NG71, patients with advanced PD should be offered BMT, which may include apomorphine delivered either as CSCI or as intermittent injection.[18] Apomorphine has been shown to reduce 'Off' time by 50%,[49] however it is associated with serious adverse events (SAEs) and poor outcomes in eliminating dyskinesia.[49-51] Poor control of dyskinesia has in fact been shown to be the leading cause of apomorphine discontinuation, with the majority of patients returning to oral therapy after discontinuation.[50] AEs have also been found to contribute to apomorphine discontinuation;[51] apomorphine is associated with hallucinations, psychosis and impulse control disorder.[48] The presence of these AEs can limit the suitability of apomorphine in the medium term. Apomorphine has therefore been considered a suitable intervention for patients waiting for alternative currently available advanced therapies, but may not be suitable for long-term use in all patients.[50] Apomorphine is contradicted in patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency, which further limits its suitability for some patients.[52] Naturally, incidence of these comorbidities increases with age, and are therefore more prevalent in older populations, and hence in the PD population.

DBS can also be considered for patients whose current medical therapy is not providing adequate symptom control. DBS is a highly invasive procedure carried out at specialist neurological units. It consists of the placement of small electrodes in the deep brain, via a surgical procedure requiring perforations in the skull. The electrodes then stimulate the brain to suppress motor symptoms via electric pulses sent from an external device, usually placed under the skin around the chest or stomach, and connected to the head via cables. The implantable pulse generator (IPG) device, part of the DBS system, requires a battery to be powered, which needs to be replaced approximately every 3–5 years via a further surgical procedure.[53]

National Health Service (NHS) clinical commissioning policy recommends DBS as the preferred therapy only when no other treatment option is available.[54] Due to the invasiveness of surgery, potentially fatal AEs have been associated with DBS. Surgery-related brain haemorrhage have been reported in 1–5% of patients, and 1.65% of surgeries have been reported to lead to permanent neurological damage.[55, 56] Additional AEs are reported postprocedural or related to the device, such as during IPG battery replacement surgery, which was shown to lead to neurological worsening in 35.5% of operated patients.[56, 57] Peri- and post-operative AEs can require DBS removal and re-operation,[58] adding to the humanistic and economic burden of complex PD.

Importantly, DBS is available only to a limited subgroup of patients, based on demographic and clinical grounds. Patients have to show poor response to other available therapies and be under 70 years of age (which excludes the majority of people with PD). Contraindications include severe speech disturbance, postural instability, dysphagia or psychological symptoms (depression, dementia, previous suicide attempts).[48, 54] Moreover, DBS does not altogether eliminate motor symptoms or the need for supportive pharmacological treatment, with the known associated complications.[18, 54] Due to the invasive nature of the surgery and associated risks, DBS is highly elective and not all suitable patients may wish to receive the treatment.

Finally, LCIG is also available for patients with advanced PD who are levodopa-responsive, unable to tolerate or unsuitable for apomorphine or unsuitable for DBS, have refused to consent for DBS or DBS has failed.[59] LCIG allows for stable plasma levels of dopamine by providing continuous delivery of levodopa/carbidopa via a percutaneous surgically-applied tube in the jejunum, connected to a pump and cartridge system containing levodopa/carbidopa gel.[18] Like DBS, LCIG requires surgical intervention to be delivered. The continuous delivery of levodopa

overcomes barriers associated with oral levodopa, reducing 'Off' time by up to 46–82% and 83% in the short (3–6 months) and long (3–5 years) term, respectively, as well as reducing the presence of dyskinesia and improving patients' QoL.[26, 31] LCIG is associated with device-related AEs; for example, the dislocation and occlusion of the gastrotomy tube can lead to sudden deterioration of PD symptoms and the need for re-operation.[31] A long-term continuation study showed that jejunal tube and gastronomy tube replacement were required at 5 years in 54% and 37% of patients, respectively.[60] The NHS clinical commissioning policy for LCIG limits eligibility to those patients who are unsuitable for DBS or other therapies and who do not have additional comorbidities.[59]

As shown, only a small number of options are available for patients with advanced PD, and these options are limited with patients not having access to one or more of these treatments depending on their locality; apomorphine is not available locally in every clinical commissioning group and DBS and LCIG are only available to patients at tertiary centres. The treatment options are further limited by narrow eligibility criteria and need for invasive surgery, which can in some cases result in SAEs.[31, 49-51, 55, 56] Additionally, a number of patients are unsuitable to receive any or have failed on these advanced non-oral therapies. Unfortunately, these patients may therefore remain on BMT despite not achieving satisfactory symptom control due to a lack of any other therapeutic alternative.

There is therefore a clear unmet need for a new non-surgical, easily accessible treatment option for patients with PD uncontrolled by oral therapy, to provide predictable symptom control and limited side effects.

Positioning of foslevodopa-foscarbidopa

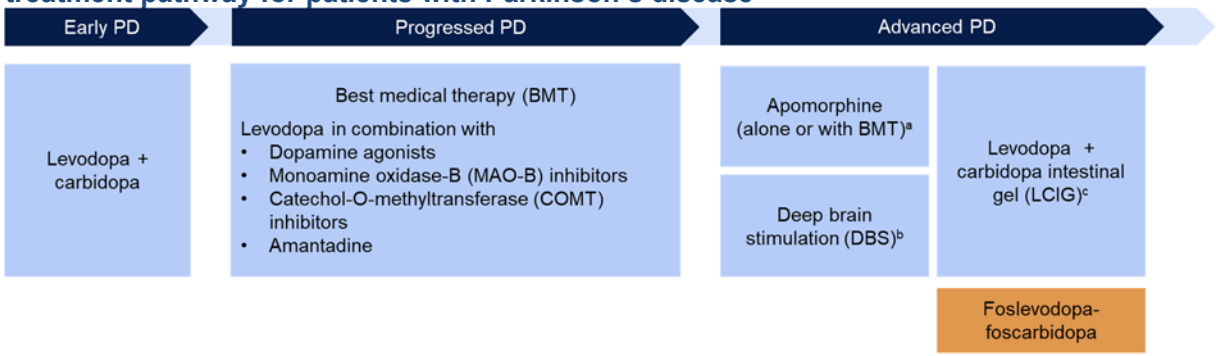
Foslevodopa-foscarbidopa is a novel formulation combining two prodrugs of levodopa and carbidopa for subcutaneous dosing, each having identical mechanisms of action to their respective active drug. The phosphate group in both active substances allows for subcutaneous delivery, and it is rapidly cleaved off in the brain capillaries to give levodopa and carbidopa. Foslevodopa-foscarbidopa is delivered via 24-hour non-invasive CSCI in order to provide constant and stable concentrations of levodopa, and eliminate fluctuations commonly associated with oral treatments.

Foslevodopa-foscarbidopa is an innovative treatment option for patients with PD who have progressed to an advanced stage of disease and who are experiencing motor symptoms uncontrolled by standard therapy. Foslevodopa-foscarbidopa is administered subcutaneously via a small external pump, which can be independently managed by patients or caregivers following initial dose optimisation, allowing for sustained and predictable symptom control. Dose optimisation via the pump allows dosing to be tailored for individual patients, with the possibility of supplementing the foslevodopa-foscarbidopa dose by bolus injection. Furthermore, the administration of treatment overnight allows for greater symptom control following sleep, a problem often reported by patients as early morning 'Off' periods.[34] This is achieved without the need for invasive surgical procedures and with a tolerable safety profile compared with other treatments currently available to patients at this stage of disease progression. Currently, for patients with advanced PD, no non-surgical levodopa treatment options are available; foslevodopa-foscarbidopa offers this choice to patients. Additionally, foslevodopa-foscarbidopa represents an easily accessible treatment option for patients, not adding to current capacity pressures at tertiary centres.

Treatment choice throughout all stages of PD is highly individualised and based on patient and clinician preference, dependent upon a range of factors including patient access to a non-oral treatment, patient characteristics, suitability for treatment and lifestyle preferences. As an advancement of continuous levodopa-carbidopa based therapies and considering the individual nature of treatment decisions, it is anticipated that foslevodopa-foscarbidopa would be used primarily in a patient population similar to that of LCIG, providing patients with greater convenience and improved 24-hour dosing. As described above, there are some patients with advanced PD who remain on BMT despite not achieving satisfactory symptom control due to being unsuitable for or having failed on apomorphine or DBS. Given the innovative, unique administration of foslevodopa-foscarbidopa, it also represents a new treatment consideration for these patients, providing them with a novel, non-surgical, option for effective, further treatment. Foslevodopa-foscarbidopa therefore represents a less invasive treatment option compared with LCIG, providing patients with an additional treatment option when not suitable for apomorphine or DBS, and the first and only 24-hour subcutaneous levodopa infusion.

Therefore, in this evaluation, foslevodopa-foscarbidopa is positioned for use in patients with advanced PD with symptoms not adequately controlled by their current medical therapy (i.e. BMT), or for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control (see Table 1).

Figure 2: Anticipated positioning of foslevodopa-foscarbidopa with respect to the current treatment pathway for patients with Parkinson's disease



[a]Apomorphine may be administered as intermittent injection in earlier stages, but is predominantly used as a CSCI in patients in the advanced PD setting.
[b]If symptoms are inadequately controlled by BMT.
[c]LCIG is restricted for use in patients who are unsuitable for DBS or apomorphine.
Abbreviations: BMT: best medical therapy; COMT: Catechol-O-methyltransferase; CSCI: continuous subcutaneous infusion; DBS: deep brain stimulation; LCIG: levodopa-carbidopa intestinal gel; PD: Parkinson's disease.
Source: Adapted from NICE NG71.[18]

B.1.4 *Equality considerations*

It is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

M15-736 and M15-741 represent the pivotal clinical trials for foslevodopa-foscarbidopa that provide the clinical evidence base for this submission.

- M15-736 is a Phase III, randomised, double-blind, double-dummy, active-controlled, parallel group, multicentre study comparing the efficacy, safety and tolerability of foslevodopa-foscarbidopa to oral carbidopa/levodopa (CD/LD) in patients with advanced PD.
- M15-741 is a Phase III open-label, single-arm study evaluating the safety and tolerability of foslevodopa-foscarbidopa delivered as a 24-hour daily CSCI in patients with PD.
- Clinical experts agreed that the baseline characteristics of both trials aligned with the patients they see in UK clinical practice who would be eligible for advanced PD therapies, and that the trial designs and methodology were consistent with previous studies in PD.[61]

In both pivotal trials, foslevodopa-foscarbidopa was demonstrated to be an effective treatment option, providing significant improvements in both motor and non-motor symptoms for patients.

M15-736

- Foslevodopa-foscarbidopa provided a [redacted] improvement compared with oral CD/LD in the primary outcome of the trial; change from baseline in daily 'On' time without troublesome dyskinesia increased by [redacted] hours compared with the oral CD/LD group.
- The foslevodopa-foscarbidopa arm further showed a [redacted] and clinically meaningful reduction in 'Off' time compared with the oral CD/LD group, with an observed least square (LS) mean difference of [redacted] hours.
- Clinically meaningful improvements were observed in the MDS-UPDRS Part II score for the foslevodopa-foscarbidopa group compared with the oral CD/LD group, and the number of patients who experienced morning akinesia greatly decreased from baseline with foslevodopa-foscarbidopa; the same decrease was not observed in the oral CD/LD group.
- Patients in the foslevodopa-foscarbidopa arm also reported greater reduction in PDSS-2 scores from baseline, indicating that the 24-hour administration had a notable impact of patients' quality of sleep.
- A decrease in symptoms also resulted in an increase in health-related QoL (HRQoL) as measured by PDQ-39 and EQ-5D-5L summary indices.

M15-741

- Efficacy was a secondary outcome of trial M15-741, which showed comparable results to M15-736 in 'On' time, demonstrating that control of motor symptoms is maintained over 52 weeks.
- [redacted] improvements in 'On' time without troublesome dyskinesia and 'Off' time were observed at all time points measured.
- The trial also showed overall clinically meaningful improvements in motor symptoms, early morning non-sleep symptoms as assessed by PDSS-2, and PD symptoms assessed by MDS-UPDRS Part I–III.
- [redacted] improvements in HRQoL were also observed by PDQ-39 and EQ-5D-5L summary indices.

Foslevodopa-foscarbidopa provides a more consistent and stable plasma concentration level of both levodopa and carbidopa over its full 24-hour administration.

- A comparative pharmacokinetic/pharmacodynamic (PK/PD) study of foslevodopa-foscarbidopa versus LCIG, M17-220, provides supportive evidence that both treatments have a similar pharmacological profile over waking hours, but foslevodopa-foscarbidopa delivers a more stable concentration of levodopa and carbidopa over the full 24-hours, highlighting its potential to deliver more predictable and sustained daily symptom control.

Foslevodopa-foscarbidopa was associated with a manageable safety profile, consistent with the known safety profile of levodopa.

- Both pivotal trials observed foslevodopa-foscarbidopa to have a manageable safety profile, with observed AEs generally consistent with those associated with levodopa, and with similar incidence of SAEs observed between the foslevodopa-foscarbidopa and oral CD/LD arms in trial M15-736.
- In M15-736, the incidence of infusion site infections was higher in the foslevodopa-foscarbidopa arm, but the majority were non-serious, mild or moderate in severity, and resolved.

Results of the NMA found foslevodopa-foscarbidopa to have similar efficacy to LCIG, and be significantly more effective at improving sleep symptoms.

- An SLR was conducted which identified 176 relevant publications reporting on 145 unique studies. Of these publications, seven met the relevant criteria for inclusion in the NMA. However, only four studies were required to appropriately connect the interventions of relevance to the decision problem in this evaluation.
- Relative efficacy was measured using 'Off' time, 'On' time without troublesome dyskinesia, and PDSS-2 outcomes in the population of interest to this submission.
- [redacted] was estimated to have a [redacted] in 'Off' time at 3 months compared with [redacted] but a [redacted] in 'On' time without troublesome dyskinesia, however neither difference reached statistical significance.
- [redacted] was found to [redacted] PDSS-2 scores at 3 months relative to [redacted], highlighting the substantial benefits foslevodopa-foscarbidopa can bring to patients, likely due to its ability to provide innovative 24-hour dosing.
- Aligned with the results of the M15-736 trials, foslevodopa-foscarbidopa was also shown in the NMA to [redacted] improve 'Off' time, 'On' time without troublesome dyskinesia, and PDSS-2 scores at 3 months relative to BMT.

Overall, foslevodopa-foscarbidopa represents an innovative treatment option for patients with advanced PD, providing a non-surgical choice that provides more consistent, 24-hour symptom control.

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted in June 2021 and updated in January 2022 and June 2022 to identify and review clinical evidence on the efficacy, safety, and QoL outcomes of treatment options in advanced PD. Overall, a total of 190 relevant publications reporting on 151 unique studies (33 clinical trials, 53 records; 118 non-comparative studies, 137 records) were identified in the SLR. Full details of the SLR, including search strategy, study selection process and detailed results are presented in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

No studies were identified in the SLR for foslevodopa-foscarbidopa as none of the trials are yet published, however data are available from the clinical study reports (CSRs) of the pivotal studies. The clinical evidence base for this evaluation of foslevodopa-foscarbidopa for treating patients with advanced PD consists of two pivotal clinical trials, M15-736 and M15-741:

- M15-736 is a Phase III, randomised, double-blind, double-dummy, active-controlled, parallel group, multicentre study comparing the efficacy, safety and tolerability of foslevodopa-foscarbidopa to oral CD/LD in patients with advanced PD. Clinical effectiveness and safety results for study M15-736 are reported in Section B.2.3.4 and Section B.2.8.1 respectively.

- M15-741 is a Phase III open-label, single-arm study evaluating the safety and tolerability of foslevodopa-foscarbidopa delivered in patients with PD. Clinical effectiveness and safety results for study M15-741 are reported in Section B.2.4.4 and Section B.2.8.2 respectively.

As the only RCT investigating foslevodopa-foscarbidopa, M15-736 informs the cost-effectiveness model (CEM). M15-741 provides supportive clinical evidence within this submission, with limited use in the CEM due to the primary outcomes focussing on safety. A summary of the clinical effectiveness evidence from M15-736 and M15-741 is presented in Table 3, with full details and data from the studies presented in Sections B.2.3 and B.2.4, respectively, based on data sourced from the clinical study reports (CSRs) of these trials.[62, 63]

Additional evidence is available from a number of pharmacokinetic/pharmacodynamic (PK/PD) studies investigating bioequivalence between LCIG and foslevodopa-foscarbidopa, which are presented as supporting evidence in Section B.2.5 for completeness.

Table 3: Clinical effectiveness evidence

Study	M15-736	M15-741
Study design	Phase III, randomised, double-blind, double-dummy, active-controlled, parallel group study	Phase III open-label, single-arm study
Population	Patients with advanced PD whose motor fluctuations were inadequately controlled by their current medications	Patients with PD who report motor complications that are inadequately controlled by oral medications and who experience a minimum of 2.5 hours of 'Off' time per day
Intervention(s)	Foslevodopa-foscarbidopa administered as 24-hour daily CSCI, plus oral placebo capsules for CD/LD IR	Foslevodopa-foscarbidopa administered as 24-hour daily CSCI
Comparator(s)	Encapsulated CD/LD IR, plus 24-hour daily CSCI of placebo solution for foslevodopa-foscarbidopa	N/A
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	Yes	Yes
Rationale for use/non-use in the model	M15-736 and M15- 741 are the pivotal Phase III trials demonstrating the safety and efficacy of foslevodopa-foscarbidopa in patients with advanced PD. These trials informed the marketing authorisation application and considered a population directly relevant to the decision problem addressed in this submission.	
Reported outcomes specified in the decision problem	*The following outcomes from the M15-736 trial each individually address one or more of the outcomes specified in the final scope of this evaluation.* **Primary outcome:** • Change from Baseline to Week 12 in hours of average daily normalised 'On' time without troublesome dyskinesia as assessed by the PD diary **Key secondary outcomes:** • Change from Baseline to Week 12 in hours of average daily normalised 'Off' time as assessed by the PD diary • Change from Baseline to Week 12 in M-EDL as assessed by the MDS-UPDRS Part II score	*The following outcomes from the M15-741 trial each individually address one or more of the outcomes specified in the final scope of this evaluation.* **Primary outcomes:** • Percentage of patients with AEs and SAEs during the study • Percentage of patients with AESIs during the study • Percentage of patients with numeric grade equal to or higher than 5 and percentage of patients with letter grade equal to or higher than D on the Infusion Site Evaluation Scale at any time during the study **Secondary outcomes:** • Average normalised daily 'Off' time and 'On' times as

	• Presence of morning akinesia at Week 12 (defined as reporting 'Off' status as the first morning symptom upon awakening) as assessed by the PD diary • Change from Baseline to Week 12 in median bradykinesia score (BK50) as assessed by the Parkinson's KinetiGraph™/Personal KinetiGraph™ (PKG) wearable device • Change from Baseline to Week 12 in interquartile range of bradykinesia score (BK75-BK25) as assessed by the PKG wearable device • Change from Baseline to Week 12 in median dyskinesia score (DK50) as assessed by the PKG wearable device • Change from Baseline to Week 12 in interquartile range of dyskinesia score (DK75-DK25) as assessed by the PKG wearable device ***HRQoL*** • Change from Baseline to final visit in PDQ-39 summary index • Change from Baseline to final visit in EQ-5D-5L summary index **Additional efficacy outcomes:** • Change from Baseline to final visit in PDSS-2 total score • Percent change from Baseline to Week 12 in time of tremor and daytime somnolence as assessed by the PKG wearable device • Change from Baseline to Week 12 in MDS-UPDRS Part I score, Part III score, Part IV score, and total score of Parts I - III • Change from Baseline to Week 12 in average daily normalised 'On' time with non-troublesome dyskinesia, and 'On' time with troublesome	assessed by the PD Diary • PD symptoms as assessed by the MDS-UPDRS Parts I-IV (or the UPDRS Parts I-V in countries where a validated translation of the MDS-UPDRS is not available) • Sleep symptoms as assessed by the PDSS-2 • HRQoL as assessed by the PDQ-39 • HRQoL as assessed by EQ-5D-5L

	dyskinesia as assessed by the PD Diary • Percent change from Baseline to Week 12 in average daily normalised 'Off' time, 'On' time without troublesome dyskinesia, 'On' time without dyskinesia, 'On' time with non-troublesome dyskinesia, and 'On' time with troublesome dyskinesia as assessed by the PD Diary • Change from Baseline to Week 12 in average daily absolute 'Off' time, 'On' time without troublesome dyskinesia, 'On' time without dyskinesia, 'On' time with non-troublesome dyskinesia, 'On' time with troublesome dyskinesia, and 'Asleep' time as assessed by the PD Diary without normalising • Change from Baseline to Final Visit in PDSS-2 domain scores • Change from Baseline to Final Visit in PDQ-39 domain scores • Change from Baseline to Final Visit in EQ-5D-5L VAS score **Safety:** • AE	
All other reported outcomes	No outcomes outside of the decision problem were reported	No outcomes outside of the decision problem were reported

Abbreviations: AE: adverse event; AESI: adverse event of special interest; BK75-BK25: interquartile range of bradykinesia score; CD/LD: carbidopa/levodopa; CSCI: continuous subcutaneous infusion; DK50: median dyskinesia score; DK75-DK25: interquartile range of dyskinesia score; EQ-5D-5L: EuroQol 5-Dimension 5-Level Questionnaire; HRQoL: health-related quality of life; IR: immediate release; MDS-UPDRS: Movement Disorders Society-Unified PD Rating Scale; M-EDL: motor aspects of experiences of daily living; PD: Parkinson's disease; PDQ-39: PD Questionnarie-39 Item; PDSS-2: PD Sleep Scale-2; QoL: quality of life; SAE: serious adverse event; VAS: visual analogue scale.
Source: Data on File. M15-736 Clinical Study Report;[63] Data on File. M15-741 Clinical Study Report.[62]

B.2.3 *M15-736*

B.2.3.1 Summary of methodology of the relevant clinical effectiveness evidence

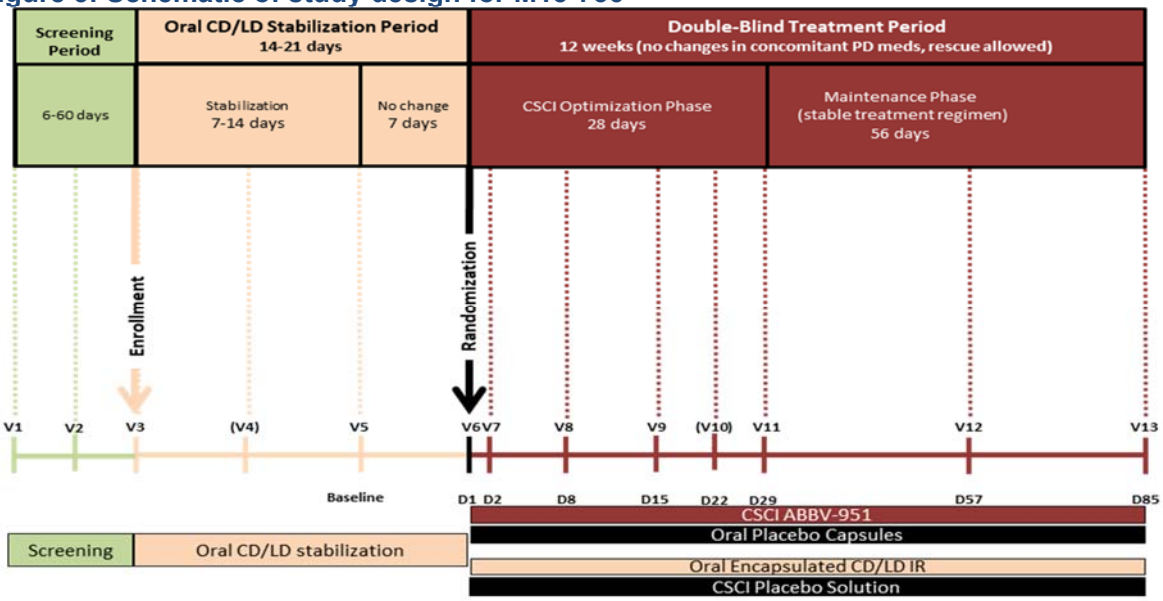
B.2.3.1.1 Trial design and methodology

Study M15-736 was a Phase III, randomised, double-blind, double-dummy, active-controlled, parallel group, multicentre study evaluating the efficacy, safety, and tolerability of 24-hour daily CSCI of foslevodopa-foscarbidopa versus oral CD/LD in the treatment of patients with advanced PD whose motor fluctuations were inadequately controlled by their current medication.

Study M15-736 consisted of a screening period (6 to 60 days), an open-label oral CD/LD stabilisation period (14 to 21 days), and a 12-week double-blind treatment period, as shown schematically in Figure 3. The double-blind treatment period informs the efficacy and safety analyses reported in Section B.2.3.4 and Section B.2.8.1, respectively.

At the start of the oral CD/LD stabilisation period, all levodopa-containing medications and catechol-O-methyltransferase (COMT) inhibitors were converted to an equivalent amount of CD/LD IR. The dose and schedule of oral CD/LD were adjusted over the first 7 to 14 days by the investigator to achieve the best possible control of each patient's motor symptoms. Once stabilised, no further adjustments were to be made for at least 7 days prior to randomisation. At the end of this stabilisation period, patients were randomised in a 1:1 ratio to either continue receiving oral CD/LD or receive CSCI of foslevodopa-foscarbidopa. The dosing of oral CD/LD attained during the stabilisation period was converted to a levodopa equivalent dose (LED) of foslevodopa-foscarbidopa for those patients in the intervention arm during the double-blind treatment period. Details of the trial methodology are provided in Table 4. The CONSORT diagram for M15-736 is presented in Appendix D.4.

Figure 3: Schematic of study design for M15-736



ABBV-951 = foslevodopa-foscarbidopa
Abbreviations: CD/LD: carbidopa/levodopa; CSCI: continuous subcutaneous infusion; D: Day; IR: immediate release; PD: Parkinson's disease; V: Visit.

Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Eligible patients who completed the 12-week double-blind treatment period in M15-736 could enter a separate open-label extension study (Study M20-098) for up to 96 weeks of foslevodopa-foscarbidopa treatment; M20-098 is ongoing.

Table 4: Summary of methodology for M15-736

Trial name	M15-736
Location	57 sites in the United States and Australia
Trial design	Phase III, randomised, double-blind, double-dummy, active-controlled, parallel group study
Duration of study	As shown in Figure 3, the study consisted of three sequential phases: **Screening (6–60 days)** Prior to trial enrolment, patients were initially screened against the trial eligibility criteria described below and outlined in full in Appendix M. **Oral CD/LD stabilisation period (14–21 days)** During this study phase, all levodopa-containing medications, regardless of formulation, as well as those containing COMT inhibitors, were converted to an equivalent amount of CD/LD IR. All other concomitant PD medications, although allowed, were required to remain unchanged until study completion, unless specific safety conditions dictated their modification. The dose and schedule of oral CD/LD were adjusted over the first 7 to 14 days of the oral stabilisation period by the investigator to achieve the best possible control of the patient's motor symptoms, including by using night-time dosing if needed and agreed upon by the patient and investigator. No changes to this regimen could be made for at least 7 days leading up to randomisation at the start of the 12-week double-blind treatment period. **Double-blind randomisation period starting at Day 1 and ending at Day 85 (12 weeks), sub-divided in:** ***CSCI stabilisation phase (28 days)*** During this study period investigators could make all necessary adjustments to the patient's CSCI rate for blinded study drug solution to achieve an optimal clinical response. Optimal clinical response was defined as maximising functional 'On' time while minimising the number of 'Off' episodes and 'On' time with troublesome dyskinesia during the day. Oral study drug and allowed concomitant PD medications were required to be maintained at the already stabilised pre-randomisation dose and schedule; changes to concomitant PD medications were not allowed unless necessary for safety reasons. ***Maintenance phase (56 days)*** During this phase, patients were to remain on a stable regimen of blinded study drug solution and blinded oral study drug as well as other concomitant medications, including any PD medications that were still being administered. Dose adjustments of non-study-drug medications could be made only if considered medically necessary. Rescue tablets of CD/LD IR could be taken in the case of sudden deterioration of clinical condition or pump malfunction lasting more than 1 hour.
Method of randomisation	Patients were randomised in a 1:1 ratio using the EndPoint Clinical® IRT randomisation algorithm following the stabilisation period in either treatment arm, receiving either:

	• Foslevodopa-foscarbidopa administered as 24-hour daily CSCI, plus oral placebo capsules for CD/LD immediate release (IR) OR: • Encapsulated CD/LD IR, plus 24-hour daily CSCI of placebo solution for foslevodopa-foscarbidopa
Method of blinding	The following measures were taken during the trial to ensure blinding of study participants and personnel investigators throughout entire trial period: • Study site personnel who provided the study drug (e.g., pharmacist or study nurse) were different from the personnel who assessed patients for the safety and efficacy endpoints • The treating investigator assessed AEs, managed the device (including dose changes during the CSCI optimisation period), performed safety assessments, and controlled the use of rescue medications • Study sites used a separate assessor (i.e., other than the site personnel who provided study drug or the treating investigator) to perform all in-person efficacy assessments (i.e., MDS-UPDRS). The infusion tubing was completely hidden from view and remained hidden while the efficacy assessor saw patients • CD/LD IR tablets were over-encapsulated and identical in appearance to the placebo capsules. The over-encapsulated CD/LD IR tablets and placebo capsules were packaged identically • Foslevodopa-foscarbidopa solution for infusion and the placebo solution for infusion were packaged identically
Trial drugs and method of administration	**Active treatment** Foslevodopa-foscarbidopa administered as 24-hour daily CSCI, plus oral placebo CD/LD capsules **Comparator treatment** Oral CD/LD capsules, plus placebo infusion administered as 24-hour CSCI
Permitted and disallowed concomitant medication	**Allowed concomitant therapies** The following medications were allowed during the stabilisation and double-blind treatment periods: • Non-ergolinic dopamine agonists (e.g., pramipexole, ropinirole, rotigotine) • Selective MAO-B inhibitors (e.g., rasagiline, selegiline) • Amantadine (IR and ER formulations) • Safinamide • Istradefylline **Prohibited concomitant therapies** The following medications were prohibited during the stabilisation and double-blind treatment periods: • Apomorphine

	• Levodopa-carbidopa intestinal gel (LCIG) / carbidopa-levodopa enteral suspension (CLES) • Dopamine-depleting agents (e.g., reserpine, tetrabenazine, amphetamines) • MAO-A inhibitors and non-selective MAO inhibitors • Ergot dopamine agonists (e.g., lisuride, bromocriptine, cabergoline) • Dopamine antagonist or partial agonist, first generation antipsychotics, or antiemetic medications that interact with brain dopamine receptors (e.g., fluphenazine, loxapine, perphenazine, thiothixene, haloperidol, metoclopramide, aripiprazole, asenapine) • Oral and/or inhaled medications containing levodopa. Oral CD/LD was allowed as a rescue therapy • COMT inhibitors (e.g., entacapone, tolcapone, opicapone)
Primary outcome	The primary endpoint is the change from Baseline to Week 12 of the Double-Blind Treatment in 'On' time without troublesome dyskinesia (hours) ('On' time without dyskinesia plus 'On' time with non-troublesome dyskinesia), based on PD Diary (normalised to a 16-hour waking day and averaged over 3 consecutive days).
Secondary outcomes	**Key efficacy outcomes:** • Change from Baseline to Week 12 in hours of 'Off' time as assessed by the PD diary • Change from Baseline to Week 12 in Movement Disorders Society- Unified PD Rating Scale (MDS-UPDRS) Part II score **Other efficacy outcomes:** • Early morning 'Off' status at Week 12, based on the first morning symptom upon awakening on the last valid PD diary day at Week 12 • Change from Baseline to final visit in PDSS-2 total score • Change from Baseline to Week 12 in median bradykinesia score (BK50) as assessed by the Parkinson's KinetiGraph™/Personal KinetiGraph™ (PKG) wearable device • Change from Baseline to Week 12 in interquartile range of bradykinesia score (BK75-BK25) as assessed by the PKG wearable device • Change from Baseline to Week 12 in median dyskinesia score (DK50) as assessed by the PKG wearable device • Change from Baseline to Week 12 in interquartile range of dyskinesia score (DK75-DK25) as assessed by the PKG wearable device **HRQoL:** • Change from Baseline to final visit in PDQ-39 summary index • Change from Baseline to final visit in EQ-5D-5L summary index
Pre-specified subgroup analyses	Subgroup analyses of change from baseline to Week 12 of the double-blind treatment period were planned for the primary and key secondary outcomes based on: • Age category (< 65 or ≥ 65 years) • Sex (male or female)

	• Race (white or other) • Country (US or Australia) • Duration of PD (< 10 years or ≥ 10 years) • Concomitant dopamine agonist use (yes or no) • Dose subgroup (low [<1800 mg] or high [≥1800 mg] levodopa dose)
Eligibility criteria	The key eligibility criteria for the trial are shown below: • Male or female patients, 30 years of age or older at the time of screening, with a diagnosis of idiopathic PD that is levodopa-responsive • Patients must be taking a minimum of 400 mg/day of LD equivalents and be judged by the investigator to have motor symptoms inadequately controlled by current therapy, have a recognizable/identifiable 'Off' and 'On' states (motor fluctuations), and have an average 'Off' time of at least 2.5 hours/day over 3 consecutive PD Diary days with a minimum of 2 hours each day. • Patient (or caregiver, if applicable) demonstrates the understanding and correct use of the delivery system, including the insertion of the cannula into the patient's abdomen, as assessed by the investigator or designee during the Screening Period A full list of eligibility criteria is given in Appendix M.

Abbreviations: AE: adverse event; CD: carbidopa; CSCI: continuous subcutaneous infusion; COMT: Catechol-O-Methyltransferase; IR: immediate release; IRT: interactive response technology; LD: levodopa; MMRM: mixed model for repeated measures; MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PD: Parkinson's Disease PDQ-39: Parkinson's Disease Questionnaire; PDSS-2: Parkinson's Disease Sleep Scale.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

B.2.3.1.2 Baseline characteristics

The baseline characteristics of patients enrolled in the double-blind treatment phase are shown in Table 5. Key characteristics were generally well balanced across the two randomised trial arms, oral CD/LD and foslevodopa-foscarbidopa, with similar mean age ([redacted] and [redacted] years, respectively), duration of PD since diagnosis ([redacted] and [redacted] years, respectively) and baseline 'Off' time ([redacted] and [redacted] hours, respectively). Clinical experts consulted at an advisory board as part of this appraisal confirmed that the baseline characteristics of patients in M15-736 were aligned with the patient population of interest in England, namely patients with advanced PD uncontrolled by standard therapy.[61] Clinicians in particular noted that the average duration of PD since diagnosis seen in the trial ([redacted] years) was representative of that seen in patients with advanced PD in clinical practice, who typically have had PD for a number of years before being diagnosed with an advanced form of the disease.[61]

Table 5: Baseline characteristics of patients in M15-736

Characteristic	Foslevodopa-foscarbidopa (N = [redacted])	Oral CD/LD (N = [redacted])	Total (N = [redacted])
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Age category, n (%)			
< 50 years	[redacted]	[redacted]	[redacted]
50–64 years	[redacted]	[redacted]	[redacted]
65–74 years	[redacted]	[redacted]	[redacted]
≥ 75 years	[redacted]	[redacted]	[redacted]
Weight, kg			
Mean (SD)	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), n (%)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Country, n (%)			
Australia	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]
LED at Baseline, mg/day			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

Median (min, max)	[redacted]	[redacted]	[redacted]
Duration of PD since diagnosis			
Mean (SD), years	[redacted]	[redacted]	[redacted]
< 10 years, n (%)	[redacted]	[redacted]	[redacted]
≥ 10 years, n (%)	[redacted]	[redacted]	[redacted]
Concomitant dopamine agonist use, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Baseline normalised 'Off' time, hours			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body-mass index; LED: levodopa equivalent dose; PD: Parkinson's disease; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

B.2.3.2 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Analysis sets in M15-736

The data sets analysed in M15-736 are presented in Table 6. All safety and efficacy endpoints were summarised by trial arm. The full analysis set (FAS) and safety analysis set (SAS) are equivalent.

Table 6: Trial populations used in the analysis of outcomes in M15-736

Analysis set	Description
Oral CD/LD analysis set, [redacted]	• Includes patients who received at least one dose of open label CD/LD IR tablets during the oral CD/LD stabilisation period (not the double-blind treatment period). • Used to summarise premature discontinuations, variables derived from PD diary and PKG wearable device, and adverse events during the oral CD/LD stabilisation period.
FAS, [redacted]	• Includes all randomised patients who received any dose of study drug during the double-blind treatment period and who have baseline and at least one post-baseline observation for at least one efficacy assessment. • Used for all efficacy and baseline analyses. • Patients were included in the analysis set according to the treatment groups that they are randomised.
SAS, [redacted]	• Includes all patients who received any dose of study drug during the double-blind treatment period. • Used for all safety analyses. • Patients were included in the analysis according to the study drug that they actually received regardless of randomisation.

Abbreviations: CD/LD: carbidopa/levodopa; FAS: full analysis set; IR: immediate release; PD: Parkinson's disease; PKG: Parkinson's KinetiGraph; SAS: safety analysis set.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Statistical analysis

The primary efficacy endpoint is the change from Baseline to Week 12 of the double-blind treatment period in average daily normalised 'On' time without troublesome dyskinesia (hours) as assessed by PD Diary. Details of the statistical analysis of the primary efficacy endpoint is shown in Table 7.

On PD Diary recording days, patients were instructed to make an entry upon waking and every 30 minutes during their normal waking time and upon awakening from time asleep for a full 24-hour period of each day from 12:00am to 11:30pm (48 entries with each entry representing 0.5 hour). Each entry could be in one of the 5 categories: Asleep, 'Off', 'On' without dyskinesia, 'On' with non-troublesome dyskinesia, and 'On' with troublesome dyskinesia.

Table 7: Statistical methods for the primary analyses of M15-736

	M15-736
Hypothesis	Clinical hypothesis: The 24-hour/day CSCI of foslevodopa-foscarbidopa will increase 'On' time without troublesome dyskinesia ('On' time without dyskinesia plus 'On' time with non-troublesome dyskinesia), improve the Motor Experiences of Daily Living, and reduce 'Off' time compared to CD/LD IR tablets in advanced PD patients whose motor fluctuations are no longer controlled by current PD medications.
Statistical analysis	• The primary analysis utilised MMRM and included data on change from Baseline to each post-baseline visit of the Double-Blind Treatment Period in average daily normalised 'On' time without troublesome dyskinesia obtained from PD diaries. • An unstructured variance covariance matrix was used. Parameter estimation was based on the REML method. The primary comparison was the contrast on change from Baseline between the investigational and active control groups at Week 12. • The sum of absolute 'On' times without dyskinesia and 'On' times with non-troublesome dyskinesia collected on each valid PD Diary day was normalised to a typical waking day (16 hours) to account for different sleep patterns across patients. • The proportion of patients who met average daily normalised 'On' time without troublesome dyskinesia responder criteria at Week 12 were summarised by investigational group and active control group at the thresholds from 0% to 100% with 5% as an increment. P-value for test difference in the distribution between two groups were provided by conducting Monte Carlo exact Kolmogorov-Smirnov test. Percentage of patients who achieved at least one certain percent reduction in average daily normalised 'Off' time at endpoint was displayed by investigational group and active control group in a figure. Further details can be found within the CSR.
Sample size, power calculation	Assuming a difference in change from Baseline to Week 12 in average daily normalised 'On' time without troublesome dyskinesia of 1.86 hours between investigational group and active control group, and a common standard deviation of 2.9 hours, a sample size of 52 patients per arm had an 90% power to detect a statistically significant difference between the 2 treatment arms with a 2-sided significance level of 0.05. Approximately 130 patients were to be randomised assuming that approximately 20% of patients would prematurely discontinue blinded study drug during the double-blind treatment period. This sample size also had approximately 90% power for key secondary endpoints of change from baseline in average normalised 'Off' time, MDS-UPDRS Part II score, and presence of morning akinesia.

Data management, patient withdrawals	**PD Diary:** A valid diary day was defined as one within seven days prior to the clinical visit but not on or after the day of the visit with no more than 2 hours of missing data (4 or less missing 30-minute entries) for the entire 24-hour diary. For Baseline, the valid diary day could not be on the day prior to randomisation visit because the patients are asked not to take any PD medications for at least 12 hours before the randomisation visit. An invalid PD diary day will not be used in the calculation of the average daily normalised or absolute 'Off' or 'On' times for the visit it is associated with. **MDS-UPDRS:** The MDS-UPDRS total score and score of each part was calculated as long as no more than 15% of the answers were missing for that assessment. The missing items were imputed as the average of the non-missing items from the same MDS-UPDRS assessment. Imputation for Part I, Part II, Part III or Part IV scores used the non-missing items within the particular part, but the imputation for the total score of Parts I - III used the non-missing items from all 59 items across the 3 parts. **PDSS-2:** There was no imputation of missing responses. If any item score was missing, the total score and the corresponding domain score were not calculated. **PDQ-39:** The PDQ-39 summary index was calculated as long as no more than 15% (i.e., 5) of the answers were missing for that assessment. It was imputed as the average of non-missing items from the same PDQ-39 assessment. The domain score was only calculated if all the questions were answered. **EQ-5D-5L:** The EQ-5D-5L summary index will only be calculated if answers were provided for all 5 individual questions. The EQ-5D-5L VAS is a single value collected and there was no imputation if VAS value was missing.

Abbreviations: CD: carbidopa; CSCI: continuous subcutaneous infusion; CSR: clinical study report; IR: immediate release; LD: levodopa; MMRM: mixed model for repeated measures; MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PD: Parkinson's Disease PDQ-39: Parkinson's Disease Questionnaire; PDSS-2: Parkinson's Disease Sleep Scale; REML: restricted maximum likelihood; VAS: Visual Analogue Scale.

Sensitivity analyses

Two sensitivity analyses were conducted on the primary efficacy endpoint to account for missing data: an analysis of covariance (ANCOVA) and a jump-to-reference (J2R) analytical approach. The results of these sensitivity analyses are presented in Appendix N.

B.2.3.3 Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of the M15-736 trial based on the M15-736 protocol and CSR and using the risk of bias checklist recommended by NICE is provided in Table 8 (Revised Cochrane risk-of-bias tool for randomised trials; RoB 2). M15-736 was methodologically robust, well-reported and considered to be at low risk of bias.

Table 8: Quality assessment of the M15-736 trial

Question	M15-736 trial
1. Was randomisation carried out appropriately?	Yes
2. Was the concealment of treatment allocation adequate?	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
5. Were there any unexpected imbalances in drop-outs between groups?	Yes
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

B.2.3.4 Clinical effectiveness results of the relevant studies

M15-736 met its primary end point, demonstrating a [redacted] improvement in daily 'On' time without troublesome dyskinesia compared with oral CD/LD.

- Change from baseline in daily 'On' time without troublesome dyskinesia increased by [redacted] hours compared with the oral CD/LD group.
- The foslevodopa-foscarbidopa arm further showed a [redacted] and clinically meaningful reduction in 'Off' time compared with the oral CD/LD group, with an observed least square (LS) mean difference of [redacted] hours.
- Clinically meaningful improvements were observed in the MDS-UPDRS Part II score for the foslevodopa-foscarbidopa group compared with the oral CD/LD group, and the number of patients who experienced morning akinesia greatly decreased from baseline with foslevodopa-foscarbidopa; the same decrease was not observed in the oral CD/LD group.
- Patients also reported a greater reduction in PD sleep scale-2 (PDSS-2) scores from baseline in the foslevodopa-foscarbidopa arm, indicating that the 24-hour administration had a notable impact of patients' quality of sleep.
- A decrease in symptoms also resulted in an increase in health-related QoL (HRQoL) as measured by PDQ-39 and EQ-5D-5L summary indices.

B.2.3.4.1 Primary outcome

'On' time without troublesome dyskinesia

The change from baseline in 'On' time without troublesome dyskinesia is presented in Table 9. Treatment with foslevodopa-foscarbidopa resulted in a [redacted] increase in 'On' time without troublesome dyskinesia from baseline when compared to treatment with oral CD/LD. At the end of the double-blind study period, patients in the foslevodopa-foscarbidopa group experienced an improvement from baseline of [redacted] hours on the average 'On' time without troublesome dyskinesia compared with [redacted] hours for patients in the oral CD/LD group, with a clinically meaningful difference between the two groups of [redacted] hours.[64] The least-square mean difference was [redacted] (p-value: [redacted]).

Improvements in the foslevodopa-foscarbidopa group were observed as early as the first visit at Day 8 and persisted through the double-blind phase (Figure 4). [redacted]. Sensitivity

analyses for the primary outcome were consistent with the results reported here and are presented in Appendix M.

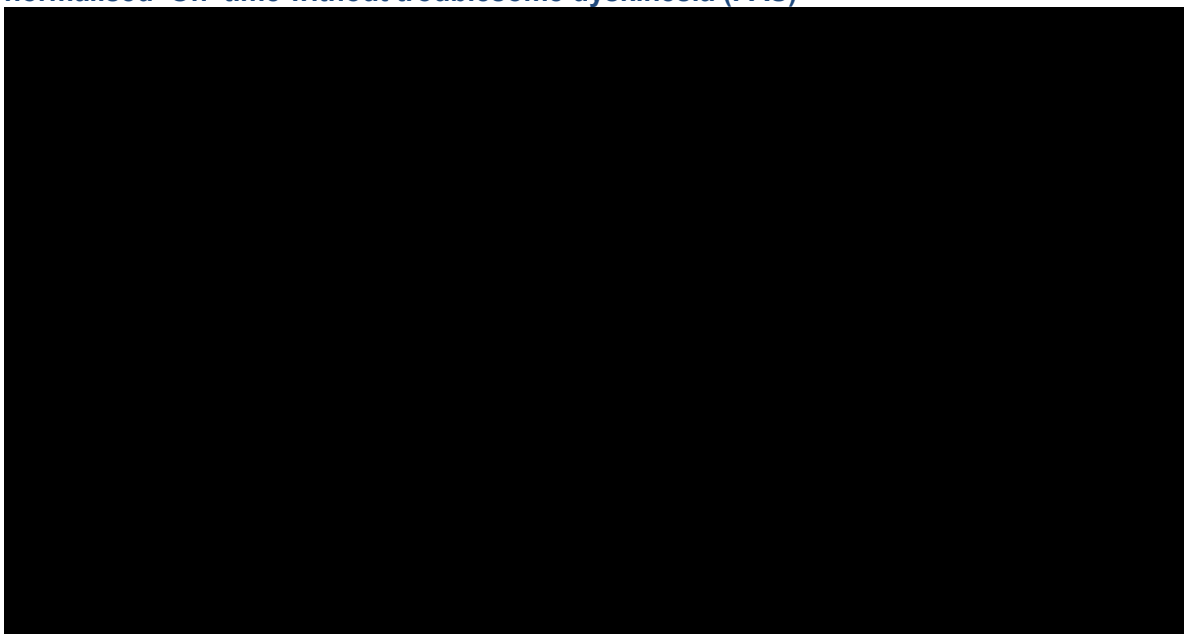
Dyskinesia represents a severe burden of disease for patients with PD, affecting their ability to perform everyday tasks, whilst 'On' time represents an important patient-reported metric of symptom control.[65] As such, the statistically significantly increased 'On' time without troublesome dyskinesia shown by foslevodopa-foscarbidopa, as compared with oral CD/LD, represents a highly promising clinical outcome: treatment with foslevodopa-foscarbidopa effectively manages symptoms, without causing dyskinesias often associated with peak dopamine concentrations linked to oral therapies.[66]

Table 9: Change from baseline to Week 12 in hours of average daily normalised 'On' time without troublesome dyskinesia (FAS)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean, hours (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change, hours (SD)	[redacted]	[redacted]
LS mean change, hours (SD)	[redacted]	[redacted]
LS mean difference, hours (SD)	[redacted]	
p-value	[redacted]	

'On' time without troublesome dyskinesia is the sum of 'On' time without dyskinesia and 'On' time with non-troublesome dyskinesia.
This endpoint was analysed with an MMRM.
Abbreviations: CD/LD: carbidopa/levodopa**;** FAS: Full Analysis Set; LS: least square; MMRM: mixed-effect model for repeat measures; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Figure 4: Plot of mean change over time (from baseline to Week 12) of average daily normalised 'On' time without troublesome dyskinesia (FAS)



'On' time without troublesome dyskinesia is the sum of 'On' time without dyskinesia and 'On' time with non-troublesome dyskinesia.
These data were analysed with an MMRM.
Day 22 was an optional visit at the investigator's discretion and based on the patient's PD symptoms.
Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; MMRM: mixed-effect model for repeat measures; PD: Parkinson's disease.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

B.2.3.4.2 Key secondary outcomes

'Off' time

The foslevodopa-foscarbidopa group results showed a [redacted] and clinically meaningful reduction in 'Off' time compared with the oral CD/LD group. At Week 12 there was a mean change reduction in the average normalised 'Off' time assessed by PD diary for the foslevodopa-foscarbidopa group of [redacted] hours, compared with [redacted] hours in the oral CD/LD group, with an observed LS mean difference of [redacted] hours (Table 10). Improvements were observed as early as the first visit at Week 1 and persisted through the double-blind period. The change from baseline of 'Off' time over time is shown in Figure 5.

[redacted]. Sensitivity analyses for the secondary outcome were consistent with the results reported here and are presented in Appendix M.

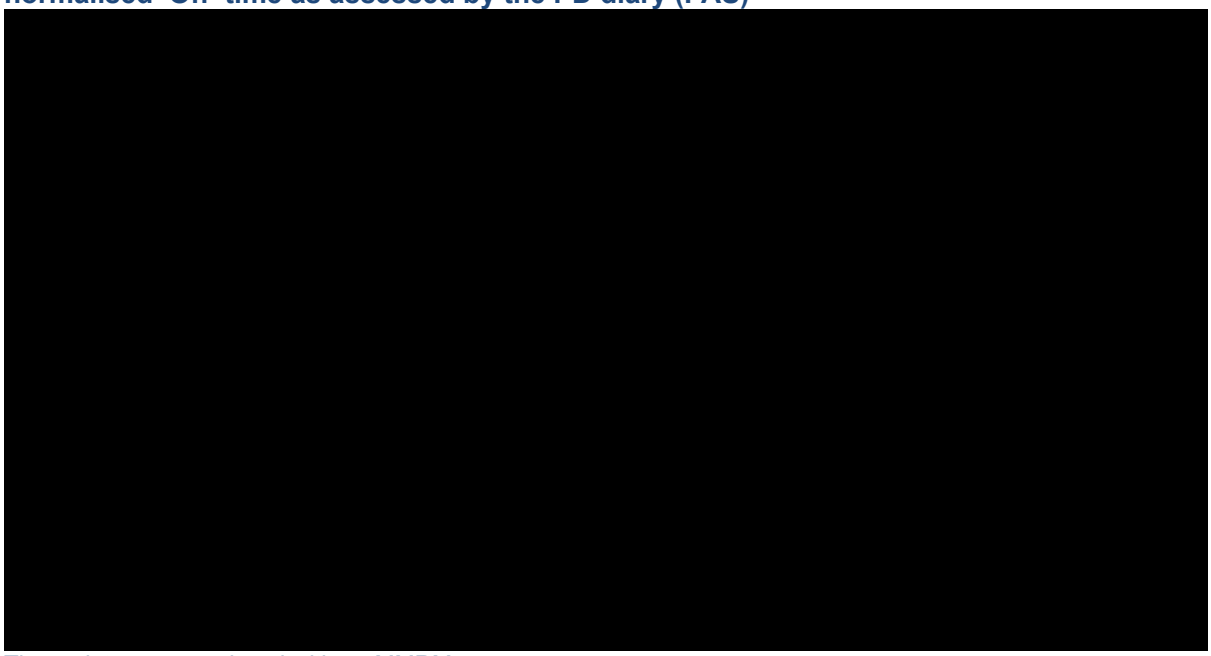
'Off' time represents a state of poor symptom control in patients, for both motor and non-motor symptoms, posing a significant burden to patients and their caregivers.[25] Reducing the 'Off' time experienced by patients therefore represents an important clinical objective for PD treatments. Such a reduction has been demonstrated by foslevodopa-foscarbidopa, both in absolute terms, and as compared with oral CD/LD, showing its potential to reduce symptom burden in patients with advanced PD uncontrolled by oral therapy, and alleviate "On/Off" motor fluctuations experienced by patients.[67]

Table 10: Change from baseline to Week 12 in hours of average daily normalised 'Off' time (FAS)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean, hours (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change, hours (SD)	[redacted]	[redacted]
LS mean change, hours (SD)	[redacted]	[redacted]
LS mean difference, hours (SD)	[redacted]	
p-value	[redacted]	

This outcome was analysed with an MMRM.
Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; MMRM: mixed-effect model for repeat measures; PD: Parkinson's disease SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Figure 5: Plot of mean change over time (from Baseline to Week 12) of average daily normalised 'Off' time as assessed by the PD diary (FAS)



These data were analysed with an MMRM.
Day 22 was an optional visit at the investigator's discretion and based on the patient's PD symptoms.
Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; MMRM: mixed-effect model for repeat measures; PD: Parkinson's disease.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

MDS-UPDRS Part II score

Improvements were observed in the MDS-UPDRS Part II score for the foslevodopa-foscarbidopa group compared with the oral CD/LD group,[68] but these [redacted] (Table 11). The change over time in MDS-UPDRS scores from baseline to Week 12 is shown in Figure 6.

The MDS-UPDRS Part II score specifically measures the impact of motor symptoms on patients' daily lives, a highly debilitating aspect of the disease which progressively worsens. As such, the reduced impact of motor symptoms on daily life reported by patients receiving foslevodopa-foscarbidopa, as measured by the MDS-UPDR Part II score, underlines foslevodopa-foscarbidopa's ability to reduce symptom burden and allow patients greater functional ability.

Table 11: Change from Baseline to Week 12 in MDS-UPDRS Part II Score (FAS)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; PD: Parkinson's disease SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Figure 6: Plot of change over time from Baseline to Week 12 in MDS-UPDRS Part II Score (FAS)

Day 22 was an optional visit at the investigator's discretion and based on the patient's PD symptoms.
Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; PD: Parkinson's disease.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Morning akinesia – early morning 'Off' status

The change from baseline to Week 12 in the proportion of patients reporting early morning 'Off' periods in their PD diary in each study group is shown in Table 12, whilst the proportion at selected timepoints in each group is shown graphically in Figure 7. In the foslevodopa-foscarbidopa group, the number of patients who experienced morning akinesia greatly decreased from baseline: [redacted] patients reported morning akinesia at baseline and only [redacted] at Week 12. The same decrease was not observed in the oral CD/LD group, where the number of patients reporting morning akinesia at baseline and at Week 12 was, [redacted] and [redacted] respectively. The LS mean OR was [redacted]. (Table 12).

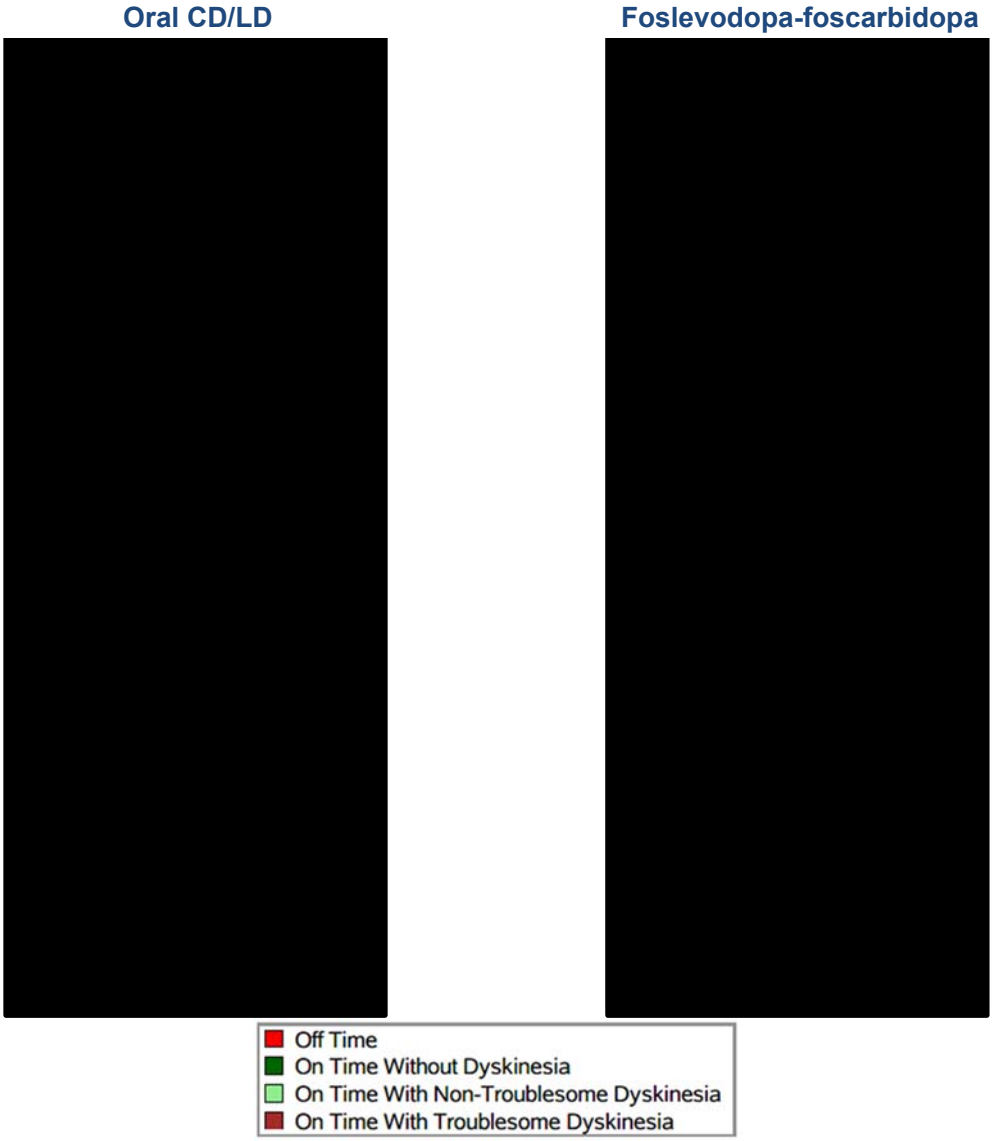
Early morning 'Off' time, or akinesia, is a feature of PD commonly reported by patients when awaking with poor motor function.[69] Commonly prescribed oral treatments are associated with delayed 'On' time, offering poor control of early morning akinesia. Early morning 'Off' time has also been shown to significantly reduce patients' QoL.[40] As foslevodopa-foscarbidopa is administered overnight, patients receiving treatment awake having received a stable dose of levodopa; the greatly reduced number of patients reporting early morning 'Off' time appear to show that this method of 24-hour delivery offers early morning symptom control, allowing patients to start their day with good functional mobility.

Table 12: Presence of morning akinesia at Week 12 (FAS)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
LS mean of OR (SE)	[redacted]	
p-value	[redacted]	

Although the nominal p-value is ≤0.05, statistical significance cannot be claimed because the second key secondary efficacy endpoint was not met.
Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; OR: odds ratio; PD: Parkinson's disease SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Figure 7: Distribution over time of early morning non-sleep symptoms (FAS)



Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

B.2.3.4.3 Other secondary endpoints

Sleep symptoms

Change in patient's sleep symptoms during the trial period is shown in Table 13. This was measured by the PDSS-2 score, a reliable and validated tool for measuring sleep disorders in PD.[70]

Patients receiving foslevodopa-foscarbidopa reported greater reductions in PDSS-2 scores from Baseline to Week 12 than those receiving oral CD/LD, indicating fewer symptoms during sleep. These results indicate that the overnight administration of stable levels of levodopa equivalents improves patients' quality of sleep, a highly desirable outcome given that PD is often associated with severe sleep disorders.[71] Related to the significantly reduced number of patients receiving foslevodopa-foscarbidopa reporting early morning 'Off' time, this overnight administration appears to control patients' symptoms during sleep and when awakening.

Table 13: Change from baseline to Week 12 in sleep symptoms as assessed by the PDSS-2 total score (FAS)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

This outcome was analysed with an ANCOVA model; the sample is balanced across baseline and Week 12. Although the nominal p-value is ≤0.05, statistical significance cannot be claimed because the second key secondary efficacy endpoint was not met
Abbreviations: ANCOVA: analysis of covariance; CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; PD: Parkinson's disease SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Dyskinesia

Table 14 shows the change in median dyskinesia DK50, as measured by the PKG, from Baseline to Week 12. The PKG is a device worn by patients on the wrist which provides continuous data on motor fluctuations and tremor during the course routine daily activity. This data can then be translated to a dyskinesia score, with reduced scores indicating reduced dyskinesia.[72]

[redacted], DK50 scores were reduced in the foslevodopa-foscarbidopa group, whilst these increased in the oral CD/LD group, indicating better control of dyskinesia in the active treatment group.

Table 14: Change from baseline to Week 12 in median dyskinesia score (DK50) as assessed by the PKG wearable device (FAS)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

This outcome was analysed with an MMRM.
Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; MMRM: mixed-effect model for repeat measures; PKG: personal kinetograph; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

All other dyskinesia/bradykinesia outcomes measured by the PKG are not presented here in the interests of brevity, but are available in the M15-736 Clinical Study Report.[63]

HRQoL outcomes

PDQ-39 summary index

As shown in Table 15, patients receiving foslevodopa-foscarbidopa reported greater reductions in PDQ-39 scores than patients in the control group during the study period, indicating greater improvement in PD-specific QoL outcomes. The PDQ-39 summary index assesses how often people with PD experience difficulties across eight dimensions of daily living, and also assesses the impact of PD on specific dimensions of functioning and wellbeing.[73] Its use in clinical practice has been suggested, due to its close association with QoL outcomes most relevant to patients.[74] As such, this improvement associated with foslevodopa-foscarbidopa represents a highly meaningful outcome, showing improvements in QoL specific to the disease.

Table 15: Change from baseline to final visit in Parkinson's Disease Questionnarie-39 Item (PDQ-39) summary index (FAS)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

This outcome was analysed with an ANCOVA model; the sample is balanced across baseline and Week 12. Although the nominal *P* value is ≤0.05, statistical significance cannot be claimed because the second key secondary efficacy endpoint was not met.
Abbreviations: ANCOVA: analysis of covariance; CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; PDQ-39: Parkinson's disease questionnaire-39; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

EQ-5D-5L summary index

Table 16 shows the change in EQ-5D-5L summary index scores reported by patients over the double-blind treatment period. These show a greater improvement in general HRQoL outcomes reported by patients receiving foslevodopa-foscarbidopa, as compared to those receiving oral CD/LD. This provides evidence, along with PDQ-39 data shown above, that the positive efficacy results demonstrated by foslevodopa-foscarbidopa directly correlate with improved HRQoL outcomes for patients. Additional EQ-5D-5L VAS data are presented in Appendix M, and show clinically meaningful improvement in the HRQoL of patients treated with foslevodopa-foscarbidopa when compared to those treated with oral CD/LD.

Table 16: Change from baseline to final visit in EQ-5D-5L summary index (FAS)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD

Baseline		
N	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

This outcome was analysed with an ANCOVA model; the sample is balanced across baseline and Week 12.
Abbreviations: ANCOVA: analysis of covariance; CD/LD: carbidopa/levodopa; EQ-5D-5L: EuroQol 5-Dimensions 5-Levels Questionnaire; FAS: Full Analysis Set; LS: least square; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

B.2.3.5 Subgroup analysis

Subgroup analyses were conducted on the primary outcome and key secondary outcome of normalised 'Off' time, as outlined in Section B.2.3.2, and are presented in Figure 8 and Figure 9 respectively.

For the primary outcome subgroup analyses indicated no treatment-by-subgroup interactions (interaction anticipated if p-value ≤0.10) for sex, race, country, duration of PD, concomitant dopamine agonist use or dose category. There was a significant treatment-by-subgroup interaction for age groups, however the treatment group difference in both age categories favoured foslevodopa-foscarbidopa.

Further subgroup analyses on the key secondary outcome, namely the change from baseline in average normalised 'Off' time assessed by the PD diary, indicated no treatment-by subgroup interactions for sex, age, race, country, duration of PD, concomitant dopamine agonist use or dose category. Treatment group differences were generally consistent with the FAS for this outcome.

Figure 8: Forest plots for the subgroup analyses of average normalised 'On' time without troublesome dyskinesia (primary outcome; FAS)

Abbreviations: CD/LD: carbidopa/levodopa; CI: confidence interval; FAS: Full Analysis Set; PD: Parkinson's disease; US: United States of America.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Figure 9: Forest plots for the subgroup analyses of average normalised 'Off' time (secondary outcome; FAS)

Abbreviations: CD/LD: carbidopa/levodopa; CI: confidence interval; FAS: Full Analysis Set; PD: Parkinson's disease; US: United States of America.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

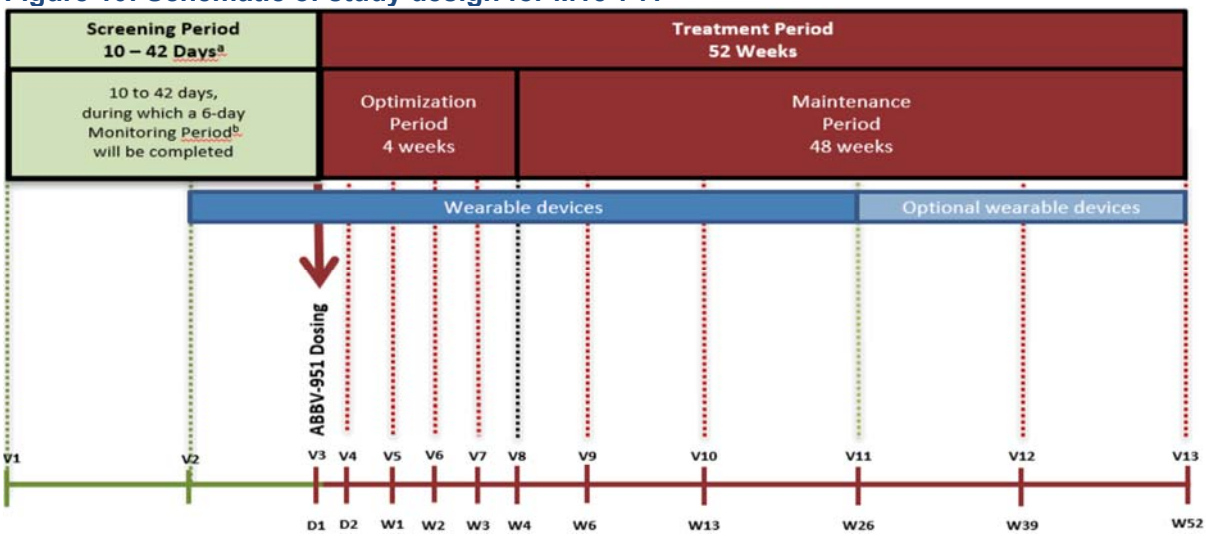
B.2.4 *M15-741*

B.2.4.1 Summary of methodology of the relevant clinical effectiveness evidence

B.2.4.1.1 Summary of trial methodology

Study M15-741 was a Phase III, open-label, single-arm, multicentre study evaluating the efficacy, safety, and tolerability of 24-hour daily CSCI of foslevodopa-foscarbidopa in the treatment of patients with advanced PD whose motor fluctuations were inadequately controlled by their current medication. The 52-week study period consisted of a 4-week optimisation period, followed by a 48-week maintenance period (Figure 10). During the optimisation period, patients' foslevodopa-foscarbidopa dose was adjusted to achieve optimal symptom control, as determined by study investigator. Patients were then continued on this optimal dose during the maintenance period. Further details of the trial methodology are given in Table 17. The CONSORT diagram for M15-741 is presented in Appendix D.4.

Figure 10: Schematic of study design for M15-741



ABBV-951 = foslevodopa-foscarbidopa
Abbreviations: D: day; V: visit; W: week.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Table 17: Summary of methodology for M15-741

Trial name	M15-741
Location	60 study sites across Australia, Belgium, Canada, Denmark, Germany, Italy, Japan, Netherlands, United States and United Kingdom. The trial included three study sites in the UK, which enrolled a total of [redacted] patients.
Trial design	Phase III, open-label single arm study
Duration of study	The study lasted 52 weeks from April 2019 to November 2021. The 52-week treatment period was preceded by a 10–42 days screening period. The treatment period was divided into two stages: **Optimisation period (4 Weeks)** During this phase investigators made all necessary adjustments to the patient's foslevodopa-foscarbidopa dose, including enabling the option for the patient to use pre-programmed alternative lower and higher infusion rates in addition to the base rate to achieve an optimal clinical response. Optimal clinical response was defined by maximizing functional 'On' time while minimising the number of 'Off' episodes and 'On' time with troublesome dyskinesia during the day. A patient's concomitant PD medications (e.g. dopamine agonists, selective monoamine oxidase B [MAO-B] inhibitors, amantadine, safinamide) could be tapered down or even suspended, in accordance with the prescribing information, to achieve the therapeutic approach that, in the investigator's opinion, could control the patient's symptoms in the most satisfactory way. **Maintenance period (48 Weeks)** During this phase, patients received their optimal therapeutic dose of foslevodopa-foscarbidopa; changes to foslevodopa-foscarbidopa were allowed during the study while concomitant PD medications remained stable unless the investigator considered changes to be medically necessary.
Method of randomisation	N/A – this was a single-arm study
Method of blinding	N/A – this was an open-label study
Trial drugs and method of administration	Foslevodopa-foscarbidopa administered as 24h daily CSCI
Permitted and disallowed	**Permitted concomitant medication** As per study protocol, all enrolled patients were required to be taking oral PD medications upon entry into the study. The following PD medications were permitted to be taken concomitantly throughout the trial period:

concomitant medication	• Non-ergolinic dopamine agonists (pramipexole, ropinirole, rotigotine) • Selective MAO-B inhibitors (e.g., rasagiline, selegiline) • Amantadine (IR and ER formulations) • Safinamide • Zonisamide • Istradefylline Adjustments to patients' concomitant PD medications (e.g., dopamine agonists, selective MAO-B inhibitors, amantadine, safinamide), including tapering down or even suspending such medications, were allowed during the optimisation period. This was in order to achieve the therapeutic approach that, in the investigator's opinion, controlled the patient's symptoms in the most satisfactory way. **Disallowed concomitant medication** The following PD medications were not permitted to be taken during the trial period: • Apomorphine • Dopamine-depleting agents (such as, but not limited to, reserpine, tetrabenazine, amphetamines) • MAO-A inhibitors and other non-selective MAO inhibitors • Ergot dopamine agonists (lisuride, bromocriptine, cabergoline, etc.) • Dopamine antagonist or partial agonist, first generation antipsychotics, antiemetic medications, and second-generation antipsychotic with higher dopamine receptors interaction (such as, but not limited to, fluphenazine, loxapine, perphenazine, thiothixene, haloperidol, metoclopramide, aripiprazole, asenapine, risperidone, paliperidone, perospiron) • Oral and/or inhaled medications containing levodopa (oral CD/LD and levodopa inhalation powder were allowed as rescue therapy) • COMT inhibitors (such as entacapone, tolcapone, opicapone) Full details of allowed and prohibited concomitant therapies are given in the study CSR.[62]
Primary outcomes	**The primary outcomes of the M15-741 trial were the following safety outcomes, measured at the end of the study period (Week 52):** • Percentage of patients with AEs and SAEs during the study • Percentage of patients with AESIs during the study • Percentage of patients with numeric grade equal to or higher than 5 and percentage of patients with letter grade equal to or higher than D on the Infusion Site Evaluation Scale at any time during the study • Change in clinical laboratory test data from Baseline to end of study • Change in vital sign measurements from Baseline to end of study • Change in ECGs from Baseline to end of study

Secondary outcomes	**Secondary outcomes:** • Average normalised daily 'Off' and 'On' time by PD diary • PD symptoms assessed by MDS-UPDRS Parts I–IV • Sleep symptoms as assessed by PDSS-2 **HRQoL:** • PDQ-39 • EQ-5D-5L
Pre-specified subgroup analyses	All analyses were performed for two dose subgroups, low dose (<1800 mg LED) or high LD dose (≥1800 mg LED). In addition, the average daily normalised time in hours for 'On' and 'Off' times from the PD Diary was also analysed for the following subgroups: • Sex (male or female) • Race (white, Asian, or other) • Age (< 65 years or ≥ 65 years) • Geographic region (North America, Europe and Australia, or Japan) • PD duration (time since diagnosis) (< 10 years or ≥ 10 years)
Eligibility criteria	The key eligibility criteria for the trial are shown below: • Male or female patients, 30 years of age or older at the time of screening, with a diagnosis of idiopathic PD that is levodopa-responsive • Patients had to meet the following disease activity criteria: o Taking a regimen of oral medications for PD that has remained unchanged for at least 30 days prior to commencing treatment with foslevodopa-foscarbidopa; this regimen had to include levodopa-containing formulations such as CD/LD IR(e.g., Sinemet, Madopar), CD/LD-CR (e.g., Sinemet CR), CD/LD extended release (e.g., Rytary), CD/LD/entacapone (e.g., Stalevo). o Have a recognisable/identifiable 'Off' and 'On' state (motor fluctuations) as established through investigator observation and confirmed by PD diary entries recorded during the concordance test performed during the screening period • Patients (or caregiver, if applicable) demonstrates the understanding and correct use of the delivery system, including the insertion of the cannula into the patient's abdomen, as assessed by the investigator or designee during the Screening Period Complete eligibility criteria can be found in Appendix M.

Abbreviations: AE: adverse event; AESI: adverse event of special interest; CD/LD: carbidopa/levodopa; CR: controlled release; CSCI: continuous subcutaneous infusion; LED: levodopa-dose equivalents.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Premature discontinuation mitigation

The study experienced a higher than anticipated number of premature discontinuations which was attributed to difficulties using the drug delivery system and to infusion site skin AEs. Study sites and patients underwent retraining, with a specific focus on the correct use and application of the infusion set cannula including aseptic technique. Neria™ guard was added as part of an updated study protocol (Version 6.0), introduced to replace the original infusion set. Since its introduction, Neria™ guard is the only intended commercial infusion set for delivery of foslevodopa-foscarbidopa.[62]

The Neria™ guard infusion set showed fewer local manipulations during human factors engineering tests, potentially contributing to improved user experience with fewer user errors. Patients who enrolled under the updated protocol Version 6.0 (on or after 08th July 2020) were required to begin the study using the Neria™ guard infusion set rather than the Cleo 90™ infusion set that had been used at the start of the trial. Patients enrolled under protocol Versions 1 through 5 (before 08th July 2020) could switch from the Cleo 90™ infusion set to the Neria™ guard infusion set after protocol Version 6 was approved at their sites.

To evaluate the effects of the mitigation strategy on treatment discontinuation, results from patients enrolled before and after the change of protocol relating to the infusion pump set to be used (effective on the 8th July 2020) were compared. The results of this analysis are presented in Section B.2.8.1.3.

B.2.4.1.2 Baseline characteristics

Table 18 shows baseline characteristics of patients enrolled into the M15-741 trial. The baseline characteristics in the M15-741 trial were generally similar to those seen in the M15-736 trial, with similar mean age ([redacted] and [redacted] years, respectively), mean duration of PD since diagnosis ([redacted] and [redacted] years, respectively) and mean normalised 'Off' time ([redacted] and [redacted] hours, respectively). Clinicians consulted as part of an advisory board indicated that the trial population in M15-741 was in line with that of the proposed indication, patients with advanced PD uncontrolled by standard therapy.[61]

Table 18: Baseline characteristics of patients in M15-741

Characteristic	Total ([redacted])
Sex, n (%)	
Male	[redacted]
Race, n (%)	
White	[redacted]
Black or African American	[redacted]
Asian	[redacted]
Other	[redacted]
Age, years	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Age category, n (%)	

< 65 years	[redacted]
≥ 65 years	[redacted]
Weight, kg	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Location, n (%)	
Europe and Australia	[redacted]
North America	[redacted]
Japan	[redacted]
LED at baseline,[a] mg/day	
N	[redacted]
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Duration of PD since diagnosis, n (%)	
Mean (SD), years	[redacted]
Median (min, max), years	[redacted]
< 10 years	[redacted]
≥ 10 years	[redacted]
Baseline normalised 'Off' time, hours	
N	[redacted]
Mean (SD)	[redacted]
Median (min, max)	[redacted]

[a] from levodopa containing medications and COM-T inhibitors
Abbreviations: LED: levodopa-equivalent dose; PD: Parkinson's disease; SD: standard deviation.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

B.2.4.1.3 Open label extension (M15-737)

Upon completion of the 52-week treatment period in M15-741 patients who continue to meet eligibility criteria outlined in Table 17 enter a separate ongoing extension study (Study M15-737) for 96 weeks of additional foslevodopa-foscarbidopa treatment.

B.2.4.2 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Analysis sets in M15-741

The different trial populations used to analyse M15-741 study endpoints is summarised in Table 19.

Table 19: Trial populations used in the analysis of outcomes in M15-741

Analysis set	Description
Full Analysis Set (FAS), [redacted]	• Consists of all patients who received foslevodopa-foscarbidopa infusion and had baseline and treatment observations for at least one efficacy outcome measure • The FAS was used for all efficacy analyses

Treatment-Naïve Analysis Set (TNAS), [redacted]	• Consists of all patients in the FAS who had initial exposure to foslevodopa-foscarbidopa in study M15-741, i.e., patients who received foslevodopa-foscarbidopa in Phase I studies before participating in study M15-741 were excluded from the TNAS • The TNAS, in addition to the FAS, was used for certain efficacy analyses
Safety Analysis Set (SAS), [redacted]	• Consists of all patients who received foslevodopa-foscarbidopa infusion • The SAS was used for all safety analyses and some other analyses and evaluations such as demographics, treatment compliance, and exposure

Abbreviations: FAS: Full Analysis Set; TNAS: Treatment-Naïve Analysis Set; SAS: Safety Analysis Set.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Statistical analysis

The primary objective of M15-741 was to assess the safety and tolerability of foslevodopa-foscarbidopa, and the secondary objective was to assess its efficacy. Details of statistical analyses of safety and efficacy outcomes are presented in Table 20.

Upon awakening and every 30 minutes during their normal waking time, each patient was to record their time in the PD Diary as asleep, 'On' without dyskinesia, 'On' with non-troublesome dyskinesia, 'On' with troublesome dyskinesia, or 'Off' Diary entries were to be made for each PD Diary recording day, which was defined as a full 24-hour period (6:00 AM to 5:30 AM of the next day), such that each patient had 48 diary entries per day with each entry representing 0.5 hour. The daily 'On' and 'Off' times were normalised to a typical waking day (16 hours) to account for different sleep patterns across patients. When 'Off' was the first morning symptom upon awakening, this was considered morning akinesia in this study.

Table 20: Statistical methods for the primary analyses of M15-741

	M15-741
Hypothesis	Hypothesis testing was not performed
Statistical analysis	**Safety** Safety analyses were performed using the Safety Analysis Set. All analyses on safety variables, with the exception of Adverse Events and Infusion Site Evaluation Scale, were performed using data collected no more than 1 day after the end of the infusion of foslevodopa-foscarbidopa. For continuous safety outcomes, the change from baseline was analysed in a descriptive manner by visit for each dose category subgroup and overall patients. For categorical safety outcomes, the number and percentage of each category was summarised by visit for each dose category subgroup and overall patients. **Efficacy** Unless stated otherwise, all analyses on efficacy variables were performed with the FAS using data collected no more than one day after the end of the infusion of foslevodopa-foscarbidopa. Paired-sample t-tests were performed for testing change from baseline.
Sample size, power calculation	Approximately 240 patients were planned to be enrolled in order to obtain exposure data from at least 100 patients treated with 24-hour daily CSCI of foslevodopa-foscarbidopa for at least 12 months. With 240 patients receiving foslevodopa-foscarbidopa, the probability of observing an AE with an annual incidence rate of 0.005, 0.01, and 0.02 was 70%, 91%, and 99%, respectively.

Data management, patient withdrawals	**PD Diary** If more than 2 valid diary days were available prior to Day 1 or post-baseline visits, the 2 days closest to the clinical visit (or closest to Day 1 for Baseline) were used. If only one valid diary day was available, that valid diary day was used. If no valid diary day was available for a visit, the average daily normalised 'Off' or 'On' times were imputed as missing for that visit. **MDS-UPDRS** The MDS-UPDRS total score and score of each part will be calculated as long as no more than 15% of the answers are missing for that assessment. The missing item will be imputed as the average of the non-missing items from the same MDS-UPDRS assessment. Imputation for Part I, Part II, Part III or Part IV scores should use the non-missing items within the particular part, but the imputation for the total score of Parts I-III should use the non-missing items from all 59 items across the 3 parts. **PDSS-2** There was no imputation of missing responses. If any item score was missing, the total score and the corresponding domain scores was not calculated. **PDQ-39** The PDQ-39 summary index was calculated as long as no more than 15% (i.e., 5) of the answers were missing for that assessment. It was imputed as the average of the non-missing items from the same PDQ-39 assessment. The domain score was only calculated if all the questions for that domain were answered. **EQ-5D-5L** The EQ-5D-5L summary index will only be calculated if answers were provided for all 5 individual questions. The EQ-5D-5L VAS is a single value collected and there was no imputation if the VAS value was missing.

Abbreviations: AE: adverse event; MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PD: Parkinson's disease; PDSS-2: Parkinson's Disease Sleep Scale; PDQ-39; Parkinson's Disease Questionnaire; VAS: Visual analogues scale.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

B.2.4.3 Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of the M15-741 trial based on the M15-741 protocol and CSR and using the risk of bias checklist recommended by NICE is provided in Table 21 (Institute of Health Economics Quality Appraisal Checklist for Case Series Studies). M15-741 was methodologically robust, well-reported and considered to be at low risk of bias.

Table 21: Quality assessment of the M15-741 trial

Question	M15-741 trial
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes
2. Was the study conducted prospectively?	Yes
3. Were the cases collected in more than one centre?	Yes
4. Were patients recruited consecutively?	Yes
5. Were the characteristics of the patients included in the study described?	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes

7. Did patients enter the study at a similar point in the disease?	Yes
8. Was the intervention of interest clearly described?	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes
10. Were relevant outcome measures established a priori?	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes
15. Was follow-up long enough for important events and outcomes to occur?	Yes
16. Were losses to follow-up reported?	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes
18. Were the adverse events reported?	Yes
19. Were the conclusions of the study supported by results?	Yes
20. Were both competing interests and sources of support for the study reported?	Yes

B.2.4.4 Clinical effectiveness results of the relevant trials

Efficacy results from M15-714 demonstrated comparable data to M15-736, providing long-term evidence that the treatment effect of foslevodopa-foscarbidopa is maintained over time

- Efficacy was a secondary outcome of trial M15-741, which showed comparable results to M15-736 in 'On' time, demonstrating that control of motor symptoms is maintained over 52 weeks.
- [redacted] improvements in 'On' time without troublesome dyskinesia and 'Off' time were observed at all time points measured.
- The trial also showed overall clinically meaningful improvement in motor symptoms, early morning non-sleep symptoms as assessed by PDSS-2, and PD symptoms assessed by MDS-UPDRS Part I–III.
- [redacted] improvements in HRQoL were also observed by PDQ-39 and EQ-5D-5L summary indices.

B.2.4.4.1 Average normalised daily 'On' time without troublesome dyskinesia, 'On' time with troublesome dyskinesia and 'Off' time based on the PD diary

Patients treated with foslevodopa-foscarbidopa showed a [redacted] improvement in 'On' time without troublesome dyskinesia and in 'Off' time at all time points measured. At the end of the study period (Week 52), the mean 'On' time without troublesome dyskinesia increased [redacted] hours (Table 22) and the decrease in 'Off' time was [redacted] hours (Table 23).

Improvements began as early as Week 1, increased throughout to Week 26, and then remained stable to the end of the treatment period at Week 52 (Figure 11).

These efficacy findings support those seen in M15-736, with similar increases in 'On' time without troublesome dyskinesia observed at Week 12 in M15-736 and Week 13 in M15-741 following treatment with foslevodopa-foscarbidopa. Importantly, M15-741 provided evidence for the longer-term efficacy of foslevodopa-foscarbidopa, with the increased mean 'On' time without troublesome dyskinesia being maintained across the year-long trial period.

Table 22: Average daily normalised 'On' time without troublesome dyskinesia

Characteristic	Baseline	Week 13	Week 26	Week 52
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

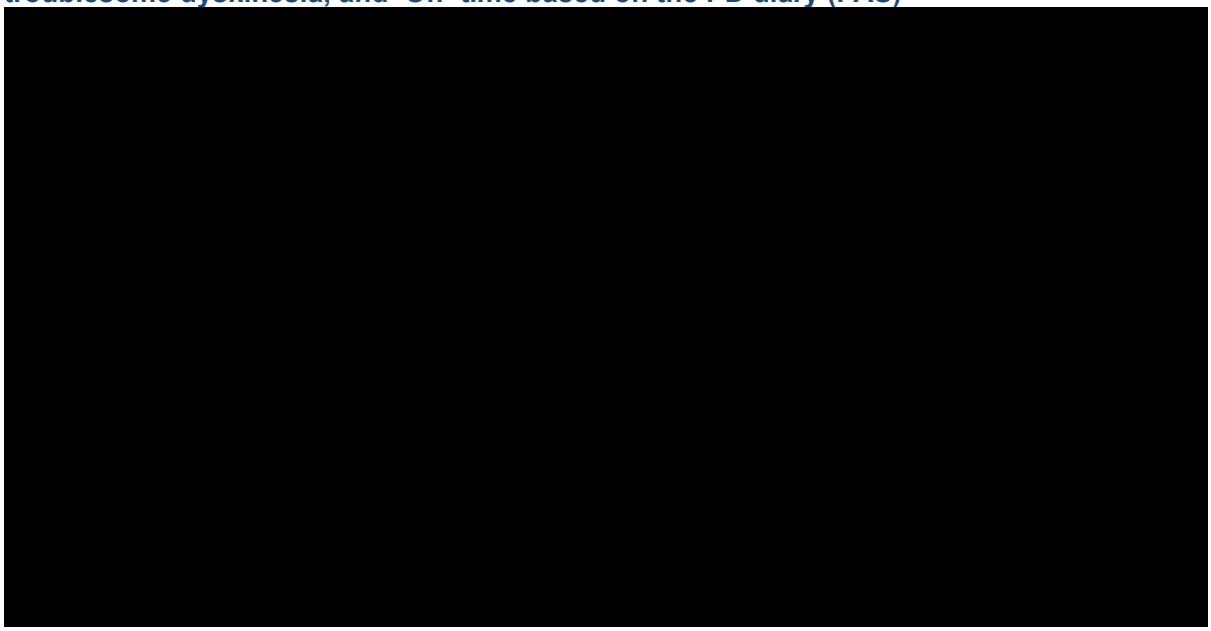
A PD diary recording day with no more than 2 hours of missing data (4 or less missing entries) or at least 12 awake hours (i.e., at least 24 'Off' or 'On' time entries) for the entire 24-hour diary is considered as a valid PD diary day
Abbreviations: PD: Parkinson's disease; SD: standard deviation; FAS: full analysis set.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Table 23: Average daily normalised 'Off' time (FAS)

Characteristic	Baseline	Week 13	Week 26	Week 52
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

A PD diary recording day with no more than 2 hours of missing data (4 or less missing entries) or at least 12 awake hours (i.e., at least 24 'Off' or 'On' time entries) for the entire 24-hour diary is considered as a valid PD diary day
Abbreviations: PD: Parkinson's disease; SD: standard deviation; FAS: full analysis set.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Figure 11: Mean average daily normalised 'On' time without troublesome 'On' time with troublesome dyskinesia, and 'Off' time based on the PD diary (FAS)



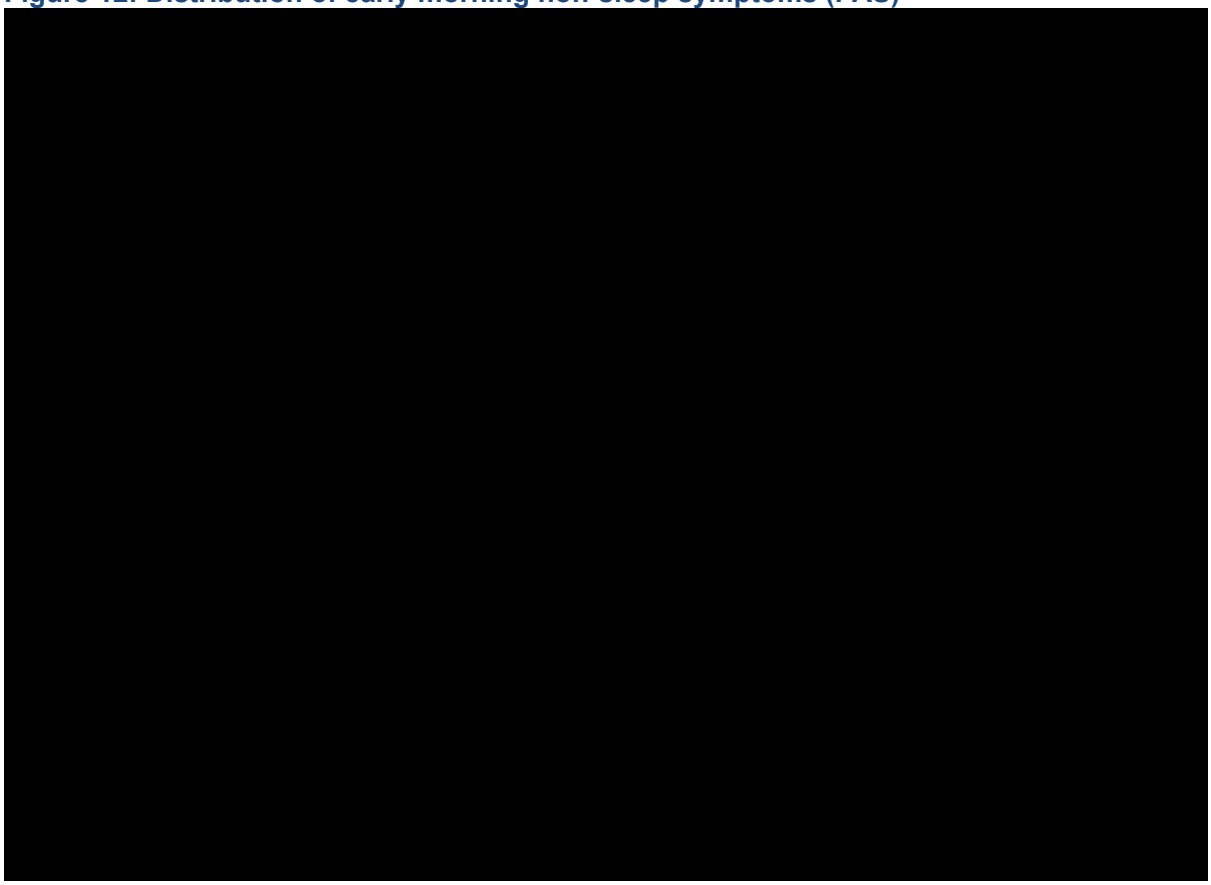
'On' time without troublesome dyskinesia is the sum of 'On' time without dyskinesia and 'On' time with non-troublesome dyskinesia.
Abbreviations: BL: baseline; PD: Parkinson's disease; FAS: full analysis set; W: Week.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Early morning non-sleep symptoms

Entries in the PD diary were used to evaluate in which state patients were when waking up in the morning. It was observed that the percentage of patients who reported awakening in 'Off' time

decreased since initiation of treatment with foslevodopa-foscarbidopa. At baseline [redacted]% of patients reported awakening in the 'Off' state and [redacted]% in 'On' state without dyskinesia, decreased to [redacted]% and increased to [redacted]% respectively at Week 1. The improvements continued over time through Week 26 ([redacted]% in 'Off' state and [redacted]% in 'On' state without dyskinesia) and then stabilised to Week 52 (Figure 12).

Figure 12: Distribution of early morning non-sleep symptoms (FAS)



Abbreviations: BL: baseline; FAS: full analysis set; PD: Parkinson's disease; W: Week.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

B.2.4.4.2 PD symptoms assessed by MDS-UPDRS

The MDS-UPDRS, composed of four parts, was used to assess symptoms of patients. The total MDS-UPDRS score is informed by Parts I–III.

Patients treated with foslevodopa-foscarbidopa showed clinically meaningful improvement from baseline throughout the study period in the MDS-UPDRS Part II (motor aspects of daily living) and Part IV (motor complications), showing the positive effect of foslevodopa-foscarbidopa in motor symptoms. Improvements began as early as Day 2 and were sustained until the end of the treatment period at Week 52 (Figure 13).

Figure 13: Mean MDS-UPDRS scores over time (FAS)

Abbreviations: BL: baseline; D: Day; FAS: full analysis set; PD: Parkinson's disease; W: Week.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

B.2.4.4.3 Sleep symptoms: Parkinson's disease sleep scale 2 (PDSS-2)

A clinically meaningful improvement from baseline in the PDSS-2 total score was observed for patients treated with foslevodopa-foscarbidopa. Notably, improvements were observed in PD symptoms at night score, motor symptoms at night score, and disturbed sleep score (Figure 14).

Figure 14: Mean PDSS-2 scores over time (FAS)

Abbreviations: BL: baseline; D: Day; FAS: full analysis set; PD: Parkinson's disease; W: Week.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

B.2.4.4.4 HRQoL

PDQ-39

As in M15-736, [redacted] improvements in the QoL of patients treated with foslevodopa-foscarbidopa were observed in the PDQ-39 summary index (Table 24). This further suggests that the positive efficacy results observed in both trials result in improved patient QoL specifically relating to their disease.

Table 24: PDQ-39 summary index total score

Characteristic	Baseline	Week 13	Week 26	Week 52
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PD: Parkinson's disease; SD: standard deviation; FAS: full analysis set.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

EQ-5D-5L

As shown in Table 25, [redacted] improvements in the EQ-5D-5L summary index were observed and maintained across the trial period, indicating increased levels of HRQoL in patients receiving foslevodopa-foscarbidopa.

Table 25: Change from baseline in the EQ-5D-5L summary index score

Characteristic	Baseline	Week 13	Week 26	Week 52
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PD: Parkinson's disease; SD: standard deviation.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

B.2.4.5 Subgroup analysis

The results of subgroup analyses (defined in Section B.2.4.1.1) were generally consistent with the results of the primary efficacy analysis; however, the number of patients for races other than white and for some geographic regions (i.e., Japan) are small (Section B.2.4.1.2).

B.2.5 *Pharmacological studies*

Additional supportive clinical data is provided by the pharmacokinetics and pharmacodynamics (PK/PD) studies of foslevodopa-foscarbidopa versus LCIG, which is presented here for completeness. The PK/PD profile of foslevodopa-foscarbidopa has been evaluated in a number of Phase I studies, with one trial, M17-220 providing comparative evidence with LCIG in patients with advanced PD.

In M17-220, trial participants (n=20 in each arm) received LCIG for two days followed by foslevodopa-foscarbidopa for three days or vice versa. M17-220 represents the pivotal trial in comparing the pharmacological profiles of foslevodopa-foscarbidopa, and as such only data obtained from that trial is presented in this section.[75]

B.2.5.1 Pharmacological results from M17-220

The levodopa exposure following administration of foslevodopa-foscarbidopa (35/700 mg carbidopa monophosphate/levodopa monophosphate) over 24 hours was similar to that of LCIG 87.5/350 mg CD/LD, administered over 16 hours, followed by two 25/100 mg oral CD/LD doses at 18 and 21 hours after the start of infusion. The mean plasma concentrations of levodopa, carbidopa and levodopa monophosphate and 3-O-methyldopa (3-OMD; a major metabolite of levodopa) presented on linear and log-linear scales in Figure 15, Figure 16 and Figure 17 respectively.

Levodopa

Foslevodopa-foscarbidopa CSCI provided equivalent levodopa levels to LCIG infusion over the 16-hour interval in which LCIG was administered, and maintained those levels throughout the night-time, with exposure difference between the two regimens less than [redacted] and well contained within the defined equivalence range. Moreover, the foslevodopa-foscarbidopa regimen, maintained constant levels of plasma levodopa, with low level of fluctuations during the 36 hours treatment period. Fluctuations in the LCIG plus oral therapy arm are noticeable after discontinuation of LCIG at 16 hours and administration of oral levodopa doses at 18 and 21 hours after treatment initiation. This demonstrates the ability of foslevodopa-foscarbidopa CSCI to maintain levodopa exposure within a more consistent narrow therapeutic window.

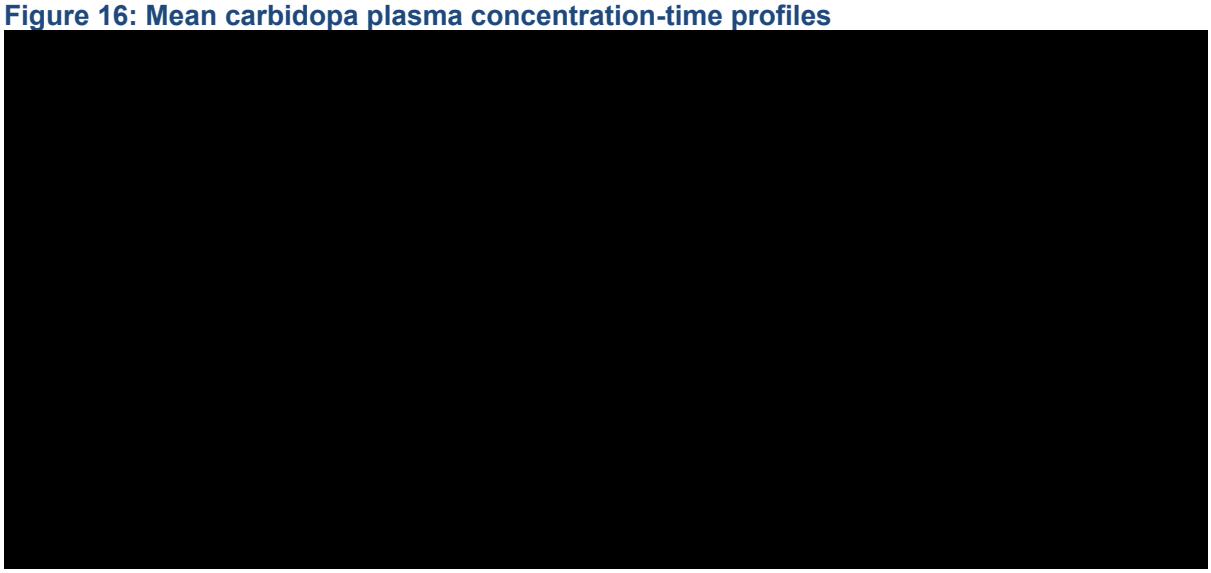
Figure 15: Mean levodopa plasma concentration-time profiles

LCIG + oral = CD/LD 87.5/350 mg LCIG + two 25/100 mg oral doses; ABBV-951 (foslevodopa-foscarbidopa) = CDP/LDP 35/700 mg. Left-hand plot is linear scale; right-hand plot is log-linear scale.
Abbreviations: CD/LD: carbidopa/levodopa; CDP: carbidopa monophosphate; LCIG: levodopa carbidopa intestinal gel; LDP: levodopa monophosphate.
Source: AbbVie Data on File (M17-220 Clinical Study Report).[75]

Carbidopa

As shown in Figure 16, patients receiving foslevodopa-foscarbidopa showed similar plasma concentrations of carbidopa over the first 16 hours in which LCIG was administered, with generally more stable levels of carbidopa.

Figure 16: Mean carbidopa plasma concentration-time profiles

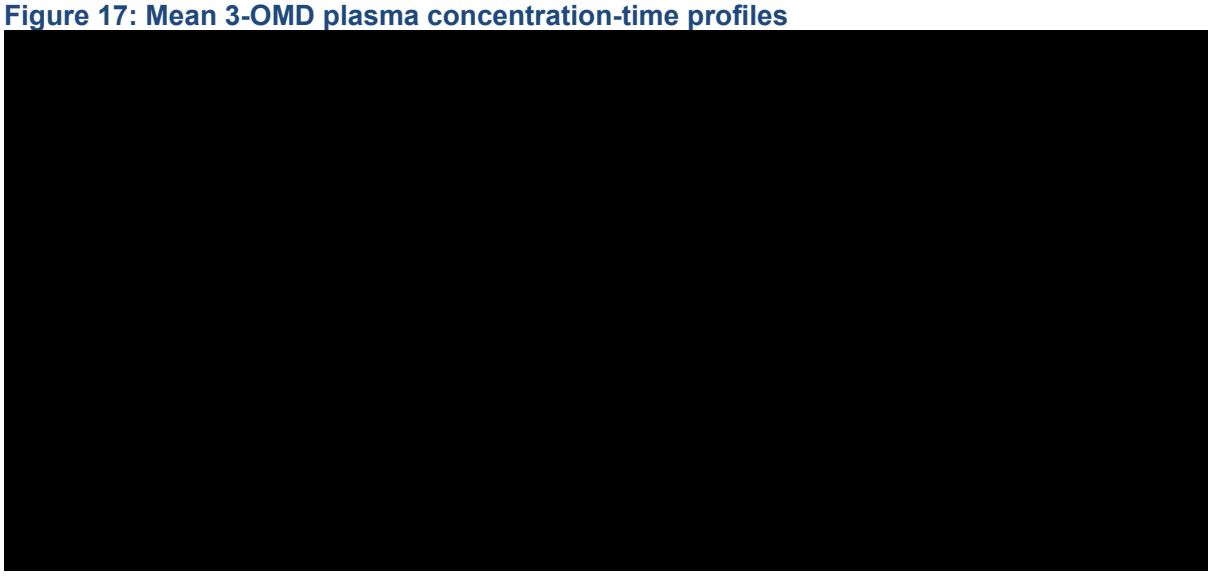


LCIG + oral = CD/LD 87.5/350 mg LCIG + two 25/100 mg oral doses; ABBV-951 (foslevodopa-foscarbidopa) = CDP/LDP 35/700 mg. Left-hand plot is linear scale; right-hand plot is log-linear scale.
Abbreviations: CD/LD: carbidopa/levodopa; CDP: carbidopa monophosphate; LCIG: levodopa carbidopa intestinal gel; LDP: levodopa monophosphate.
Source: AbbVie Data on File (M17-220 Clinical Study Report).[75]

3-OMD

3-OMD is the major metabolite of levodopa, with higher physiological levels observed in patients with PD having received long term treatment with levodopa.[76] Whilst its long-term physiological effects are not fully understood, it is believed to play a role in the long-term side effects associated with prolonged exposure to levodopa medications, and is therefore an important biomarker in PK/PD studies evaluating treatments in PD.[76] In M17-220, patients receiving foslevodopa-foscarbidopa showed very similar plasma concentrations of 3-OMD to those receiving LCIG, indicating similar metabolisation of levodopa between treatments.

Figure 17: Mean 3-OMD plasma concentration-time profiles



LCIG + oral = CD/LD 87.5/350 mg LCIG + two 25/100 mg oral doses; ABBV-951 (foslevodopa-foscarbidopa) = CDP/LDP 35/700 mg ABBV-951. Left-hand plot is linear scale; right-hand plot is log-linear scale.
Abbreviations: 3-ODM: 3-O-methyldopa; CD/LD: carbidopa/levodopa; CDP: carbidopa monophosphate; LCIG: levodopa carbidopa intestinal gel; LDP: levodopa monophosphate.
Source: AbbVie Data on File (M17-220 Clinical Study Report).[75]

Conclusion of pharmacological data

Overall, the PK/PD data comparing foslevodopa-foscarbidopa to LCIG showed both treatments to have a similar pharmacological profile over waking hours in which both treatments are administered. However, foslevodopa-foscarbidopa is shown to be able to deliver a more stable plasma concentration level of both levodopa and carbidopa over its full 24-hour administration, highlighting its potential to deliver predictable and sustained daily symptom control.

B.2.6 *Meta-analysis*

Due to the lack of head-to-head RCT data for foslevodopa-foscarbidopa versus LCIG, an NMA (presented in Section B.2.7) was conducted.

B.2.7 *Indirect and mixed treatment comparisons*

Results of the NMA found foslevodopa-foscarbidopa to have similar efficacy to LCIG, and be significantly more effective at improving sleep symptoms.

- An SLR was conducted which identified 176 relevant publications reporting on 145 unique studies. Of these publications, seven met the relevant criteria for inclusion in the NMA. However, only four studies were required to appropriately connect the interventions of

relevance to the decision problem in this evaluation.

- Relative efficacy was measured using 'Off' time, 'On' time without troublesome dyskinesia, and PDSS-2 outcomes in the population of interest to this submission.
- [redacted] was estimated to have a [redacted] in 'Off' time at 3 months compared with [redacted] but a [redacted] in 'On' time without troublesome dyskinesia, however neither difference reached statistical significance.
- [redacted] was found to [redacted] PDSS-2 scores at 3 months relative to [redacted], highlighting the substantial benefits foslevodopa-foscarbidopa can bring to patients, likely due to its ability to provide innovative 24-hour dosing.
- Aligned with the results of the M15-736 trials, foslevodopa-foscarbidopa was also shown in the NMA to [redacted] improve 'Off' time, 'On' time without troublesome dyskinesia, and PDSS-2 scores at 3 months relative to BMT.

B.2.7.1 Identification and selection of relevant studies from the clinical SLR

An SLR (Section B.2.1) was conducted in June 2021 and updated in January 2022 and again in June 2022 to identify and review clinical evidence on the efficacy, safety, and QoL outcomes of advanced PD treatment options.

A total of 3,323 publications were identified from the databases and registers (MEDLINE, EMBASE and the Cochrane Library) which were screened for eligibility. A total of 2,522 publications were excluded in the title/abstract screening phase leaving 801 full-text publications assessed for eligibility based on pre-specified criteria. A total of 635 publications were excluded after full-text screening. After review of the grey literature, an additional 24 studies were included. Overall, a total of 190 publications reporting on 151 unique studies (33 clinical trials, 53 records; 118 non-comparative studies, 137 records) were included in this SLR; a full list of these studies is provided in Appendix D.2.1, with a full list of all references excluded at the full text stage of review, with reason for exclusion, provided in the reference pack (Appendix D.2.2).

A risk bias assessment was performed on all included clinical trials (except foslevodopa-foscarbidopa clinical studies since they were not published at the time of the conduct of the SLR[62, 63]) using the Cochrane risk of bias tool. For non-comparative studies, the quality assessment checklist from the Centre for Reviews and Dissemination (CRD) Guidance for Undertaking Reviews in Health Care (2009)[77] was applied. Results of the quality assessment can be found in Appendix D.5.

B.2.7.2 Eligibility for the NMA

The scope of the literature review used was defined by the criteria for relevant population, intervention, comparators, outcomes, and study design (PICOS), and were aligned with the final scope for this submission; a wide scope in terms of the comparator choices was initially considered to ensure that all possible connections between foslevodopa-foscarbidopa and LCIG were captured. The eligibility criteria for consideration for inclusion in the NMA are shown in Table 26.

Table 26: PICOS criteria for Indirect Treatment Comparisons

PICOS	Inclusion criteria	Exclusion criteria
Population[a]	• PD patients, levodopa-responsive, but inadequately controlled by current therapy • Patients aged ≥18 years	• Patients with early (non-severe) PD • PD patients which are not levodopa-responsive

		• Sample size < 20 patients
Interventions	• Foslevodopa-foscarbidopa • Apomorphine • DBS • LCIG • Lecigon (LECIG)	• Non-pharmacological management of symptoms • No intervention listed as inclusion criteria
Comparators	• Placebo • Interventions (as above) • Levodopa (oral) monotherapy • Standard oral medication for treating Parkinson's disease, including levodopa plus adjunctive treatments	• Non-pharmacological management of symptoms
Outcomes	• Efficacy • 'Off' time • 'On' time without troublesome dyskinesia • 'On' time without dyskinesia • 'On' time with non-troublesome dyskinesia • 'On' time with troublesome dyskinesia • Hoehn & Yahr • Sleep symptoms by the PDSS-2 • Morning akinesia (or morning 'Off') • PD Symptoms as assessed by the UPDRS or MDS-UPDRS, parts I – IV • Safety / Adverse events • QoL outcomes	• Studies with none of the relevant outcomes
Study design	• Prospective clinical trials o RCTs - Phase 2, 3, 4, blinded or, open-label • Observational studies (prospective and retrospective)	• Study designs apart from those mentioned in inclusion criteria • Preclinical studies • Prognostic studies • Validation studies • Case reports, case series • Commentaries and letters • Consensus reports • Systematic literature reviews/meta-analysis[b] • Narrative reviews • Abstracts
Countries	• All countries	• Not applicable
Language	• English	• Publications in other languages

[a]Up to three recent reviews were retrieved to check citations for studies of interest not captured in the search. [b]All criteria for population are required for inclusion. Inclusion criteria for other PICOS follow OR rationale unless otherwise indicated.

Abbreviations: DBS: deep brain stimulation; LCIG: levodopa-carbidopa intestinal gel; LECIG: levodopa-Entacapone-Carbidopa Intestinal Gel; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PD; Parkinson's disease; PDSS-2; PD Sleep Scale-2; QoL: quality of life; RCT: randomised controlled trials.

Of the 190 studies included in the SLR, 7 studies met the inclusion criteria and were considered for inclusion in the NMA; 183 studies did not meet the inclusion criteria, and the long-term extension M20-098 of the M15-736 RCT was excluded since it was a single-arm long-term extension where all patients received foslevodopa-foscarbidopa treatment. The trials considered for inclusion are shown in Table 27.

Table 27: Trials considered for inclusion in the NMAs

Trial name	Treatment
M15-736[63], (NCT04380142)	CD/LD
	Foslevodopa-foscarbidopa
Weaver 2009[78], (NCT00056563)	BMT
	DBS
PD SURG[79], (ISRCTN34111222)	BMT
	DBS
Olanow 2014[80], (NCT00660387 and NCT0357994)	CD/LD
	LCIG
DYSCOVER[81], (NCT02799381)	BMT
	LCIG
INSIGHTS[82], (NCT02549092)	BMT
	LCIG
TOLEDO[83], (NCT02006121)	PBO
	Apomorphine

Abbreviations: BMT: best medical treatment; CD/LD: carbidopa/levodopa; DBS: deep brain stimulation; LCIG: levodopa-carbidopa intestinal gel; PBO: placebo.

Of the seven studies identified, only four were required to appropriately connect the interventions of relevance to the decision problem in this evaluation, i.e. foslevodopa-foscarbidopa, BMT and LCIG (Table 27). Details of the studies included in the NMAs are presented in Appendix D.3.

It should be noted that, for completeness, the NMA included treatments for advanced PD which are not considered relevant comparators to this submission, i.e. apomorphine and DBS. However, due to the shape of the network, these additional trials do not influence the results of the NMA relating to the comparisons of foslevodopa-foscarbidopa to BMT and LCIG, and only the results for the relevant comparators are presented below, with the full networks presented for transparency.

B.2.7.3 NMA methodology

All analyses were conducted in a Bayesian analysis framework using Monte Carlo Markov Chain (MCMC) and implemented using OpenBUGS software.[84] Fixed effect (FE) and random effects (RE) models were evaluated for the base case analyses, and selection was determined based on the deviance information criterion (DIC) model fit statistic. Vague prior distributions (e.g., normal with mean 0 and variance 10^5) on model parameters were used so that model outcomes would be determined primarily by the clinical trial data. These priors were selected using the recommended priors in the NICE Technical Support Document 2.[85] There was no a priori reason to believe that the included studies are likely to be heterogeneous. Posterior outcome distributions were based on at least 50,000 simulations after a burn-in of at least 50,000.

Adequate convergence was assessed by visual inspection of the OpenBUGS autocorrelation and history plots.

'On' time without troublesome dyskinesia and 'Off' time measures are continuous data based on sample means and standard errors which were analysed using the normal likelihood and the normal link function (NICE Technical Support Document 2 Section 3.4).[85] For studies where measures of uncertainty were not reported, the standard deviation was imputed using the sample size-weighted average of the available standard deviations. The mean difference of 'On' time without troublesome dyskinesia and 'Off' time measures for each treatment versus oral standard of care is the NMA output.

For both outcomes of 'Off' time and 'On' time without troublesome dyskinesia, fixed-effects (FE) and random-effects (RE) models were fitted and compared on deviance information criteria (DIC) to determine the better fitting model (lower DIC values indicate better fit to the data). When DIC differences are small (i.e., less than 3 to 5 points) across different fitted models, common practice is to choose the simplest model because the additional complexity does not result in better model fit.[85, 86] The dataset was seemed too sparse to appropriately inform the RE model. As such, and as the RE model did not converge, FE models were selected. The surface under the cumulative ranking curve (SUCRA) values associated with each treatment were also calculated in order to determine the overall ranking of treatments. The values range from 0-100% (higher SUCRA i.e., closer to 100%, represents higher likelihood of that treatment ranking at the top)[87]. An NMA was also run for the outcome, PDSS-2. Only two RCTs were considered appropriate for potential inclusion into this analysis and thus, an FE model was fitted.

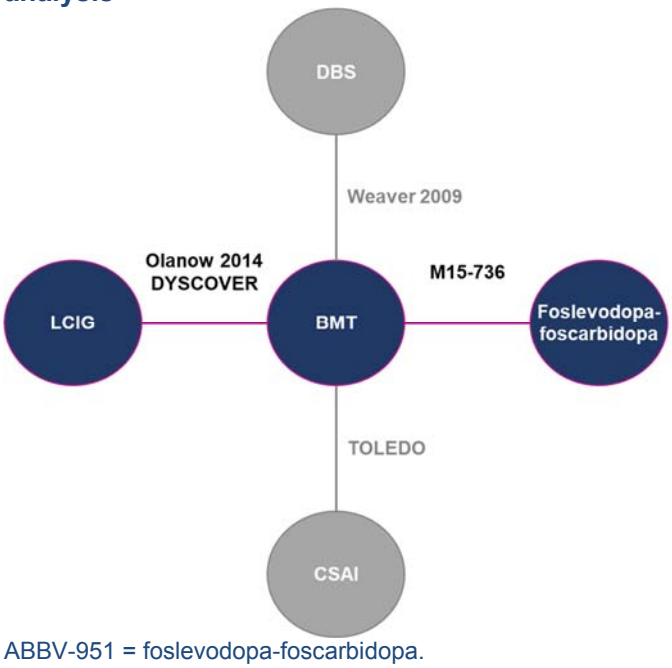
Before conducting the NMA, a random effects pairwise meta-analysis was conducted, when at least two studies examined the same intervention and comparator for a particular endpoint.[88] No evidence for statistical heterogeneity within the pairwise comparisons was found ('Off' time network: LCIG vs BMT [p= 0.70, I^2=0%] and DBS vs BMT [p=0.80, I^2=0%]; 'On' time network: LCIG vs BMT [p=0.32, I^2=0%]).

B.2.7.4 NMA results

B.2.7.4.1 'On' time without troublesome dyskinesia

Three studies were included in the 'On' time without troublesome dyskinesia network to connect foslevodopa-foscarbidopa to LCIG (DYSCOVER, M15-736 and Olanow 2004) (Figure 18). The FE model had a lower DIC and therefore was a better fit to the base case analysis than the RE model. In the base case analysis, mean change from baseline in 'On' time without troublesome dyskinesia relative to BMT was [redacted] (Table 28). In the base case FE analysis, [redacted] demonstrated the highest likelihood of ranking as the top treatment as given by the highest SUCRA amongst all treatment options (Table 28). The forest plots are displayed in Figure 19 and Figure 20.

Figure 18: Network of studies included in the 'On' time without troublesome dyskinesia analysis



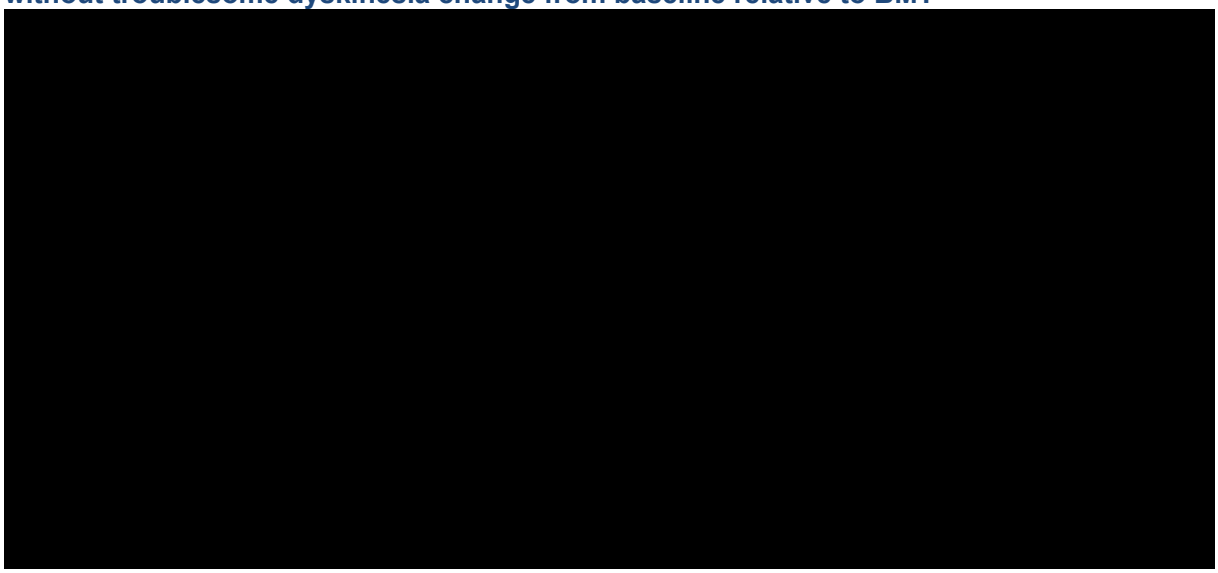
ABBV-951 = foslevodopa-foscarbidopa.
Abbreviations: BMT: best medical therapy; CSAI: continuous subcutaneous apomorphine infusion; DBS: deep brain stimulation; LCIG: levodopa-carbidopa intestinal gel.

Table 28: Difference in mean 'On' time without troublesome dyskinesia change from baseline (95% CrI) relative to BMT, base case analysis

Treatment	RE (DIC= [redacted])	FE (DIC = [redacted])	FE SUCRA
BMT	-	-	[redacted]%
Foslevodopa-foscarbidopa	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])	[redacted]%
LCIG	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])	[redacted]%

Abbreviations: BMT: best medical treatment; CrI: credible interval; DIC: deviance information criterion; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects; SUCRA: surface under the cumulative ranking curve.

Figure 19: Forest plot for the FE base case analysis of difference in mean 'On' time without troublesome dyskinesia change from baseline relative to BMT



Abbreviations: BMT: best medical therapy; CrI: credible interval; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel.

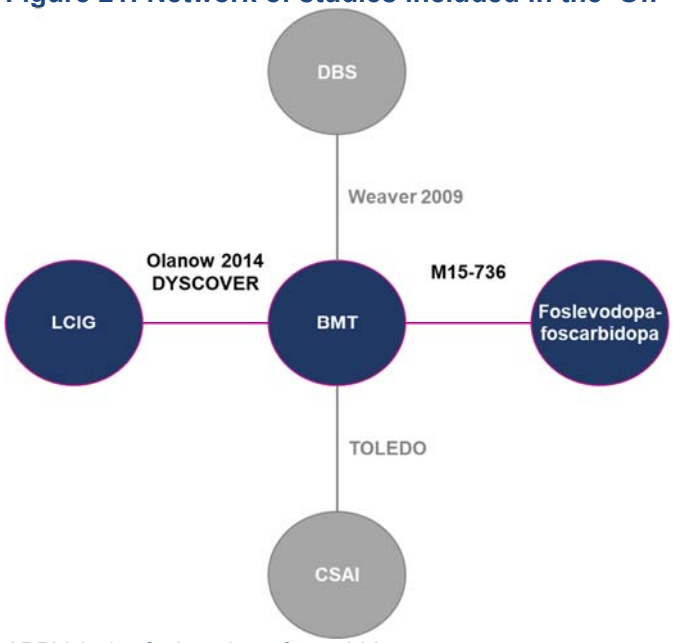
Figure 20: Forest plot for the RE base case analysis of difference in mean 'On' time without troublesome dyskinesia change from baseline relative to BMT

Abbreviations: BMT: best medical therapy; CrI: credible interval; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.

B.2.7.4.2 'Off' time

Three studies were included into the 'Off' time network to connect foslevodopa-foscarbidopa to LCIG (DYSCOVER, M15-736 and Olanow 2004) (Figure 21). The FE model had a lower DIC and therefore was a better fit to the base case analysis than the RE model. In the base case analysis, mean change from baseline in 'Off' time relative to BMT was the largest for [redacted] (Table 29). In the base case FE analysis, [redacted] also demonstrated the highest likelihood of ranking as the top treatment as given by the highest SUCRA amongst all treatment options (Table 29). The forest plots are displayed in Figure 22 and Figure 23.

Figure 21: Network of studies included in the 'Off' time analysis



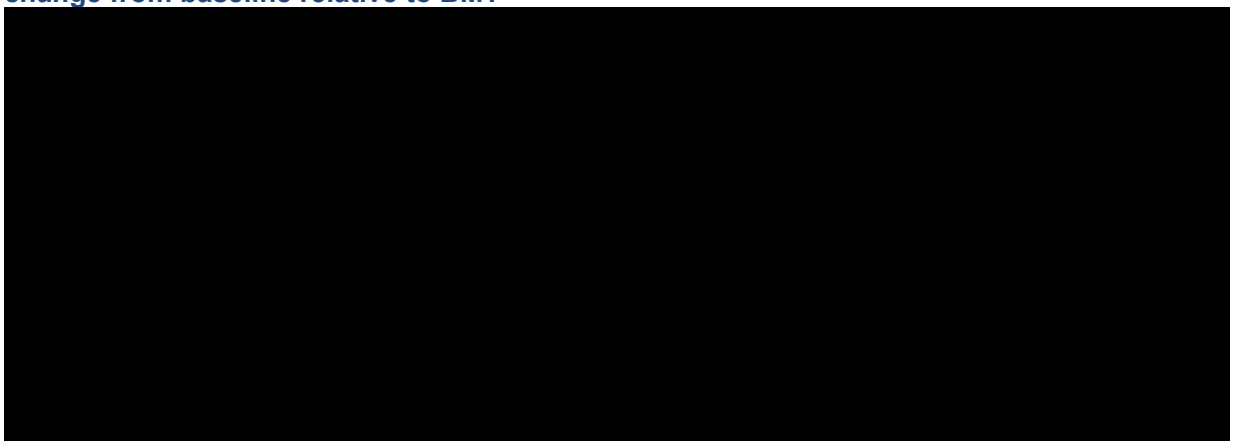
ABBV-951 = foslevodopa-foscarbidopa
Abbreviations: BMT: best medical therapy; CSAI: continuous subcutaneous apomorphine infusion; DBS: deep brain stimulation; LCIG: levodopa-carbidopa intestinal gel.

Table 29: Difference in mean 'Off' time change from baseline (95% CrI) relative to BMT, base case analysis

Treatment	RE (DIC= [redacted])	FE (DIC = [redacted])	FE SUCRA
BMT	-	-	[redacted]%
Foslevodopa-foscarbidopa	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])	[redacted]%
LCIG	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])	[redacted]%

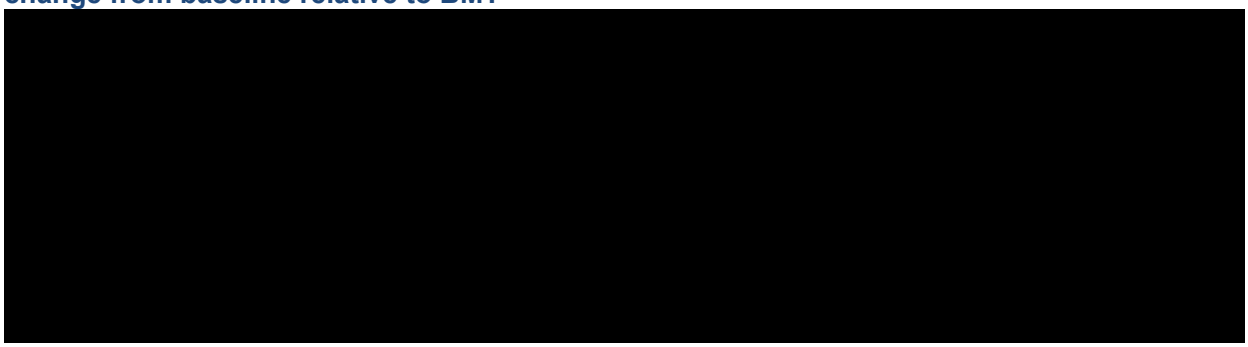
Abbreviations: BMT: best medical treatment; CrI: credible interval; DIC: deviance information criterion; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects; SUCRA: surface under the cumulative ranking curve.

Figure 22: Forest plot for the FE base case analysis of difference in mean 'Off' time change from baseline relative to BMT



Abbreviations: BMT: best medical therapy; CrI: credible interval; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel.

Figure 23: Forest plot for the RE base case analysis of difference in mean 'Off' time change from baseline relative to BMT



Abbreviations: BMT: best medical therapy; CrI: credible interval; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.

B.2.7.4.3 PDSS-2

Only two studies could be considered for the PDSS-2 outcome analysis (INSIGHTS, M15-736) (Figure 24). Mean change from baseline relative to BMT was [redacted] compared to LCIG (Table 30). [redacted] also demonstrated the highest likelihood of ranking as the top treatment as given by the highest SUCRA amongst all treatment options. The forest plot is displayed in Figure 25.

Figure 24: Network of studies included in the PDSS-2 analysis

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel.

Table 30: PDSS-2 change from baseline (95% CrI) relative to BMT

Treatment	FE	FE SUCRA
BMT	-	[redacted]%
Foslevodopa-carbidopa	[redacted] ([redacted], [redacted])	[redacted]%
LCIG	[redacted] ([redacted], [redacted])	[redacted]%

Abbreviations: BMT: best medical treatment; CrI: credible interval; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; SUCRA: surface under the cumulative ranking curve.

Figure 25: Forest plot for the FE base case analysis of PDSS-2 change from baseline relative to BMT

Abbreviations: BMT: best medical treatment; CrI: credible interval; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel.

B.2.7.5 Limitations of the NMA

There are some limitations of the NMA that should be noted. Firstly, the timing of the study follow-ups and outcome reporting has limited the analysis. The comparative foslevodopa-foscarbidopa data had a relatively short follow-up of 3 months, limiting the ability to assess comparative effectiveness in the long-term.

The network in the analysis was small, with only two connections and limited studies informing them. This leads to relatively large uncertainty intervals, as can be seen in the analysis results, primarily due to the small sample sizes (and resulting statistical power), with few comparisons reaching statistical significance.

Finally, no head-to-head data were available comparing the treatments of interest with each other directly in RCTs. Thus, the analysis relied solely upon indirect evidence, and as a result the innate limitations accompanying indirect comparison are present.

Despite the above limitations (which are addressed where data allows), the analysis used the available data to produce an indirect treatment comparison in line with NICE guidance and was based on data from high-quality randomised trials, to estimate the relative efficacy of foslevodopa-foscarbidopa versus therapeutic options for advanced PD and is appropriate to support inform decision making.

B.2.7.6 Conclusions of the indirect and mixed treatment comparisons

Foslevodopa-foscarbidopa was estimated to have a [redacted] in 'Off' time at 3 months compared with LCIG but a [redacted] in 'On' time without troublesome dyskinesia. However, neither difference reached statistical significance with small number of studies and low patient numbers informing the NMA networks, meaning the results are associated with substantial uncertainty. In comparison, foslevodopa-foscarbidopa was estimated to have a [redacted] in PDSS-2 compared with LCIG at 3 months, highlighting the

substantial benefits foslevodopa-foscarbidopa can bring to patients due to its ability to provide innovative 24-hour dosing.

Aligned with the results of the M15-736 trial, foslevodopa-foscarbidopa was shown in the NMA to have [redacted] in comparison with BMT.

Overall, foslevodopa-foscarbidopa is a more efficacious treatment than BMT, and the results of the NMA demonstrated similar efficacy to LCIG with significant improvement in PDSS-2 scores, an outcome of substantial importance to patients in their daily lives.

B.2.8 *Adverse reactions*

Foslevodopa-foscarbidopa was associated with a manageable safety profile, consistent with the known safety profile of levodopa.

- Both pivotal trials observed foslevodopa-foscarbidopa to have a manageable safety profile, with observed AEs generally consistent with those associated with levodopa, and with similar incidence of SAEs observed between the foslevodopa-foscarbidopa and oral CD/LD arms in trial M15-736.
- In M15-736, the incidence of infusion site infections were higher in the foslevodopa-foscarbidopa arm, but the majority were non-serious, were mild or moderate in severity, and resolved.

The safety and tolerability of foslevodopa-foscarbidopa in patients with levodopa-responsive advanced PD with motor fluctuations uncontrolled by standard therapy was evaluated as a secondary endpoint in M15-736 and as the primary endpoint of M15-741. Full safety results for both trials have been presented below, based on data available from the CSRs.

Clinical experts consulted at an advisory board for this evaluation were generally satisfied that AEs associated with foslevodopa-foscarbidopa were not unexpected, and were not a cause for concern.[61]

B.2.8.1 M15-736

B.2.8.1.1 Drug exposure and interruptions

Patients were exposed to foslevodopa-foscarbidopa for a mean of [redacted] days and to oral CD/LD for a mean of [redacted] days during the double-blind treatment period (Table 31). A total of [redacted] of patients in the foslevodopa-foscarbidopa group and [redacted] of patients in the oral CD/LD group completed 12 weeks of treatment. Overall, [redacted] patients had infusion interruptions ([redacted] in the foslevodopa-foscarbidopa group and [redacted] in the oral CD/LD group). The main reasons for infusion interruption, which were not mutually exclusive, were "other" ([redacted] patients), pump malfunction ([redacted] patients), adverse event ([redacted] patients), and COVID-19 infection ([redacted] patient) as shown in Table 32. The majority of "other" reasons for infusion interruption were personal hygiene/shower or swimming, accidentally stopping the pump but not noticing, or inadvertently forgetting to restart the pump.

The mean number of days of study drug interruption was [redacted] for [redacted] patients in the foslevodopa-foscarbidopa group and [redacted] for [redacted] patients in the oral CD/LD. The duration of study drug interruption was categorised by time intervals of <1 day up to ≥10 days. Most patients who had study drug interruptions had interruptions of <1 day (Table 31).

Table 31: Duration of study drug exposure and dose interruptions during 12-week double-blind treatment period (SAS)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Duration of study drug exposure		
N	[redacted]	[redacted]
Mean, days (SD)	[redacted]	[redacted]
Duration of study drug interruption		
N	[redacted]	[redacted]
Mean change, days (SD)	[redacted]	[redacted]
<1 day, n (%)	[redacted]	[redacted]
1– <2 days, n (%)	[redacted]	[redacted]
2– <3 days, n (%)	[redacted]	[redacted]
3– <4 days, n (%)	[redacted]	[redacted]
4– <5 days, n (%)	[redacted]	[redacted]
5– <10 days, n (%)	[redacted]	[redacted]
≥10 days, n (%)	[redacted]	[redacted]

Abbreviations: CD/LD: carbidopa/levodopa; SAS: safety analysis set; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Table 32: Patient disposition (all screened patients)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Patient flow		
Initiated treatment, n (%)	[redacted]	[redacted]
Completed treatment, n (%)	[redacted]	[redacted]
Discontinued, n (%)	[redacted]	[redacted]
Infusion interruptions, n (%)	[redacted]	[redacted]
All reasons for treatment discontinuation		
Infusion site related infections, n (%)	[redacted]	[redacted]
Infusion site related non infection reactions, n (%)	[redacted]	[redacted]
Hallucinations/psychosis, n (%)	[redacted]	[redacted]
Falls and associated injuries, n (%)	[redacted]	[redacted]
Withdrawal of consent, n (%)	[redacted]	[redacted]
Lack of efficacy, n (%)	[redacted]	[redacted]
Difficulty with drug delivery system, n (%)	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]
Reason for infusion interruptions		
COVID-19 infection, n (%)	[redacted]	[redacted]
Pump malfunction, n (%)	[redacted]	[redacted]
Adverse event (not COVID-19 infection), n (%)	[redacted]	[redacted]

Other, n (%)	[redacted]	[redacted]

One patient can be counted multiple times.
Abbreviations: CD/LD: carbidopa/levodopa.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

B.2.8.1.2 Overview of AEs

AEs were reported for [redacted] patients in the foslevodopa-foscarbidopa group and for [redacted] patients the oral CD/LD group (Table 33). The majority of AEs in both treatment groups were non-serious and were mild or moderate in severity. SAEs were reported for [redacted] and [redacted] patients in the foslevodopa-foscarbidopa and oral CD/LD group respectively. [redacted] had an AE leading to death in the oral CD/LD group, with [redacted] in the foslevodopa-foscarbidopa group (Section B.2.8.1.5).

The incidence of AEs leading to discontinuation of study drug was higher in the foslevodopa-foscarbidopa group than in the oral CD/LD group. AEs led to study drug discontinuation in [redacted] patients in the foslevodopa-foscarbidopa group and [redacted] patient in the oral CD/LD group. The AEs leading to discontinuation in ≥2 patients in the foslevodopa-foscarbidopa group were infusion site AEs (Section B.2.8.1.3).

All AEs that occurred in ≥5% of patients during the study period are reported in Table 34.

Table 33: Overview of AEs (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])	Oral CD/LD (N = [redacted])
Any TEAE, n (%)	[redacted]	[redacted]
Any serious TEAE, n (%)	[redacted]	[redacted]
Any TEAE leading to study drug discontinuation, n (%)	[redacted]	[redacted]
Any severe TEAE, n (%)	[redacted]	[redacted]
Any TEAE considered related to study drug, n (%)	[redacted]	[redacted]
Any TEAE associated with product complaints[a], n (%)	[redacted]	[redacted]
Foslevodopa-foscarbidopa or placebo solution[b], n (%)	[redacted]	[redacted]
PM-PDSC Infusion pump and its accessories, n (%)	[redacted]	[redacted]
Vial adapter, n (%)	[redacted]	[redacted]
Syringes, n (%)	[redacted]	[redacted]
Neria™ guard infusion set (6 mm) , n (%)	[redacted]	[redacted]
Neria™ guard infusion set (9 mm) , n (%)	[redacted]	[redacted]
PKG wearable device, n (%)	[redacted]	[redacted]

[a] For each AE, the investigator recorded whether the event was associated with a product complaint. A product complaint was any complaint related to the drug component or to the medical device component of the product.
[b] Foslevodopa-foscarbidopa was provided as an option when the investigator could not determine the exact component of the device to which the event was associated. Foslevodopa-foscarbidopa or placebo solution associates with foslevodopa-foscarbidopa for the foslevodopa-foscarbidopa group and associates with placebo solution for the oral carbidopa/levodopa group.

Only reasons reported by >1 patient are included.
One patient can be counted multiple times.
Abbreviations: AE: adverse event; CD/LD: carbidopa/levodopa; PKG: personal KinetiGraph®; PM-PDSC: Phillips-Medisize Parkinson's Disease Subcutaneous; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Table 34: AEs that occurred in ≥ 5% of patients in either treatment group during the double-blind treatment period

AE category	Foslevodopa-foscarbidopa (N = [redacted])	Oral CD/LD (N = [redacted])
Infusion site erythema, n (%)	[redacted]	[redacted]
Infusion site pain, n (%)	[redacted]	[redacted]
Infusion site cellulitis, n (%)	[redacted]	[redacted]
Infusion site oedema, n (%)	[redacted]	[redacted]
Dyskinesia, n (%)	[redacted]	[redacted]
Fall, n (%)	[redacted]	[redacted]
Infusion site bruising, n (%)	[redacted]	[redacted]
Infusion site haemorrhage, n (%)	[redacted]	[redacted]
Infusion site nodule, n (%)	[redacted]	[redacted]
'On' and 'Off' Phenomenon, n (%)	[redacted]	[redacted]
Hallucination, n (%)	[redacted]	[redacted]
Balance disorder, n (%)	[redacted]	[redacted]
Constipation, n (%)	[redacted]	[redacted]
Hallucination, visual, n (%)	[redacted]	[redacted]
Infusion site induration, n (%)	[redacted]	[redacted]
Infusion site infection, n (%)	[redacted]	[redacted]
Infusion site pruritus, n (%)	[redacted]	[redacted]
Peripheral swelling, n (%)	[redacted]	[redacted]

Patients are counted once in each row, regardless of the number of events they may have had.
Abbreviations: CD/LD: carbidopa/levodopa.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

B.2.8.1.3 AEs leading to study drug discontinuation

AEs that led to study drug discontinuation were observed in [redacted] patients in the foslevodopa-foscarbidopa group and [redacted] patient in the oral CD/LD group. The AEs leading to discontinuation in ≥ 2% of all patients were infusion site AEs occurring in [redacted] and [redacted] patients in the foslevodopa-foscarbidopa and oral CD/LD group respectively (Table 35). Most of the events in each treatment group that led to discontinuation of study drug were mild or moderate in severity and considered by the investigator to have a reasonable possibility of being related to study drug.

Table 35: TEAEs occurring in ≥ 2% of patients leading to treatment discontinuation (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])	Oral CD/LD (N = [redacted])
Any TEAE, n (%)	[redacted]	[redacted]

General disorders and administration site conditions, n (%)	[redacted]	[redacted]
Asthenia, n (%)	[redacted]	[redacted]
Infusion site bruising, n (%)	[redacted]	[redacted]
Infusion site erythema, n (%)	[redacted]	[redacted]
Infusion site haemorrhage, n (%)	[redacted]	[redacted]
Infusion site nodule, n (%)	[redacted]	[redacted]
Infusion site oedema, n (%)	[redacted]	[redacted]
Infusion site pain, n (%)	[redacted]	[redacted]
Infections and infestations, n (%)	[redacted]	[redacted]
Cellulitis, n (%)	[redacted]	[redacted]
Infusion site cellulitis, n (%)	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders, n (%)	[redacted]	[redacted]
Mobility decreased, n (%)	[redacted]	[redacted]
Nervous system disorders, n (%)	[redacted]	[redacted]
Dizziness postural, n (%)	[redacted]	[redacted]
Hypokinesia, n (%)	[redacted]	[redacted]
Psychiatric disorders, n (%)	[redacted]	[redacted]
Hallucination, n (%)	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders, n (%)	[redacted]	[redacted]
Diaphragm muscle weakness, n (%)	[redacted]	[redacted]

Patients are counted once in each row, regardless of the number of events they may have had.
Abbreviations: CD/LD: carbidopa/levodopa; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

B.2.8.1.4 Adverse events of special interests (AESIs)

Infusion site infection and non-infusion reactions

The incidence of infusion site events was higher in the foslevodopa-foscarbidopa group than in the oral CD/LD group; however, the majority of these events were non-serious, were mild or moderate in severity, and resolved (Table 36).

Infusion site infections were reported for [redacted] patients in the foslevodopa-foscarbidopa group and for [redacted] patients in the oral CD/LD group. In the majority of patients in each treatment group, these events were non-serious, were mild or moderate in severity, and resolved, and no action was taken with study drug. The median time to onset was [redacted] days, and most events resolved with a median duration of [redacted] days. [redacted] patients in the foslevodopa-foscarbidopa group had serious infusion site infection events ([redacted] infusion site cellulitis and [redacted] catheter site cellulitis). [redacted] were hospitalised and treated with antibiotics and subsequently discharged without any systemic complications (Table 36).

Infusion site reactions were reported for [redacted] patients in the foslevodopa-foscarbidopa group and for [redacted] patients in the oral CD/LD group. The nature of these reactions reported by ≥ 5% of patients was classed as infusion site erythema ([redacted]), infusion site pain ([redacted]), infusion site oedema ([redacted]), infusion site bruising ([redacted]), infusion site haemorrhage ([redacted]), infusion site nodule

([redacted]), infusion site induration ([redacted]), and infusion site pruritus ([redacted]). In the majority of patients in each treatment group, these events were non-serious, were mild or moderate in severity, and resolved with or without treatment, and no action was taken with study drug. The median time to onset was [redacted] days, and most events resolved with a median duration of [redacted] days. No serious, fatal, or life-threatening infusion site reactions were reported in either treatment group (Table 36).

Table 36: Infusion site related AEs (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])	Oral CD/LD (N = [redacted])
Infections		
Any TEAE, n (%)	[redacted]	[redacted]
Mild, n (%)	[redacted]	[redacted]
Moderate, n (%)	[redacted]	[redacted]
Severe, n (%)	[redacted]	[redacted]
Related to study drug[a] n (%)	[redacted]	[redacted]
Any SAE related to infusion pump[a] n (%)	[redacted]	[redacted]
Possible, n (%)	[redacted]	[redacted]
Probable, n (%)	[redacted]	[redacted]
Causal relationship, n (%)	[redacted]	[redacted]
Non-infection reactions		
Any TEAE, n (%)	[redacted]	[redacted]
Mild, n (%)	[redacted]	[redacted]
Moderate, n (%)	[redacted]	[redacted]
Severe, n (%)	[redacted]	[redacted]
Related to study drug[a] n (%)	[redacted]	[redacted]
Any SAE related to infusion pump[a] n (%)	[redacted]	[redacted]

[a]As assessed by investigator
Abbreviations: CD/LD: carbidopa/levodopa; SAE: serious adverse event; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Falls and associated injuries

The incidence of falls and associated injuries was higher in the oral CD/LD group than in the foslevodopa-foscarbidopa group. Falls and associated injuries were reported for [redacted] patients in the foslevodopa-foscarbidopa group and for [redacted] patients in the oral CD/LD group. [redacted] experienced serious falls and associated injuries or orthostatic hypotension events in the foslevodopa-foscarbidopa group, compared with [redacted] in the oral CD/LD group (Table 37). In the majority of patients in each treatment group, falls and associated injuries and orthostatic hypotension events were mild or moderate in severity. In the foslevodopa-foscarbidopa group, the median time to onset of these events was [redacted] days, and the majority of these events resolved, with a median duration of [redacted] days.

Orthostatic hypotension was reported for [redacted] of patients in the foslevodopa-foscarbidopa group and for [redacted] of patients in the oral CD/LD group.

Table 37: Falls and associated injuries (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])	Oral CD/LD (N = [redacted])
Any TEAE, n (%)	[redacted]	[redacted]
Any serious TEAE, n (%)	[redacted]	[redacted]
Any TEAE leading to study drug discontinuation, n (%)	[redacted]	[redacted]
Any severe TEAE, n (%)	[redacted]	[redacted]
Any TEAE considered related to study drug, n (%)	[redacted]	[redacted]

Abbreviations: CD/LD: carbidopa/levodopa; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Hallucinations/psychosis

The incidence of hallucination/psychosis events was higher in the foslevodopa-foscarbidopa group than in the oral CD/LD group; however, most of the hallucination events in the foslevodopa-foscarbidopa group were non-serious, were mild or moderate in severity, and were consistent with what is expected in patients with advanced PD taking LD/CD medications.[89, 90]

Hallucinations/psychosis events were reported for [redacted] patients in the foslevodopa-foscarbidopa group and for [redacted] patients in the oral CD/LD group. In the [redacted] patients who reported hallucinations/psychosis events in the foslevodopa-foscarbidopa group, [redacted] were using dopamine agonists at Baseline and continued using these drugs concomitantly during the double-blind treatment period. [redacted] of the [redacted] patients had a medical history of hallucinations. In the majority of patients in each treatment group, hallucinations/psychosis events were non-serious and mild or moderate in severity, and no action was taken with study drug. The median time to onset was [redacted] days, and the median duration of the events was [redacted] days. Serious hallucinations/psychosis events were reported for [redacted] patient in the foslevodopa-foscarbidopa group (Table 38). The events resulted in hospitalisation and were subsequently resolved. foslevodopa-foscarbidopa was interrupted temporarily in response to the event and the dose of the concomitant medication (ropinirole) was reduced because the investigator felt the high dose of ropinirole was contributing to the event. No fatal or life-threatening hallucinations/psychosis events were reported in either treatment group.

Table 38: AESI: hallucinations and psychosis (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])	Oral CD/LD (N = [redacted])
Any TEAE, n (%)	[redacted]	[redacted]
Any serious TEAE, n (%)	[redacted]	[redacted]
Any TEAE leading to study drug discontinuation, n (%)	[redacted]	[redacted]
Any severe TEAE, n (%)	[redacted]	[redacted]
Any TEAE considered related to study drug, n (%)	[redacted]	[redacted]

Abbreviations: CD/LD: carbidopa/levodopa; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[63]

Polyneuropathy

[redacted] in the foslevodopa-foscarbidopa group and [redacted] in the oral CD/LD group experienced at least one polyneuropathy (peripheral neuropathy) event.

Weight loss

[redacted] in the foslevodopa-foscarbidopa group and [redacted] in the oral CD/LD group experienced at least one weight loss event. In [redacted], weight loss events were non-serious and mild or moderate in severity, and no action was taken with study drug in response to the events.

Somnolence

[redacted] in the foslevodopa-foscarbidopa group and [redacted] in the oral CD/LD group experienced at least one somnolence event. In [redacted], somnolence events were non-serious and mild in severity, and no action was taken with the study drug in response to the events.

B.2.8.1.5 Study deaths

[redacted] in the foslevodopa-foscarbidopa group died, and [redacted] patient in the oral CD/LD group died [redacted].

B.2.8.1.6 Additional Safety Outcomes

- [redacted] patients in the foslevodopa-foscarbidopa group and [redacted] patients in the oral CD/LD group had at least one observation of numeric Grade ≥5 and a letter Grade ≥D on the Infusion Site Evaluation Scale.
- There was no evidence of increased suicidality due to foslevodopa-foscarbidopa based on review of the Columbia-Suicide Severity Rating Scale (C-SSRS) data.
- There were no meaningful differences in the rates of Impulsive-Compulsive Disorders and related behaviour parameters between the foslevodopa-foscarbidopa and oral CD/LD treatment groups.

B.2.8.2 M15-741

B.2.8.2.1 Drug exposure and interruptions

Overall, [redacted] patients were exposed to study drug for ≥274 days both excluding and including study drug interruptions. A total of [redacted] patients had completed the 52-week treatment period at the time of the data cut-off (Table 40). Overall, patients were exposed to the study drug for a mean of [redacted] days including dose interruptions. The majority ([redacted]) of patients reported an infusion interruption in less than 2 days (Table 39). Reasons for infusion interruption, which were not mutually exclusive, were classed as “other” ([redacted] patients), adverse event ([redacted] patients), pump malfunction ([redacted] patients), and COVID-19 logistical restrictions ([redacted] patients). The majority of "other" reasons for infusion interruption were personal hygiene/shower or swimming, accidentally stopping the pump but not noticing, inadvertently forgetting to restart the pump, problems with cannula/connector, or patient not feeling well.

Table 39: Duration of study drug exposure and dose interruptions during the treatment period (SAS)

Characteristic	Foslevodopa-foscarbidopa
Duration of study drug exposure	
N	[redacted]
Mean, days (SD)	[redacted]
Duration of study drug interruption	
N	[redacted]
Mean, days (SD)	[redacted]
<1 day, n (%)	[redacted]
1 – <2 days, n (%)	[redacted]
2 – <3 days, n (%)	[redacted]
3 – <4 days, n (%)	[redacted]
4 – <5 days, n (%)	[redacted]
5 – <10 days, n (%)	[redacted]
10 – <20 days, n (%)	[redacted]
20 – <30 days, n (%)	[redacted]
≥30 days, n (%)	[redacted]

Abbreviations: SAS: safety analysis set; SD: standard deviation.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Table 40: Patient disposition (all screened patients)

Characteristic	Foslevodopa-foscarbidopa
Patient flow	
Initiated treatment, n (%)	[redacted]
Completed treatment, n (%)	[redacted]
Discontinued, n (%)	[redacted]
Ongoing treatment, n (%)	[redacted]
Infusion interruptions, n (%)	[redacted]
Reason for treatment discontinuation	
Infusion site related infections, n (%)	[redacted]
Infusion site related non-infection reactions, n (%)	[redacted]
Withdrawal of consent	[redacted]
Lack of efficacy, n (%)	[redacted]
Difficulty with drug delivery system, n (%)	[redacted]
Other, n (%)	[redacted]

Only reasons reported by >1 patient are included; one patient can be counted multiple times.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

B.2.8.2.2 Overview of AEs

An overview of AEs for the entire study period is presented in Table 41. AEs were reported for [redacted] patients, and the majority ([redacted]) were non-serious and were mild or moderate in severity with SAEs reported for [redacted] patients. Deaths were reported in [redacted] because of TEAEs, and [redacted] died more than 30 days after the last foslevodopa-foscarbidopa

infusion because of non-TEAEs (Section B.2.8.2.5). [redacted], TEAEs leading to death were considered by the investigator as having no reasonable possibility of being related to foslevodopa-foscarbidopa.

The most common AEs reported for ≥ 10% of patients were infusion site events, hallucination, fall, anxiety, and dizziness (Table 42).

When considering a subgroup analysis conducted by dose category for age, sex, race, geography and duration of PD, the overall incidence of AEs across the subgroups was similar to that of the overall study population.

Table 41: Overview of AEs (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])
Any TEAE, n (%)	[redacted]
Mild, n (%)	[redacted]
Moderate, n (%)	[redacted]
Severe, n (%)	[redacted]
Any serious TEAE, n (%)	[redacted]
Any TEAE leading to death, n (%)	[redacted]
Any TEAE leading to study drug discontinuation, n (%)	[redacted]
Any severe TEAE, n (%)	[redacted]
Any TEAE considered related to study drug,[a] n (%)	[redacted]
Any TEAE associated with product complaints,[a, b] n (%)	[redacted]
Foslevodopa-foscarbidopa,[c] n (%)	[redacted]
Infusion pump, n (%)	[redacted]
Vial adapter, n (%)	[redacted]
Syringes, n (%)	[redacted]
Cleo 90 infusion set, n (%)	[redacted]
Neria™ guard infusion set (6 mm), n (%)	[redacted]
PKG wearable device, n (%)	[redacted]

Patients are counted once in each row, regardless of the number of events they may have had.
[a] As assessed by the investigator.
[b] For each AE, the investigator recorded whether the event was associated with a product complaint. A product complaint was any complaint related to the drug component or to the medical device component of the product.
[c] foslevodopa-foscarbidopa was provided as a selectable option for product complaints to capture AEs associated with the device but may have been selected to represent the drug/device system in its entirety.
Abbreviations: AE: adverse event; PKG: personal KinetiGraph®; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Table 42: AEs observed in ≥ 10% of patients during the whole study period (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])
Infusion site erythema, n (%)	[redacted]
Infusion site nodule, n (%)	[redacted]

Infusion site cellulitis, n (%)	[redacted]
Infusion site oedema, n (%)	[redacted]
Hallucination, n (%)	[redacted]
Fall, n (%)	[redacted]
Infusion site pain, n (%)	[redacted]
Infusion site reaction, n (%)	[redacted]
Anxiety	[redacted]
Infusion site abscess	[redacted]
Dizziness	[redacted]

Patients are counted once in each row, regardless of the number of events they may have had.
Abbreviations: AE: adverse event; SAS: safety analysis set.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

B.2.8.2.3 AEs leading to study drug discontinuation

An overview of AEs that led to study drug discontinuation in ≥3 patients are presented in Table 43. In total, [redacted] patients had AEs that led to study drug discontinuation. The AEs leading to discontinuation in ≥2% patients were hallucination in [redacted] patients, infusion site cellulitis in [redacted] patients, infusion site erythema in [redacted] patients, and dyskinesia in [redacted] patients.

As highlighted in Section B.2.4.1.1, a mitigation strategy was introduced to account for problems with the Cleo 90 pump infusion set originally adopted. To evaluate the effects of the mitigation strategy, results from Sample 1 (patients enrolled before the 8th July 2020) and Sample 2 (patients enrolled on or after the 8th July 2020) were compared. The results of this analysis are reported in Table 44 and showed that the discontinuation rate during the first 12 weeks was lower for Sample 2 than the rate for Sample 1 ([redacted] and [redacted], respectively).

AEs that led to study drug interruption were reported by [redacted] patients. Of these AEs, those reported for ≥ 2% of patients that led to study drug interruption were infusion site cellulitis ([redacted]), infusion site erythema ([redacted]), infusion site abscess ([redacted]), infusion site pain ([redacted]), and infusion site oedema ([redacted]), and hallucination ([redacted]).

Table 43: AEs that led to study drug discontinuations in ≥ 3 patients (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])
Any AE that led to study drug discontinuation[a]	[redacted]
General disorders and administration site conditions	
Infusion site erythema	[redacted]
Infusion site nodule	[redacted]
Infusion site oedema	[redacted]
Infusion site reaction	[redacted]
Infections and infestations	
Infusion site abscess	[redacted]
Infusion site cellulitis	[redacted]
Nervous system disorders	
Dyskinesia	[redacted]
On and off phenomenon	[redacted]

Parkinson's disease	[redacted]
Psychiatric disorders	
Hallucination	[redacted]

Patients are counted once in each row, regardless of the number of events they may have had.
Abbreviations: AE: adverse event; SAS: safety analysis set.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Table 44: Reason for treatment discontinuation during first 12 weeks (All enrolled patients)

Reason for treatment discontinuation	Sample 1[a] [redacted]	Sample 2[b] [redacted]	All patients [redacted]
Foslevodopa-foscarbidopa prematurely discontinued, n (%)	[redacted]	[redacted]	[redacted]
Primary reason for premature discontinuation			
AEs, n (%)	[redacted]	[redacted]	[redacted]
Infusion site related infections, n (%)	[redacted]	[redacted]	[redacted]
Infusion site related non infection reactions, n (%)	[redacted]	[redacted]	[redacted]
Hallucinations/psychosis, n (%)	[redacted]	[redacted]	[redacted]
Withdrew consent, n (%)	[redacted]	[redacted]	[redacted]
Lost to follow-up, n (%)	[redacted]	[redacted]	[redacted]
Lack of efficacy, n (%)	[redacted]	[redacted]	[redacted]
Difficulty with drug delivery system, n (%)	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]

[a] Patients enrolled before applying the mitigation strategy on the 8th July 2020
[b] Patients enrolled after applying the mitigation strategy on the 8th July 2020
Patients are counted once in each row, regardless of the number of events they may have had.
Abbreviations: AE: adverse event.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

B.2.8.2.4 AESIs

An overview of AESI is given in Table 45. The AESI with the most cases were infusion site non-infection reactions, infusion site infections, and falls and associated injuries, occurring in [redacted], [redacted] and [redacted] patients respectively.

Table 45: Summary of AESIs (SAS)

AE category	Foslevodopa-foscarbidopa ([redacted])
Infusion site related non-infection reactions	[redacted]
Infusion site related infections	[redacted]
Falls and associated injuries	[redacted]
Hallucinations/psychosis	[redacted]
Weight loss	[redacted]
Somnolence	[redacted]
Polyneuropathy (narrow search)	[redacted]

Abbreviations: AE: adverse event; AESI: adverse event of special interest; SAS: safety analysis set.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Infusion site non-infection reactions

Infusion site reactions were reported for [redacted] patients. The preferred terms reported for ≥ 5% of patients were infusion site erythema ([redacted]), infusion site nodule ([redacted]), infusion site oedema ([redacted]), infusion site pain ([redacted]), infusion site reaction ([redacted]), infusion site extravasation ([redacted]), infusion site bruising ([redacted]), infusion site papule ([redacted]), infusion site hematoma ([redacted]), and injection site erythema ([redacted]). In the majority ([redacted]) of patients with these events, the infusion site reactions were non-serious and were mild or moderate in severity ([redacted] patients). Serious infusion site reactions were reported for [redacted] patients. These were infusion site injury ([redacted]) and infusion site hematoma ([redacted]), which were all assessed by the investigator to be reasonably possibly related to study drug. For [redacted] of these patients, an infusion site injury (hit the abdominal infusion site against a table) resulted in infusion site cellulitis. No life-threatening or fatal infusion site reactions were reported (Table 46).

Table 46: Overview of infusion site reactions during the entire study period (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])
Patients with any TEAE	[redacted]
AEs considered related to study drug[a]	[redacted]
Severe AEs	[redacted]
SAEs	[redacted]
AE leading to treatment discontinuation	[redacted]
AE resulting in death	[redacted]

Patients are counted once in each row, regardless of the number of events they may have had.
[a] Assessed by the investigator.
Abbreviations: AE: adverse event; SAE: serious adverse event; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Infusion site infections

Infusion site infections were reported for [redacted] patients. The preferred terms reported for ≥ 5% of patients were infusion site cellulitis ([redacted]), infusion site abscess ([redacted]), and infusion site infection ([redacted]). In the majority ([redacted]) of patients with these events, the infusion site infections were non-serious and were mild or moderate in severity ([redacted] patients). Serious infusion site infections were reported for [redacted] patients, most of which resulted in hospitalisation. In [redacted] patient, the event (cellulitis) was not at the infusion site and was considered not related to foslevodopa-foscarbidopa. The SAEs were infusion site cellulitis for 10 (4.1%) patients, infusion site abscess for [redacted] patients, cellulitis for [redacted] patient, and infusion site infection for [redacted] patient. [redacted] patients experienced systemic complications of sepsis and/or metabolic encephalopathy because of infusion site infections that resulted in hospitalisation. The events were treated with antibiotics and/or intervention (i.e., incision and/or drainage), and the patients were subsequently discharged from the hospital. No life-threatening or fatal infusion site infections were reported. Overall, [redacted] patients discontinued study drug because of infusion site infections; [redacted] of these events were considered by the investigator to be reasonably possibly related to study drug (Table 47). The infusion site infections resolved for the majority of patients.

Table 47: Overview of infusion site infections during the entire study period (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])

Patients with any TEAE	[redacted]
AEs considered related to study drug[a]	[redacted]
Severe AEs	[redacted]
SAEs	[redacted]
AE leading to treatment discontinuation	[redacted]
AE resulting in death	[redacted]

Patients are counted once in each row, regardless of the number of events they may have had.
[a] Assessed by the investigator.
Abbreviations: AE: adverse event; SAE: serious adverse event; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Falls and associated injuries and orthostatic hypotension

Falls were reported in [redacted] patients. The preferred terms reported for ≥ 2% of patients were fall ([redacted]), contusion ([redacted]), and skin laceration ([redacted]). In the majority of patients, the falls and associated injuries events were non-serious and were mild or moderate in severity, with severe events of falls and associated injuries reported for [redacted]) patients. [redacted] experienced a SAE of fall. [redacted] died from a cerebral mass effect and subdural hematoma after a fall that was reported as non-serious with no reasonable possibility of being related to study drug (Table 48).

Orthostatic hypotension AEs were reported in [redacted] patients. The preferred terms for ≥2% of patients were dizziness ([redacted]), orthostatic hypotension ([redacted]), and dizziness postural ([redacted]). In the majority of patients, the orthostatic hypotension events were non-serious and were mild or moderate in severity. Serious events of orthostatic hypotension occurred in [redacted] patients, [redacted] of which experienced an AE of dizziness concurrent to a fall (Table 48).

Falls and associated injuries and orthostatic hypotension events had a median time to onset of [redacted] days and recovered/resolved with a median duration of [redacted] day.

Table 48: Overview of falls and injuries during the entire study period (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])
Falls and associated injuries	
Patients with any TEAE	[redacted]
AEs considered related to study drug[a]	[redacted]
Severe AEs	[redacted]
SAEs	[redacted]
AE leading to treatment discontinuation	[redacted]
AE resulting in death	[redacted]
Orthostatic hypotension	
Patients with any TEAE	[redacted]
AEs considered related to study drug[a]	[redacted]
Severe AEs	[redacted]
SAEs	[redacted]
AE leading to treatment discontinuation	[redacted]
AE resulting in death	[redacted]

Patients are counted once in each row, regardless of the number of events they may have had.
[a] Assessed by the investigator.
Abbreviations: AE: adverse event; SAE: serious adverse event; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Hallucinations/psychosis

Hallucinations/psychosis were reported in [redacted] patients. The preferred terms reported for ≥2% of patients were hallucination ([redacted]), hallucination visual ([redacted]), delusion ([redacted]), hallucination auditory ([redacted]), and psychotic disorder ([redacted]). In the majority ([redacted]) of patients, the hallucinations/psychosis events were non-serious and were mild or moderate in severity ([redacted] patients). The median time to onset of these events was [redacted] days, and the majority of the events resolved, with a median duration of [redacted] days. Serious hallucinations/psychosis events were reported for [redacted] patients. The events were hallucination ([redacted] patients), psychotic disorder ([redacted] patients), delusion ([redacted] patients), and delusional disorder, unspecified type ([redacted] patient). Hallucinations/psychosis led to drug discontinuation for [redacted] patients. [redacted] of these events were considered by the investigator to be reasonably possibly related to study drug. [redacted] fatal hallucinations/psychosis events were reported.

The outcome for the majority of hallucinations/psychosis events was reported as recovered/resolved.

Table 49: Overview of hallucinations/psychosis during the entire study period (SAS)

AE category	Foslevodopa-foscarbidopa (N = [redacted])
Patients with any TEAE	[redacted]
AEs considered related to study drug[a]	[redacted]
Severe AEs	[redacted]
SAEs	[redacted]
AE leading to treatment discontinuation	[redacted]
AE resulting in death	[redacted]

Patients are counted once in each row, regardless of the number of events they may have had.
[a] Assessed by the investigator.
Abbreviations: AE: adverse event; SAE: serious adverse event; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

Weight loss

[redacted] patients experienced at least one weight loss event. The most commonly reported preferred term was weight decreased [redacted]. In the majority of patients, the weight loss events were mild or moderate in severity and considered by the investigator as reasonably possibly related to study drug. Approximately half of the weight loss events were reported as resolved. [redacted] of the events was serious or led to discontinuation of study drug, and [redacted] fatal events were reported

Somnolence

[redacted] patients experienced at least [redacted] somnolence event. In all [redacted] patients, the somnolence events were mild or moderate in severity, and in the majority of patients, these events were considered by the investigator as reasonably possibly related to study drug. The outcome for the

majority of the somnolence events was reported as resolved. [redacted] of the events was serious or led to study drug discontinuation, and [redacted] fatal events were reported.

Polyneuropathy

[redacted] patients experienced at least [redacted] polyneuropathy event. All the events of polyneuropathy were non-serious, and in the majority of the patients, the events were mild or moderate in severity. [redacted] of the events led to discontinuation of study drug, and [redacted] fatal events were reported

B.2.8.2.5 Study deaths

Death was reported in [redacted] patients due to TEAEs within 30 days of the last foslevodopa-foscarbidopa infusion ([redacted]), and [redacted] patients died more than 30 days after the last foslevodopa-foscarbidopa infusion due to non-TEAEs ([redacted]). [redacted] of the events were considered by the investigator to be related to study drug.

B.2.8.2.6 Additional Safety Outcomes

- [redacted] patients had at least one observation of numeric Grade ≥5 and a letter Grade ≥D on the Infusion Site Evaluation Scale. The SAEs were considered by the investigator as reasonably possibly related to study drug.
- There was no evidence of increased suicidality with foslevodopa-foscarbidopa based on the review of the C-SSRS data.
- AEs of impulse-control disorder and impulsive behaviour were reported for [redacted] patients and [redacted] patient, respectively. The events were mild or moderate in severity. The impulse-control disorder events for [redacted] patients were considered by the investigator as reasonably possibly related to study drug. [redacted] patient had an SAE of dopamine dysregulation syndrome. The SAE was assessed by the investigator as severe and as having no reasonable possibility of being related to study drug. None of the events led to discontinuation of study drug.

B.2.9 *Ongoing studies*

There are a number of ongoing studies for foslevodopa-foscarbidopa:

- **M20-098:** open-label extension study of trials M15-736 and M20-339, evaluating the long-term safety, tolerability, and efficacy of foslevodopa-foscarbidopa in patients with advanced PD (NCT04750226)[91]
- **M15-737:** open-label extension study of trial M15-741, evaluating the long-term safety, tolerability, and efficacy of foslevodopa-foscarbidopa in patients with advanced PD (NCT04379050)[92]
- **M20-339:** a randomised, open-label comparative study of levodopa and carbidopa bioavailability when foslevodopa-foscarbidopa is administered at different subcutaneous sites in patients with PD (NCT05094050)[93]

B.2.10 *Interpretation of clinical effectiveness and safety evidence*

B.2.10.1 Principle findings from clinical evidence base

Foslevodopa-foscarbidopa provided clinically meaningful and statistically significant improvements in PD symptom control compared with oral CD/LD.

The key clinical effectiveness and safety evidence for foslevodopa-foscarbidopa was provided by two multicentre Phase III trials, M15-736 and M15-741.

Study M15-736 was a Phase III, randomised, double-blind, double-dummy, active-controlled, parallel group, multicentre study, which directly compared the efficacy of foslevodopa-foscarbidopa to oral CD/LD in patients with advanced PD uncontrolled with standard oral therapy. The results of this trial showed foslevodopa-foscarbidopa to be effective at controlling patients' motor and non-motor symptoms, demonstrating a significant increase in patient-reported 'On' time without troublesome dyskinesia, and significantly reduced 'Off' time as compared with oral CD/LD.[63] These are clinically meaningful outcomes, representing increased PD symptom control without the dyskinesia that is often associated with peak dopamine concentrations linked to oral treatments, and reduced fluctuations in symptom control.[11] Foslevodopa-foscarbidopa proved effective in not only controlling symptoms during waking hours, but also during patients' sleep and as they awoke, problems often reported by patients with PD.[63, 69, 71] Indeed, PDSS-2 scores were found to be significantly correlated with QoL as measured by PDQ-39.[38] These positive outcomes relating to early morning akinesia and sleep symptoms show that the 24-hour infusion administration of foslevodopa-foscarbidopa provides continuous and reliable symptom control in patients with advanced PD.

The presence of Parkinsonian symptoms present a substantial disease burden, and reductions in these symptoms are associated with improvements in patients' HRQoL as patients' functional mobility and ability to perform everyday tasks improve.[15, 17, 41] Indeed, the improved symptom control outcomes seen in M15-736 directly translated to improved HRQoL outcomes reported by patients receiving foslevodopa-foscarbidopa, in both the PD-specific PDQ-39 and generic EQ-5D patient questionnaires.

Efficacy results demonstrated in the M15-736 RCT were supported by those in the Phase III, open-label, single arm study, M15-741. Similarly, clinically meaningful increases in 'On' time without troublesome dyskinesia and reductions in 'Off' time were observed in M15-741, which were statistically significant at all measured timepoints as compared to baseline. These improvements were seen after just one week and were sustained over the whole 52-week study period. As seen in M15-736, these improvements in key efficacy outcomes were accompanied with improved HRQoL scores in the PDQ-39 and EQ-5D scores as compared with baseline values.

Collectively, the results from both M15-736 and M15-741 demonstrate the clinical efficacy of foslevodopa-foscarbidopa both compared with oral CD/LD and as maintained over 52-weeks. Foslevodopa-foscarbidopa would introduce a new, effective treatment option, providing patients with 24-hour symptom control, delivered via a less invasive system than current advanced therapies for PD.

Additional supportive evidence from the PK/PD trial, M17-220, comparing foslevodopa-foscarbidopa to LCIG showed both treatments to have a similar pharmacological profile during waking hours. However, foslevodopa-foscarbidopa delivered a more stable plasma concentration level of both levodopa and carbidopa over its full 24-hour administration, highlighting its potential to deliver predictable and sustained daily symptom control.

Results of the NMA found foslevodopa-foscarbidopa to have similar efficacy to LCIG, and be significantly more effective at improving sleep symptoms.
In the NMA, foslevodopa-foscarbidopa was estimated to have a [redacted] in 'Off' time at 3 months compared with LCIG but a [redacted] in 'On' time without troublesome dyskinesia. However, neither difference reached statistical significance with small number of studies and low patient numbers informing the NMA networks, meaning the results are associated with substantial uncertainty. PDSS-2 scores at 3 months, however, were found to be [redacted] with foslevodopa-foscarbidopa, further supporting the substantial benefits foslevodopa-foscarbidopa can bring to patients due to its innovative 24-hour dosing regimen.

Foslevodopa-foscarbidopa is associated with a manageable safety profile, consistent with the known safety profile of levodopa.

In addition to the positive efficacy outcomes shown in both trials, foslevodopa-foscarbidopa was found to have a manageable and tolerable safety profile. Observed AEs were generally consistent with those associated with levodopa, with similar incidence of SAEs observed between the foslevodopa-foscarbidopa and oral CD/LD arms in M15-736.[89, 90] The incidence of infusion site infection were predictably higher in the foslevodopa-foscarbidopa arm, but the majority were non-serious, were mild or moderate in severity, and resolved.

B.2.10.2 Strengths and limitations

Internal validity of M15-736 and M15-741

As discussed in Section B.2.3.3 and Section B.2.4.3, the M15-736 and M15-741 trials were methodologically robust and well reported. The results were considered to be at low risk of bias. For example:

- Randomisation was carried out appropriately in M15-736
- The sample sizes were sufficient to detect a difference in the primary objectives ('On' time without troublesome dyskinesia in M15-736, safety outcomes in M15-741)
- Care providers, participants and outcome assessors were appropriately blinded to treatment allocation in M15-736

External validity

The results of the M15-736 and M15-741 trials can be generalised to the UK population and are well aligned to the decision problem addressed within this submission. The external validity of these trials is supported by the following:

- **Population –** The study populations in M15-736 and M15-741 are of direct relevance to the epidemiology of advanced PD in the UK. Patients in both trials had a similar age of diagnosis and duration of PD since diagnosis to those seen in the population of interest, and clinical experts consulted at an advisory board for this evaluation confirmed that the baseline

characteristics of both trials aligned with the patients they see in UK clinical practice who would be eligible for advanced PD therapies.[61] Clinicians further noted that the trial designs and methodology were consistent with previous studies in PD.[61] Whilst M15-736 was conducted in Australia and the US only, clinical experts had no concerns around the generalisability of this trial to UK clinical practice, and M15-741 included 13 clinical trial sites across the UK.[61]

- **Intervention and comparators** – Foslevodopa-foscarbidopa was directly evaluated as a treatment option for patients with advanced PD by comparing foslevodopa-foscarbidopa with oral CD/LD in M15-736, and with longer-term supportive evidence further provided by M15-741. The direct comparison to oral CD/LD facilitated indirect comparison through an NMA with the relevant comparator, LCIG.
- **Outcomes** – The primary efficacy outcome in M15-736, and also measured in M15-741, was the change from baseline in 'On' time without troublesome dyskinesia, as measured by PD diary.[62, 63] This is a well-established, validated and reliable measure of disease activity, well correlated with patient's experience of their disease. As such, this represents an appropriate primary efficacy endpoint. Additionally, 'Off' time, which informs the treatment efficacy in the submission's cost-effectiveness analysis (see Section B.3.2), was a key secondary outcome measured in M15-736, and was also measured in M15-741. Reducing 'Off' time is an important clinical objective for PD treatments, representing an improved state of symptom control.[25] The trials additionally measured other outcomes of direct relevance to patients with PD, exploring outcomes including impact on morning akinesia, sleep, safety and HRQoL.

Limitations

- There has been no direct comparison of efficacy and safety between foslevodopa-foscarbidopa and LCIG, requiring an NMA to be conducted. Limited studies are available to inform the network, resulting in relatively large credible intervals and uncertainty.
- The M15-736 trial had a relatively short follow-up of 3 months, limiting the ability to assess comparative effectiveness in the long-term; this uncertainty also exists within the NMA. The M15-741 trial, however, provides longer-term reassurance that the efficacy of foslevodopa-foscarbidopa is maintained over a longer time frame of 52 weeks.
- M15-741 experienced a higher than anticipated number of premature discontinuations in the early phase of the trial due to difficulties using the initial drug delivery system. This led to a reduced sample size within the trial and a high proportion of censoring within the data. A mitigation strategy was implemented where patients were evaluated separately depending on which device they received treatment with (e.g. the original infusion set or the later introduced Neria™ guard infusion set; the set intended for commercial delivery of foslevodopa-foscarbidopa). The mitigation strategy resolves some of the uncertainty relating to these discontinuations, however intention-to-treat (ITT) data are still impacted by the early challenges within the trial.

B.2.10.3 Conclusion

The quality of evidence provided by the pivotal clinical trials for foslevodopa-foscarbidopa is supported by robust methodology, and the trial results are directly relevant to the treatment of patients with advanced PD in UK clinical practice. Foslevodopa-foscarbidopa has been demonstrated to be effective at controlling both motor and non-motor symptoms, with symptom control improved through waking hours but also during sleep and in the early morning as patients

awoke. These efficacy gains were combined with a manageable safety profile in line with the known safety profile of levodopa.

Results of the NMA demonstrated similar efficacy to LCIG with significant improvement in PDSS-2 scores. Combined with the PK/PD studies indicating improved consistency in levodopa plasma concentrations, foslevodopa-foscarbidopa represents an innovative treatment alternative to both LCIG and BMT, providing patients with a non-surgical, effective treatment that provides more consistent, 24-hour symptom control.

B.3 Cost effectiveness

A *de novo* cost-utility analysis was undertaken based on a cohort Markov model identified following comprehensive secondary research looking at existing PD models.

- A cohort Markov model was developed based on patients' daily hours of 'Off' time with 18 states (OFF0 to OFF16 and a 'Death' state).
- The base case analysis compared foslevodopa-foscarbidopa to both LCIG and BMT in line with the population considered in the model: adult patients with advanced PD that is responsive to levodopa, with symptoms not adequately controlled by their current medical therapy and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control.
- The analysis was consistent with the NICE reference case: a cost-utility analysis with an NHS and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and a lifetime-equivalent time horizon was used.
- Clinical outcomes were based primarily on the M15-736 trial, with supportive data from M15-741 where appropriate, to inform 'Off' time, treatment discontinuation rates and occurrence of AEs.
- Health state utilities were informed by EQ-5D-5L data collected during the M15-736 trial and mapped onto EQ-5D-3L.
- Costs and healthcare resource use were captured in the analysis for active treatment costs, treatment administration and management, AE management costs and health state specific costs.

In the base case, foslevodopa-foscarbidopa was found to be the most cost-effective treatment option for patients with advanced PD with symptoms not adequately controlled by their current medical therapy and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control

- Foslevodopa-foscarbidopa had a probability of being the most cost-effective treatment of 83% at list price and [redacted] with-PAS at a WTP threshold of £30,000 per quality-adjusted life year (QALY).
- Against BMT, foslevodopa-foscarbidopa was dominant at both list price and with-PAS. Against LCIG, foslevodopa-foscarbidopa yielded a SW quadrant ICER of £192,741 per QALY foregone at list price and [redacted] per QALY foregone with-PAS. The net health benefit (NHB) for foslevodopa-foscarbidopa versus LCIG was 0.55 at list price and [redacted] with-PAS, and versus BMT was 4.62 at list price and [redacted] with-PAS, at a WTP of £30,000 per QALY gained.
- Foslevodopa-foscarbidopa incurs fewer costs than LCIG, however yields fewer QALYs (incremental difference of 0.10 at list price, [redacted] with-PAS) compared with LCIG. This difference is primarily driven by the higher rates of discontinuations modelled for foslevodopa-foscarbidopa, and patients therefore transitioning onto the less effective BMT. High discontinuation rates are common across advanced PD therapies; clinical experts have indicated that high initial discontinuation rates are typical for treatments administered by continuous subcutaneous infusion.[61]
- A number of key areas of value for foslevodopa-foscarbidopa are unable to be captured within the cost-effectiveness model (see Section B.3.13), indicating that the QALY estimates likely underestimate the true value foslevodopa-foscarbidopa can bring to patients and the NHS relative to LCIG.
- The DSA results identified a small number of key influential parameters (RR from the NMA, utility values in the lower OFF health states and discontinuation rates for foslevodopa-foscarbidopa) with the model being largely robust to uncertainty in the majority of parameters.
- Scenario analyses demonstrated that whilst there was variation in the NHB, the cost-effectiveness conclusions remained the same, with foslevodopa-foscarbidopa remaining cost-effective against both comparators at a WTP threshold of £30,000 per QALY across all scenarios.

B.3.1 *Published cost-effectiveness studies*

An economic SLR was conducted on the 10th August 2021 and was subsequently updated using the same review protocol on 12th January 2022, and 3rd June 2022 to identify all relevant literature published on the following topics:

- Economic evaluations of therapies for the treatment of advanced PD
- Healthcare resource use (HCRU) and cost studies on advanced PD
- Studies on utilities associated with advanced PD

The SLR was conducted following current best practices, as recommended by the Cochrane Collaboration.[94] The reporting of the methods and results of the SLR were conducted in line with the guidance provided by the NICE and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[95-97] Full details of the economic SLR search strategy, study selection process and results for economic evaluations, HCRU and utility studies are reported in Appendices G, H and I, respectively.

In total, 28 economic evaluations of therapies for the treatment of advanced PD were identified in the SLR. Of the 28 included studies, 25 were cost-utility analyses (CUA) and three were cost-benefit analyses (CBA). The majority of studies were conducted in the UK and United States, with ten and five studies, respectively. Among studies reporting the model type used (n=23), all but five employed a Markov modelling approach. A number of different approaches were taken to modelling treatment efficacy and disease progression in the models identified (see Section B.3.2.2). As none of the models have been appraised as part of a NICE technology assessment (TA), no clear consensus has emerged as to the most appropriate approach to modelling advanced PD.

Fifteen studies reporting HCRU and costs relating to advanced PD were identified in the SLR. The majority of these studies reported costs (n=12), while only a few reported HCRU (n=6). Most studies were observational (n=14), and the majority were conducted in Europe (n=12).

In the SLR, utility values relating to advanced PD were identified in two studies. One publication predicted utility values by 'Off' category and Hoehn and Yahr (H&Y) stage, a 5-component system used to describe symptoms of Parkinson's disease, among idiopathic PD patients in Sweden identified using the National Parkinson's Disease Patient Registry. One publication reported utility values by using EQ-5D, with lower utility values in patients with advanced PD compared to without advanced PD.

B.3.2 *Economic analysis*

The SLR found no economic evaluations investigating foslevodopa-foscarbidopa for the treatment of advanced PD and therefore a *de novo* cost-effectiveness analysis was conducted for the purpose of this appraisal, and is described in the sections below. The cost-effectiveness model was developed in Microsoft Excel®.

The objective of this economic analysis was to assess the cost-effectiveness of foslevodopa-foscarbidopa within part of its marketing authorisation for the treatment of adult patients with advanced PD responsive to levodopa, with symptoms not adequately controlled by their current

medical therapy and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control.

In line with the NICE reference case, the analysis of costs was conducted from the perspective of the NHS and Personal Social Services (PSS) in the UK and included direct medical costs over a lifetime horizon.[98] The perspective on outcomes was that of patients, with carer utilities investigated as part of a scenario analysis.

B.3.2.1 Patient population

In line with the decision problem addressed in this submission (Section B.1.1), the patient population considered in the economic analysis was the following:

Adult patients with advanced PD responsive to levodopa, with symptoms not adequately controlled by their current medical therapy and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control.

B.3.2.2 Model structure

The cost-effectiveness analysis of foslevodopa-foscarbidopa in advanced PD utilised a transition-state Markov model, consisting of 17 health states, and one absorbing 'Death' state. Each health state was defined by the number of daily 'Off' hours - normalised to a 16-hour day - experienced by patients, ranging from 0 to 16 hours, in one-hour increments.

The model was divided into two distinct periods: the within trial period and beyond trial period, which are described in detail below. The Markov model used for both periods was considered the most appropriate modelling methodology due to its simplicity and transparency compared with other modelling techniques.[99] For example, discrete event simulations were not possible due to limitations in data availability in advanced PD. Full justification for the model structure is given below and in Table 51.

Justification of model structure

Secondary research was conducted to evaluate potential existing models in PD based on previous cost-effectiveness models in advanced PD. A summary of the characteristics of the identified models is included in Table 50. The majority of models for device-aided therapies (DATs) in advanced PD were Markov models based on a combination of health states based on H&Y stages and daily 'Off' time.[100-104] Several potential models were also assessed which included Markov models with health states based on (i) H&Y scale and 'ON' time without troublesome dyskinesia, (ii) responder 'OFF' time, (iii) responder 'OFF' time and H&Y scale, and (iv) unified Parkinson's disease rating scale (UPDRS). All potential model structures were assessed based on clinical relevance, ability to capture outcomes that are important to patients and availability of data (costs, utilities, and relative efficacy in both the short-term and the long-term). The variety of model approaches identified highlights the lack of consensus in terms of endpoint utilisation for modelling purposes.

The availability of data to inform model transitions was a key factor when determining the most appropriate model structure. Based on this research, model structures based on the following three outcomes were deemed the most feasible and appropriate, considering the data available to inform treatment efficacy in the model:

- ‘OFF’ time
- ‘ON’ time without troublesome dyskinesia
- H&Y

The ‘OFF’ time model structure has previously been used for the apomorphine (Movapo®) submission to CADTH.[105] The ‘OFF’ and H&Y model structure has previously been used for a Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) submission for LCIG, as published in Kalabina et al. 2019,[106] and in the LCIG cost-effectiveness model developed by Chaudhuri et al. 2022.[101] This model dates back to a cost-effectiveness model developed by Lowin et al. 2011.[102] Further details of the secondary research are given in Appendix N.

Table 50: Summary of the results from the model structure secondary research

Outcomes informing model structure	Key consideration(s)	Reference
‘OFF’ time and H&Y	• Consistent with majority of models in advanced PD, including LCIG	Kalabina et al. 2019,[100] Chaudhuri et al. 2022,[101] Lowin et al. 2011,[102] Lowin et al. 2017,[103] Walter et al., 2015[104]
‘ON’ time without troublesome dyskinesia and H&Y	• ‘ON’ time without troublesome dyskinesia aligned with the primary outcome from M15-736 • Less comparative data for ‘ON’ time compared to ‘OFF’ time	N/A – no previous models identified with this model structure
Responder (‘OFF’ or ‘ON’ time improvement) and H&Y	• Less complex model structure • Response definition varies based on clinical opinion • Limited efficacy and cost data by response definition	N/A – no previous models identified with this model structure
‘OFF’ time	• Less complex model structure • Does not capture improvements in H&Y	CADTH 2018[105]
H&Y (ON and OFF)	• Driven by improvement in H&Y (postural stability) • Does not capture improvement in ‘ON’/’OFF’ time	Dams et al. 2013[107]
Residence-based model (home, full-time care)	• Limited efficacy and cost data by residence status • Driven by UPDRS part 3 improvement	NICE NG71[108]
MDS-UPDRS Part 3 (Motor Examination)	• May not capture clinical improvements in ‘OFF’ time and ADL • UPDRS part 3 might favour DBS	N/A – no previous models identified with this model structure

Given the timescales required for economic model development, the economic evaluations considered here are based on an earlier TLR of previous CEMs than the final SLR conducted for the submission.

Abbreviations: ADL: activities of daily living; CEM: cost-effectiveness model; H&Y: Hoehn and Yahr; LCIG: levodopa-carbidopa intestinal gel; MDS-UPDRS: Movement Disorders Society-Unified PD Rating Scale; PD: Parkinson's disease; SLR: systematic literature review; TLR: targeted literature review.

Although some previous model structures included H&Y status in addition to 'OFF' time, H&Y is a proxy of postural stability and therefore not fully representative of disease progression. In addition, H&Y is not widely assessed to capture treatment effect; it is not a reported outcome in the foslevodopa-foscarbidopa clinical trials,[63] and is not commonly reported as an outcome in previous trials in advanced PD.[80, 83] As such, it was concluded that inclusion of H&Y into the model structure was not feasible. Finally, 'OFF' time was favoured instead of 'ON' time without troublesome dyskinesia, as clinical experts indicated that 'OFF' time is more intuitive and widely assessed in clinical practice; it is the relevant outcome clinicians treat for, and is easier for patients to report compared with 'ON' time (for example, 'ON' time without troublesome dyskinesia could potentially be confused with 'ON' time with troublesome dyskinesia). Furthermore, the research indicated that efficacy, costs and utilities were more widely available for 'OFF' time compared to 'ON' time without troublesome dyskinesia (Appendix N).

Taking into consideration the above findings, including clinical expert input, the decision was made to develop a *de novo* cost-effectiveness model, utilising a Markov model structure informed by 'OFF' time. One-hour increments in 'OFF' time were used to define health states in the cost-effectiveness model in line with the minimal clinically meaningful reduction in 'OFF' time.[64, 109] Whilst one-hour increments leads to a relatively large number of transitions (17 x 17) needing to be estimated based on a relatively small number of patients (e.g., 73 patients in the foslevodopa-foscarbidopa arm of M15-736 used in the base case analysis), resulting in many transitions having a 0% or a 100% probability of occurring, this level of granularity provides the most complete use of data from the clinical trial.

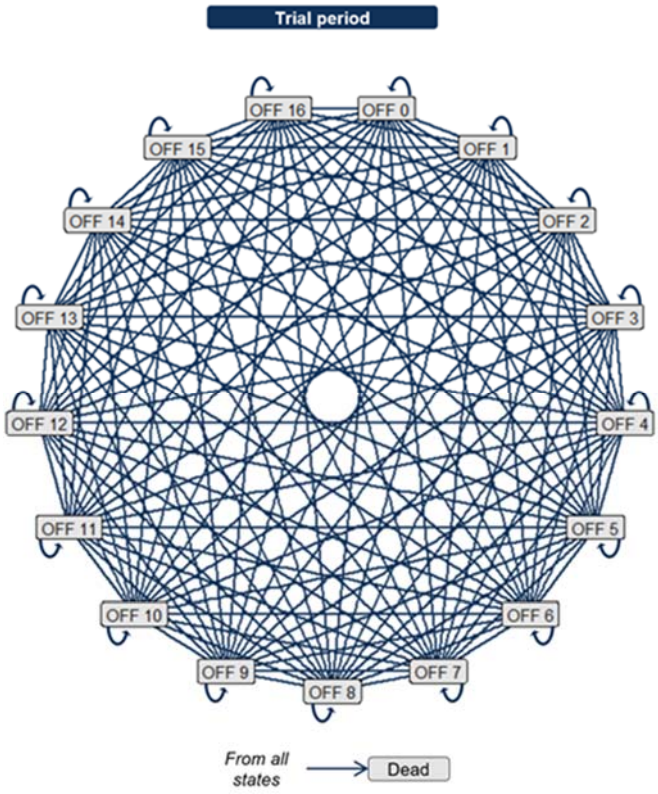
Furthermore, the scientific advice provided by NICE on the evaluation of foslevodopa-foscarbidopa highlighted that "*it will be more relevant for the health economic model to capture the benefit of ABBV-951 in terms of HRQL gains associated with its use, rather than to try to demonstrate a slowing of disease progression*." The use of 'OFF' time health states aligns with this approach by using an outcome that is of direct relevance to patients' everyday lives.[110] Overall, this model structure was therefore considered to better align to the assessment of advanced PD observed in clinical practice.

The model structure is detailed in the sections below.

Within trial period

The within trial period modelled the first three months of the model time horizon (20 years). In this trial period, patients could transition freely from any health state to any other health state in the model, as depicted diagrammatically in Figure 26. During the initial treatment period, large changes in 'Off' period are expected as patients respond to treatment. As not all patients respond to treatment, and the disease progresses, patients were modelled as transitioning to both increasing and decreasing 'Off' time health states.

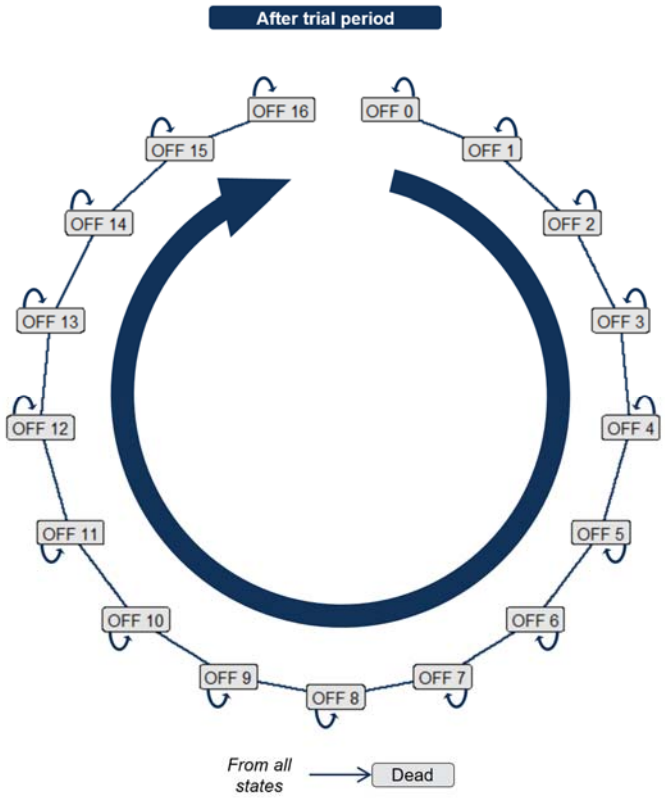
Figure 26: Model structure for within trial and LOCF periods



Beyond trial period

The beyond trial period modelled cost-effectiveness of foslevodopa-foscarbidopa from the end of Month 3 onward within the CEM. In this period, patients could only transition to adjacent, worsening health states in the model (i.e. only increases of one hour of daily 'Off' time were allowed in each model cycle), shown diagrammatically in Figure 27. The limit to single hour transitions was applied as transition probabilities between health states two or more hours apart would be informed by too low a number of patients to be estimated; as response to treatment stabilises following the initial treatment period, very few patients would be anticipated to "jump" multiple states, as was noted by clinical experts during an advisory board.[61] Further to this, transitions were only allowed to worsening health states, i.e. increasing daily 'Off' time. This is rationalised by the progressive nature of PD, associated with incurable symptoms, which inevitably worsen over time.[7, 23] Patients whose response to treatment has stabilised would be expected to experience gradually worsening motor control, and therefore gradually increasing 'Off' time.

Figure 27: Model structure for beyond trial and LOCF periods



Cycle length and half cycle correction

In the first and second model cycle, the cycle length is three months. This initial cycle length was chosen as treatments in advanced PD have been shown to provide the most benefit early on following exposure to treatment, and was chosen because M15-736 and the pivotal RCTs for LCIG have a follow-up of three months.[111, 112] This level of granularity increases model sensitivity to treatment effect. Beyond the first two cycles, the cycle length is six months. This is considered sufficient to accurately capture the clinical outcomes reported for patients with advanced PD in the clinical trials and is in line with previous cost-effectiveness models.[102, 103, 106] As clinical outcomes may occur mid-cycle, a half-cycle correction is applied to estimate costs, life years (LYs) and QALYs in every cycle.

Mortality

In both the within trial period and beyond trial period, the absorbing 'Death' state could be reached from any health state.

Features of the *de novo* analysis (base case)

Table 51: Features of the economic analysis

	Current evaluation	
Factor	**Chosen values**	**Justification**
Model structure	• Cohort simulation Markov model • The Markov structure consisted of 17 health states,	Based on secondary research conducted to evaluate potential model structures based on previous cost-effectiveness models in advanced PD.

	representing daily normalised 'Off' time experienced by patients, ranging from 0 hours of 'Off' time to 16 hours. The model also included an absorbing 'Death' state, which could be reached from any of the 'Off' states	The model structure was considered to appropriately reflect improvements in symptom control experienced by patients receiving treatment, using a clinically important outcome, validated by clinical experts
Time horizon	Lifetime (20 years)	As per NICE reference case[98]
Discount rate	3.5% per annum	As per NICE reference case[98]
Perspective	NHS and PSS	As per NICE reference case[98]
Cycle length	**Within trial period:** Cycle 1 = three months **Beyond trial period:** Cycle 2 = three months; Cycles 3+ = six months	Within trial period: three months chosen as treatments have shown to provide the most benefit early on when the patient is first exposed to the treatment, and since M15-736, as well as landmark RCTs from some of the comparators,[80, 83] have a follow-up of three months. Beyond trial period: three months for cycle 2, then six months chosen as this is considered sufficient to accurately capture the clinical outcomes reported for patients with advanced PD in the clinical trials and is in line with previous cost-effectiveness models[100, 102, 103]
Health state transitions	**Within trial period:** 'Off' can change by any level from one cycle to the next **Beyond trial period:** transitions limited to worsening one level from one cycle to the next	Within trial period: During the initial treatment period, large changes in 'Off' period are expected as patients respond to treatment and as such, transition probabilities between 'Off' states >1 hour are able to be informed by an appropriately large number of patients. As not all patients respond to treatment, and the disease progresses, patients were modelled as transitioning to both increasing and decreasing 'Off' time health states. Beyond trial period: The proportion of patients with changes of more than one level would be too small to enable estimates of corresponding transition probabilities. Furthermore, 'jumping' multiple states may be realistic in the beginning, but not in the longer term because patients' responses stabilise which means that shifts of multiple hours of 'Off' time are unlikely to occur.
Treatment waning effect?	No	As long as patients are on treatment, the treatments are effective in controlling motor symptoms (i.e., 'OFF' time). As patients progress over time, 'OFF' time symptom control will worsen, which is captured in the model, but the relative treatment effect is expected to

		remain the same. Clinical feedback received as part of this appraisal indicated that modelling treatment waning for PD treatments would be inappropriate, given that treatments do not stop working, rather the disease progresses and symptoms become more difficult to control.[61]
Source of utilities	**Patient utilities:** EQ-5D-3L utility weights applied to the 17 PD states (OFF 0 to OFF 16) in the model were estimated by fitting linear mixed models to EQ-5D values from a combined dataset of foslevodopa-foscarbidopa studies: M15-736, M20-098, M15-741, and M15-737. **Caregiver utilities:** Adelphi 2010, 2012, and 2017–2019 data was used, including patients from EU5, US and Japan.[21] All utilities were converted with UK tariffs.	As per NICE reference case[98]
Source of costs and resource use	• 2019/2020 NHS reference cost • British National Formulary (BNF) • Published literature	Established sources of costs within the NHS. In line with the NICE reference case[98]
Measure of health effects	QALYs	As per NICE reference case[98]

Abbreviations: NICE: National Institute of Health and Care Excellence; NHS: National Health Service; PD: Parkinson's disease; PSS: Personal Social Services; QALYs: quality-adjusted life years.

B.3.2.3 Intervention technology and comparators

As described in Section B.1.2, the intervention considered in the cost-effectiveness analysis was foslevodopa-foscarbidopa.

The comparators of relevance to this submission are LCIG and BMT (See Section B.1.3 for further details). BMT comprises a number of different treatments used in UK clinical practice. These exact treatment regimens, along with the proportions of patients expected to receive each one, is detailed in Section B.3.5.1.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Summary of clinical trial data used in the cost-effectiveness analysis

The clinical efficacy inputs for foslevodopa-foscarbidopa were derived from the M15-736 trial, a 52-week Phase III, randomised, double-blind, double-dummy, active-controlled, parallel group, multicentre study. Full details of the M15-736 trial are provided in Section B.2.3. In the absence of head-to-head data for foslevodopa-foscarbidopa versus LCIG, efficacy for LCIG was modelled using efficacy inputs derived from an NMA (Section B.2.7.4), expressed as a risk ratio relative to foslevodopa-foscarbidopa. The risk ratio was calculated by the dividing the foslevodopa-foscarbidopa change from baseline in 'Off' time by LCIG's change from baseline. Given that the

population modelled was uncontrolled by BMT, BMT was modelled as having no treatment effect, and was instead modelled as following natural disease progression (see Section B.3.3.4.2).

Results from the M15-741 trial have not been used as, contrary to the pivotal M15-736 trial, the primary outcomes of this trial centred around safety rather than efficacy (which were secondary outcomes). This trial was a single arm study, in comparison to the robust RCT M15-736 which provides the efficacy inputs. M15-741 therefore provides supporting evidence to M15-736, but was not considered an appropriate source of efficacy data for the economic model.

B.3.3.2 Baseline characteristics

The baseline characteristics for the patients entering the model were derived from the M15-736 trial (Section B.2.3). The mean age of the M15-736 population was [redacted], and [redacted]% were female (Table 52).

Table 52: Baseline characteristics for the population used in the economic model

Characteristic	Model population
Sex, n (%)	
Female	[redacted]
Age, years	
Mean (SD)	[redacted]

Abbreviations: SD: standard deviation.

B.3.3.3 Baseline distribution of patients

In the base case, the starting proportions of patients in each health state were based on the baseline distribution of the ITT population in the M15-736 trial. The numbers were converted to a proportional distribution across health states within the model. The percentage of patients in each health state at the start of the model are shown in Table 53.

Table 53: Baseline distribution of patients entering the model

Health state	Base case (M15-736 ITT population)
OFF 0	[redacted]
OFF 1	[redacted]
OFF 2	[redacted]
OFF 3	[redacted]
OFF 4	[redacted]
OFF 5	[redacted]
OFF 6	[redacted]
OFF 7	[redacted]
OFF 8	[redacted]
OFF 9	[redacted]
OFF 10	[redacted]
OFF 11	[redacted]
OFF 12	[redacted]
OFF 13	[redacted]

OFF 14	[redacted]
OFF 15	[redacted]
OFF 16	[redacted]
Death	[redacted]
Total	[redacted]

Abbreviations: ITT: intention-to-treat.

B.3.3.4 Within trial periods transitions

B.3.3.4.1 Foslevodopa-foscarbidopa transitions

In the base case, the foslevodopa-foscarbidopa treatment effect for the first three months was modelled based on the initial three-month effect observed in the ITT population of the M15-736 trial. The distribution of patients at the start and at the end of the within trial period is shown in Figure 28.

Figure 28: Distribution of patients receiving foslevodopa-foscarbidopa at the start and end of the within trial period (M15-736 ITT population)

The percentage of patients in each health state over time is represented by the coloured bands as per the figure key.

B.3.3.4.2 Treatment effect derivation

LCIG

Treatment effect of the comparator, LCIG, was estimated related to foslevodopa-foscarbidopa. In the base case, the relative risk was based on the results of the NMA (see Section B.2.7.4). Relative risk estimations are shown in Table 54. Relative risk was calculated by the dividing the foslevodopa-foscarbidopa change from baseline in 'Off' time by LCIG's change from baseline. The relative risk was implemented by multiplying the foslevodopa-foscarbidopa transition probabilities by the relative risk for worsening transitions (e.g., OFF 1 to OFF 2) and by 1/relative risk for improving transitions (e.g., OFF 2 to OFF 1); a proportion of patients also remained in the same health state. In the base case, the relative risk is applied for the first three months, after which last observation carried forward (LOCF) is applied from Months 3–36 (see Section B.3.3.5).

Table 54: Relative risk estimated for LCIG by the NMA

Treatment	Comparators mean change in 'Off' hours versus foslevodopa-foscarbidopa	Relative risk versus foslevodopa-foscarbidopa
LCIG	[redacted]	[redacted]

Abbreviations: LCIG: levodopa-carbidopa intestinal gel; NMA: network meta-analysis.

This approach transforms the outputs of the NMA into a way that captures differences in 'Off' time that aligns with the structure of the cost-effectiveness model. The assumptions imply that the average effect can be translated to a difference in only improving or worsening health states. As 'Off' time is a symptomatic effect of PD, this allows for greater flexibility in the model to capture the symptomatic changes over time than simply progression of Parkinson's disease that may fluctuate at a marginal level over time.

BMT: natural disease progression

Given the anticipated license for foslevodopa-foscarbidopa is for treatment of patients whose symptoms are not controlled by standard therapy, BMT was assumed to impart no clinical benefit. As such, BMT efficacy was modelled based on natural history in the base case. This same approach has been used and accepted by NICE previously in other indications, including notably in multiple sclerosis and rheumatoid arthritis. Literature to directly populate natural disease transitions probabilities was not available, therefore this consisted of constant transition probabilities derived by fitting an exponential model to data from Palmer et al.,[113] in line with the approach by Kalabina et al.[106] An exponential model, opposed to a linear model, was fitted to the Palmer et al. data because it would be expected that patients in higher 'OFF' states are less likely to move to the next worse 'OFF' state than patients in the lower 'OFF' states. The probability of remaining within the same health state between cycles is equal to 1 minus the probability of transitioning, with mortality accounted for separately by applying a mortality rate directly to the model traces (see Section B.3.3.9).

Table 55: Transition probabilities for natural disease progression, based on an exponential model fitted to Palmer et al.[113]

From	To	6 months transition probability
OFF 0	OFF 1	[redacted]

OFF 1	OFF 2	[redacted]
OFF 2	OFF 3	[redacted]
OFF 3	OFF 4	[redacted]
OFF 4	OFF 5	[redacted]
OFF 5	OFF 6	[redacted]
OFF 6	OFF 7	[redacted]
OFF 7	OFF 8	[redacted]
OFF 8	OFF 9	[redacted]
OFF 9	OFF 10	[redacted]
OFF 10	OFF 11	[redacted]
OFF 11	OFF 12	[redacted]
OFF 12	OFF 13	[redacted]
OFF 13	OFF 14	[redacted]
OFF 14	OFF 15	[redacted]
OFF 15	OFF 16	[redacted]

B.3.3.5 Beyond trial period transitions

Last observation carried forward

Treatment effects for both foslevodopa-foscarbidopa and LCIG in the beyond trial period were firstly based on the last observation carried forward (LOCF) (Months 3–36). For Months 3–36, the transition probabilities calculated for the trial period (Month 0–3) were applied. This is based on the supportive evidence from M15-741 which demonstrated a sustained long-term effect for foslevodopa-foscarbidopa. Natural disease progression is then considered from Months 36+. Treatment waning was not included in the model based on feedback from clinical experts during an advisory board who confirmed that as long as patients are on treatment, the treatments are effective in controlling motor symptoms (i.e., 'OFF' time; Table 51).

Natural disease progression

Given the progressive nature of PD, it is anticipated that over long periods of time, disease symptoms will no longer be controlled by treatment, and will progressively worsen. This was reflected in the model by applying natural disease progression, which was applied directly after the period in which LOCF was applied, from Months 36 onwards. As patients progress over time, 'OFF' time symptom control will worsen, which is captured in the model, but the relative treatment effect is expected to remain the same. This is in line with previous cost-effectiveness analyses in PD, where relative treatment effectiveness was assumed to be constant for the full lifetime of the model.[100, 101]

B.3.3.6 Subsequent treatments

Subsequent treatments were not considered as part of the model. When patients fail on advanced therapies, considering the late stage of the disease, they will not be suitable/eligible for further advanced treatment, thus are given standard therapies. As such, patients treated with foslevodopa-foscarbidopa and LCIG are modelled as receiving BMT upon treatment discontinuation, meaning patients experience natural disease progression, and incur the costs and utilities modelled for BMT. These transitions are based on natural disease progression, as described in Section B.3.3.4.2. The assumption of lack of treatment effect of BMT as a subsequent treatment, modelled as natural disease progression, was tested as part of a scenario analysis which modelled BMT's treatment effect based on the relative risk derived in the NMA (see Section B.2.7).

Patients treated with BMT were modelled as receiving BMT throughout the disease course without discontinuation (see Section B.3.3.8), and as such were not modelled as receiving any subsequent treatments.

B.3.3.7 Adverse events

AEs were included in the model due to the impact on health care in terms of costs incurred in the treatment and management of these events as well as the impact on patients' HRQoL. AEs are included as one-off AEs in terms of costs, whilst utility decrements applied for the duration of the event, as shown in Table 56. When data on duration were not available, duration for AEs was assumed to be four weeks, a period that would allow for potential hospitalisation and a recovery period afterwards.

Table 56: Incidence of AEs with foslevodopa-foscarbidopa, BMT and LCIG

AE	Foslevodopa-foscarbidopa		BMT		LCIG		AE duration	
	Estimate	Source	Estimate	Source	Estimate	Source	Estimate (days)	Source
Infusion site erythema	[redacted]	CSR M15-736[63]	[redacted]	CSR M15-736[63]	13%	Fernandez et al. (2015)[112]	7	NICE TA720
Infusion site nodule	[redacted]		[redacted]		0%	Assumption	28	Assumption
Infusion site cellulitis	[redacted]		[redacted]		0%	Assumption	28	Assumption
Infusion site pain	[redacted]		[redacted]		23%	Standaert et al. (2017)[114]	7	Walter 2015
Infusion site reaction	[redacted]		[redacted]		29.7%	Olanow et al. (2014)[80]	7	NICE TA720
Dizziness	[redacted]		[redacted]		[redacted]	Same as foslevodopa-foscarbidopa	28	Assumption
Hallucination	[redacted]		[redacted]		8.3%	Nyholm et al. (2005)[115]	28	Assumption
Depression	[redacted]		[redacted]		10.8%	Olanow et al. (2014)[80]	28	Assumption
Anxiety	[redacted]		[redacted]		0.1%	Nyholm et al. (2005)[115]	28	Assumption
Nausea	[redacted]		[redacted]		29.7%	Olanow et al. (2014)[80]	28	Assumption
Falls (hospitalisation)	[redacted]		[redacted]		10.8%	Olanow et al. (2014)[80]	42	Assumption based on an average of six weeks in a cast
Diarrhoea	[redacted]		[redacted]		[redacted]	Same as foslevodopa-foscarbidopa	15	NICE TA581

Dyskinesia	[redacted]		[redacted]		7.0%	Walter and Odin (2015)[104]	28	Assumption

Abbreviations: AE: adverse event: BMT: best medical therapy; CSR: clinical study report; LCIG: levodopa-carbidopa intestinal gel.

Recurring AEs relating to the need to replace and or reposition the infusion set used to administer LCIG were included in the model. The incidence of these AEs is shown in Table 57, and were applied on a per-cycle basis in the model, based on published data.[60, 112]

Table 57: Incidence of recurring AEs for LCIG

AE	Proportion Cycle 1	Proportion Cycle 2	Proportion Cycle 3	Proportion Cycle 4+	Source
Replace/reposition tube with surgery	6.57%	6.57%	12.70%	11.89%	Fernandez et al. (2015),[112] Fernandez et al. (2018)[60]
Replace/reposition tube without surgery	7.47%	7.47%	14.39%	16.35%	Fernandez et al. (2015),[112] Fernandez et al. (2018)[60]

Abbreviations: AE: adverse event; LCIG: levodopa-carbidopa intestinal gel.

B.3.3.8 Discontinuation

Foslevodopa-foscarbidopa

Discontinuation rates for foslevodopa-foscarbidopa are derived from Sample 2 of the M15-741 trial. As described in Section B.2.4.1.1, a number of patients in M15-741 discontinued prematurely, which was attributed to difficulties using the drug delivery system and to infusion site skin AEs. Following steps taken to mitigate these issues (effective on the 8th July 2020), including introducing a new infusion set that is now the only intended commercial infusion set for delivery of foslevodopa-foscarbidopa, a much lower number of discontinuations was observed (see Section B.2.3.1.3). Given that this new delivery system is reflective of that which would be used in UK clinical practice, the cohort of patients using this delivery system in the M15-741 trial (Sample 2) was considered the most appropriate source to model treatment discontinuation in the base case. This choice has been validated by a clinical expert who confirmed that the data for Sample 2 was the most appropriate source. Data from M15-741 are used for Months 0–12, with a standard rate of [redacted]% applied from Month 12 onwards.

Given the uncertainty associated with using the smaller cohort size, a number of scenario analyses were explored, using different sources of data for transparency purposes. The discontinuation rates for foslevodopa-foscarbidopa, derived from these different data sources (including using discontinuation data from M15-736) for the base case and scenarios, are shown in Table 58.

As discussed in Section B.2.8, discontinuation rates were high across both pivotal clinical trials, M15-736 and M15-741, with the leading cause for discontinuation being AEs related to administration. Feedback received as part of an advisory board conducted as part of this submission indicated that high initial discontinuation rates would typically be expected for treatments administered by continuous infusion, something also seen in clinical trials for CSAI.[61, 83] Therefore, in these scenarios, discontinuation rates from M15-741 were additionally supplemented for the economic model with longer-term data from the ongoing M15-737 trial to account for the easing of discontinuations beyond the initial use of foslevodopa-foscarbidopa. Discontinuation rates and reasons for discontinuation in the ongoing open-label extension trial M15-737 are presented in Appendix M.5.

Table 58. Discontinuation rates for foslevodopa-foscarbidopa from clinical trials

Time	M15-741 sample 2 (base case)[a]	M15-741 and M15-737 sample 1 (scenario)[b]	M15-736, M15-741 and M15-737 (scenario)[c]	M15-741 and M15-737 full cohort (scenario)[d]
0–3 months	[redacted]	[redacted]	[redacted]	[redacted]
3–6 months	[redacted]	[redacted]	[redacted]	[redacted]
6–12 months	[redacted]	[redacted]	[redacted]	[redacted]
12–18 months	[redacted]	[redacted]	[redacted]	[redacted]
18–24 months	[redacted]	[redacted]	[redacted]	[redacted]
24 + months	[redacted]	[redacted]	[redacted]	[redacted]

[a]0–12 months: M15-741 sample 2; 12+ months: standard rate.
[b]0–12 months: M15-741 sample 1; 12–24 months: M15-737 sample 1; 24+ months: standard rate.
[c]0–3 months: M15-736; 3–12 months: M15-741; 12–24 months: M15-737; 24+ months: standard rate.
[d]0-12 months: M15-741; 12–24 months: M15-737; 24+ months: standard rate.

Comparators

Discontinuation rates for LCIG are shown in Table 59. Base case discontinuation rates are based on published data by Nyholm et al.[116]

It is acknowledged that patients cannot strictly discontinue BMT in UK clinical practice, as patients will remain on some form of therapy despite their symptoms being inadequately controlled as opposed to receiving no treatment. Therefore, no discontinuation rate was applied to BMT.

Table 59. Discontinuation rates for LCIG

Time	LCIG
0–3 months	2.0%
3–6 months	1.0%
6–12 months	2.1%
12–18 months	2.1%
18–24 months	4.3%
24+ months	3.5%

Abbreviations: LCIG: levodopa-carbidopa intestinal gel.

After discontinuing treatment, patients remain in the model. They move to a separate 'off-treatment cohort' in the subsequent cycle and are assumed to receive BMT, which means that BMT's treatment effect, costs and utilities are applied to these patients. Discontinued patients cannot re-initiate active treatment.

B.3.3.9 Mortality

Mortality was accounted for in the model by applying a mortality rate ratio of 2.51 to general population mortality estimated from the 2018–2020 UK life tables published by the Office for

National Statistics (ONS).[117] The mortality rate ratio of 2.51 was derived from the study by Okunoye et al,[118] assuming an average of seven years following PD diagnosis.

The SLR did not identify any literature that reported mortality rates in PD based on 'OFF' time. As no such study was identified in the review, the Okunoye et al. study, which explores how mortality rates change over time using a large UK cohort of patients with PD and non-PD patients as controls was utilised instead. The study was selected as it was the most recent UK based study with a large sample size. The mortality ratio selected was based on the estimate for seven years following PD diagnosis, as this corresponds to the value identified in the clinical SLR where the mean/median duration of PD starts at seven years. This mortality rate was applied to all non-death health states in the model, due to the lack of evidence for one hour-based 'OFF' time mortality.

A scenario analysis was conducted in which no disease-specific mortality rate was applied, the results of which are shown in Section B.3.11.3.

B.3.4 *Measurement and valuation of health effects*

As outlined in Section B.3.2.2, the model includes 17 health states, based on the number of daily 'OFF' hours patients experience, ranging from 0 to 16 hours in one-hour increments, as well as one absorbing 'Death' state. Each distinct 'OFF' health state is associated with a specific utility value, derived from EQ-5D data collected in clinical trials evaluating foslevodopa-foscarbidopa. Each utility value was considered to be independent of treatment received.

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

EQ-5D-3L utility weights applied to the 17 PD states (OFF 0 to OFF 16) in the model were estimated by fitting linear mixed models to EQ-5D values from a combined dataset of foslevodopa-foscarbidopa studies: M15-736, M20-098, M15-741, and M15-737. EQ-5D-5L data collected in the trials were mapped to EQ-5D-3L based on the algorithm and English value set developed by Hernandez et al.,[119, 120] in line with the latest recommendations from the NICE DSU.[121]

In these trials, utility information was collected repeatedly over time for the same patients and hence observations are correlated between time points, resulting in non-independence of the data. Linear mixed models are able to account for the repeated nature of the utility data and are frequently used to analyse utility data from clinical trials.[122] Combining the EQ-5D data from all four studies allowed an increase in the sample size for more severe PD health states, which in turn improved the precision of the utility estimations for these health states. Further details of the linear mixed models used to estimate utility weights are provided in Appendix O.

The utility values for each model health state are shown in Table 60.

Table 60: Utility values based on a linear mixed model regression used in the model base case

Health state	Utility value (SE*)
OFF 0	[redacted]
OFF 1	[redacted]

OFF2	[redacted]
OFF 3	[redacted]
OFF 4	[redacted]
OFF 5	[redacted]
OFF 6	[redacted]
OFF 7	[redacted]
OFF 8	[redacted]
OFF 9	[redacted]
OFF 10	[redacted]
OFF 11	[redacted]
OFF 12	[redacted]
OFF 13	[redacted]
OFF 14	[redacted]
OFF 15	[redacted]
OFF 16	[redacted]
Dead	[redacted]

*In the absence of an observed SE, an estimate of ±20% of the mean is utilised in the model.
Abbreviations: SE: standard error.

In addition, the health state utilities in the model are adjusted for age, using population norms from Janssen et al. (Table 61).[123] This is included by multiplying the utility per cycle by the relative age-related utility adjustment based on the mean age of the M15-736 full trial population in that cycle, as per the NICE methods guide.[98]

Table 61: Age-specific UK population norms for EQ-5D-3L

Age	UK population norm
55–64	0.81
65–74	0.773
75+	0.703

Abbreviations: EQ-5D-3L: EuroQol 5-Dimension 3-Level Questionnaire; UK: United Kingdom.
Source: Janssen et al.[123]

B.3.4.2 Health-related quality-of-life studies

Details of the economic SLR conducted are presented in Section B.3.1. The SLR identified only one relevant study reporting utility values in patients with advanced PD.[124] This study reported predicted utility values by 'Off' category and H&Y stage among idiopathic PD patients in Sweden identified using the National Parkinson's Disease Patient Registry, retrieved in April 2020. As outlined in Section B.3.2.2, the model does not consider H&Y states, therefore the utility values associated with this study were not deemed suitable for use in the model developed as part of this submission. Details of the study's reported utility values are given in Appendix H.5.

B.3.4.3 Adverse reactions

For all AEs included in the model (see Section B.3.3.7, Table 56 and Table 57), disutilities were incurred for the duration over which the AE was experienced by patients. An overview of disutilities modelled for each AE is provided in Table 62. Disaggregated results of the economic model, including the impact of AEs on the total costs and QALYs, are presented in Appendix J.

Table 62: Disutilities and durations assumed for AEs

AE	Utility for the duration of the AE	Source	Duration (days)	Source	QALY Loss[a]
Infusion site erythema	−0.03	TA720[125]	7	TA720[125]	−0.001
Infusion site nodule	−0.03	Same as erythema	28	Assumption	−0.002
Infusion site cellulitis	−0.03	Same as erythema	28	Assumption	−0.002
Infusion site pain	−0.18	Walter et al. (2015)[104]	7	Walter et al. (2015)[104]	−0.003
Infusion site reaction	−0.03	TA720[125]	7	TA720[125]	−0.001
Dizziness	−0.03	Doyle et al. (2011)[126]	28	Assumption	−0.002
Hallucination	−0.01	Assumption	28	Assumption	−0.001
Depression	−0.12	Walter et al. (2015)[104]	28	Assumption	−0.009
Anxiety	−0.07	Roberts et al. (2014)[127]	28	Assumption	−0.005
Nausea	−0.14	TA720[125]	28	Assumption	−0.010
Falls (hospitalisation)	−0.16	Mean of hip, vertebral and wrist fracture; Borgstrom et al. (2006)[128]	42	Assumption based on an average of 6 weeks in a cast	−0.018
Diarrhea	−0.14	TA316[129]	15	TA581[130]	−0.006
Dyskinesia	−0.076	Graham et al. (2014)[131]	28	Assumption	−0.016
Replace/reposition tube with surgery	−0.25	NG71[108]	2	NG71[108]	−0.0014

Replace/repositi on tube without surgery	−0.25	NG71[108]	1	NG71[108]	−0.0007

[a]Calculated by multiplying the disutility of the AE by the duration in years. For example, for infusion site erythema, it is calculated as 0.03*7/365.25.
Abbreviations: AE: adverse event; QALY: quality-adjusted life year.

B.3.4.4 Carer quality of life

Advanced PD imposes a significant burden upon the patient's caregiver. Mental health aspects of the caregiver's quality of life are known to be especially affected by the disease severity of the patient with advanced PD for whom they care for.[132] Therefore, the model includes the functionality to incorporate the disutility associated with non-professional caregivers, the inclusion of which was explored as part of a scenario analysis presented in 0. This analysis was performed in two steps:

- Estimating health state specific proportion of patients with a non-professional caregiver
- Estimating the health state specific utility decrements for non-professional caregivers

For step 1, a probit model and a logit model were fitted. These models use non-linear functions to model the conditional probability function of a binary dependent variable. Hence, they are useful to predict the fraction of the population with a non-professional caregiver, as having a non-professional caregiver is a binary outcome, and the estimated probability should be between 0 and 1. Based on statistical fit, the logit model was selected. Estimated coefficients are presented in Appendix O. For step 2, a linear mixed effect model was fitted. Estimated coefficients are presented in Appendix O.

To maximise the data that could be used for these analyses, Adelphi 2010, 2012, and 2017–2019 data were used, including patients from EU5, US and Japan. Data from each of these countries were used to maximise the same size available, with all utilities converted with UK tariffs.[21]

The estimated health state specific probability of having a non-professional caregiver and the utility decrement of non-professional caregivers are presented in Table 63. The probability was multiplied by the utility decrement to estimate the total impact on health state disutilities.

Table 63: Non-professional caregiver disutilities

Health state	Probability of having a non-professional caregiver	Utility decrement for non-professional caregivers	Total impact on health state disutilities
OFF 0	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]	[redacted]
OFF2	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]	[redacted]

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

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

A summary of the utility values used in the base case analysis is provided in Table 64; caregiver disutilities are not presented as these are considered in a scenario only. These show a clear decrease in patient utility as daily 'OFF' time increases, indicating the substantial impact decreasing daily symptom control has on patients' QoL.

Table 64: Summary of utility values used in the base case cost-effectiveness analysis

State	Utility value: mean (standard error)	95% CI	Reference in submission (section and page number)	Justification
Health state utilities				
OFF 0	[redacted]	[redacted]	Section B.3.4.1, page 115	'Off' time is a clinically relevant outcome, representing an important clinical objective for PD treatments. Modelling 'Off'', allowed patients' experience of their disease to be reflected within the model, with suitable data sources identified in the secondary research looking at all existing PD models. A net
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]		decrease in quality of life is expected with worsening 'OFF' time, as patients' control of symptoms worsen.
OFF 15	[redacted]	[redacted]		
OFF 16	[redacted]	[redacted]		
AE disutilities				
Infusion site erythema	[redacted]	[redacted]	Section B.3.4.3, page 117	Common adverse events associated with PD medication. Based on previously published literature[108, 125-129, 131, 133]
Infusion site nodule	[redacted]	[redacted]		
Infusion site cellulitis	[redacted]	[redacted]		
Infusion site pain	[redacted]	[redacted]		
Infusion site reaction	[redacted]	[redacted]		
Dizziness	[redacted]	[redacted]		
Hallucination	[redacted]	[redacted]		
Depression	[redacted]	[redacted]		
Anxiety	[redacted]	[redacted]		
Nausea	[redacted]	[redacted]		
Falls (hospitalisation)	[redacted]	[redacted]		
Diarrhoea	[redacted]	[redacted]		
Dyskinesia	[redacted]	[redacted]		
Replace/reposition tube with surgery	[redacted]	[redacted]		
Replace/reposition tube without surgery	[redacted]	[redacted]		

Abbreviations: AE: adverse event; CI: confidence interval; PD: Parkinson's disease.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

B.3.5.1 Intervention and comparators' costs and resource use

Acquisition costs

The drug acquisition costs for foslevodopa-foscarbidopa and LCIG are shown in Table 65, and the costs for BMT are shown in Table 66. The costs were based on the BNF 2022. The proportion were based on real-world data from 700 patients on BMT in the Adelphi 2017–2019 data. Also the fraction of patients receiving each individual medication as part of BMT and the average dose were based on Adelphi 2017–2019 data.

Treatment costs

Table 65: Drug acquisition costs for foslevodopa-foscarbidopa and Duodopa

Drug	Costs per package (£)	Units per package	List price per unit (£)	Net price per unit (£)	Source
Foslevodopa-foscarbidopa	592.90	7	84.70	[redacted]	AbbVie
LCIG	539.00	7	77.00	[redacted]	BNF 2022; AbbVie

[a]Includes the PAS for foslevodopa-foscarbidopa.
[b][redacted].
Abbreviations: BNF: British National Formulary; LCIG: levodopa-carbidopa intestinal gel; NHS: National Health Service.

Table 66: Drug acquisition costs for BMT

Drug	Dose/strength (mg)	Units per package	Cost per package (£)[a]	Proportion of patients[b]	Dose (mg)
Amantadine	10	150	140.00	9.00%	336.51
Apomorphine rescue (i.e injection)	30	5	123.91	1.29%	66.64
CR Levodopa + carbidopa (e.g sinemet CR)	250	100	11.60	18.57%	402.74
Entacapone	200	30	5.05	6.00%	761.90
Numient (modified release Levodopa + carbidopa)	50	150	11.60	0.29%	1306.25
IR Levodopa + carbidopa (e.g sinemet)	110	100	7.30	64.00%	605.81
Opicapone (Ogentys)	50	30	93.90	0.29%	50.00
Pramipexole (once daily)	1.05	30	51.98	4.29%	1.94
Pramipexole (standard form)	0.7	30	1.69	3.71%	2.57
Rasagiline	1	28	2.55	17.29%	1.02
Ropinirole (once daily)	8	28	18.94	12.71%	11.61
Ropinirole (standard form)	2	28	5.64	5.86%	14.76
Rotigotine	8	28	149.93	10.86%	7.13
Safinamide	100	30	69.00	0.29%	75.00
Selegiline	10	100	32.23	2.29%	8.05

[a]CSAI was not included as a separate comparator, but considered an adjunctive therapy for BMT.
Abbreviations: BMT: best medical therapy; BNF: British National Formulary; CR: controlled release; CSAI: continuous subcutaneous apomorphine infusion; IR: immediate release; LCIG: levodopa-carbidopa intestinal gel.
Source: [a]BNF 2022. [b]Adelphi 2017-2019.

Wastage

Wastage is not modelled as part of the base case analysis, however is accounted for in scenario analyses presented as part of this submission. Both scenarios account for wastage by applying a percentage (5% and 10%) of wastage of vials for LCIG, due to unused (i.e., non-administered) medication. This wastage is applied only to LCIG as infusion needs to be stopped overnight, in comparison with foslevodopa-foscarbidopa which is a 24-hour continuous infusion. The results of each scenario analysis shown in Section B.3.11.3.

The total drug acquisition costs per three months (excluding wastage) for the intervention and comparators are shown in Table 67.

Table 67: Summary of drug costs per patient per three months

Drug	Costs per three months, list price (£)
Foslevodopa-foscarbidopa	7,734.17
BMT	428.26
LCIG	7,031.06

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel.

Adjunctive therapies

Adjunctive therapies for patients receiving LCIG are considered in the cost-effectiveness analysis. The costs of the different adjunctive therapies are presented in Table 66, with the frequencies and dosing presented in Table 68. These are based on 2017–2019 Adelphi data. As no data were available for patients receiving foslevodopa-foscarbidopa in real-world practice, frequencies and doses were assumed to be the same as those of LCIG. Of note, the sample size from which these frequencies and doses were estimated was small, based on only six patients. Therefore, these estimates are associated with a degree of uncertainty.

Table 68: Frequencies and dosing of adjunctive therapies with LCIG

Drug	Proportion of patients	Dose (mg)
Amantadine	[redacted]	[redacted]
CR Levodopa + carbidopa (e.g sinemet CR)	[redacted]	[redacted]
IR Levodopa + carbidopa (e.g sinemet)	[redacted]	[redacted]
Rasagiline	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]

[a]CSAI is not included as a comparator, but considered an add-on therapy for BMT.
Abbreviations: CR: controlled release; IR: immediate release. LCIG: levodopa-carbidopa intestinal gel.
Source: Adelphi 2017–2019

The total costs for adjunctive treatment per three months for LCIG is therefore calculated as £[redacted].

Administration costs

Costs associated with the administration of treatment during the initial treatment phase are shown in Table 69. The treatment-specific quantities and proportion of patients to which these administration costs apply are shown in Table 70. These numbers are based on the NICE

guideline [NG71],[108] trial data from M15-741,[62] and the cost-effectiveness study by Chaudhuri et al.[101] These are included as one-off costs at the start of the first model cycle.

Table 69: Treatment administration costs

Component	Unit cost (£)	Source
NG tube insertion (hospital day)	1,463.90	NHS National Cost Collection data DRG code FF05Z, [134]
PEG tube insertion (inpatient day)	1,115.83	NHS National Cost Collection data DRG code FE12A, [134]
Titration and monitoring (1 visit)	726.60	Chaudhuri et al.,[101] inflated to 2021 costs

Abbreviations: NG: nasogastric; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; PEG: percutaneous endoscopic gastrostomy.

Table 70: Treatment-specific quantities and proportion of patients to which treatment administration cost apply

Drug	Quantity		Proportion of patients (%)	
	Foslevodopa-foscarbidopa	LCIG	Foslevodopa-foscarbidopa	LCIG
NG tube insertion (hospital day)	N/A	1	N/A	80
PEG tube insertion (inpatient day)	N/A	1	N/A	100
Titration and monitoring (1 visit)	[redacted]	5	[redacted]	100
Source	NG171[108]/ M15-741[62, a]	Chaudhuri et al.[101]	NG171[108]/ M15-741[62, a]	Chaudhuri et al.[101]

[a]Two sources are provided. The first source is for the number of overnight hospital stay, the second source is for titration and monitoring.
Abbreviations: LCIG: levodopa-carbidopa intestinal gel; N/A: not applicable; NG: nasogastric; PEG: percutaneous endoscopic gastrostomy.

The total administration costs for all treatments are specified in Table 71.

Table 71: Total one-off cost of treatment administration during the initial treatment phase

Drug	Costs (£)
Foslevodopa-foscarbidopa	[redacted]
BMT	N/A
LCIG	5,959.94

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; N/A: not applicable.

B.3.5.2 Health-state unit costs and resource use

Management costs

The model includes costs related to treatment management, applied per treatment cycle, using NHS reference costs 2019–2020.[134] The unit cost of the different components of treatment management are shown in Table 72. The frequencies of treatment management usage are shown in Table 73. These frequency estimates were sourced from the NICE guideline [NG71],[108] shared care guidelines from the Wirral University Teaching Hospital, [135] and a previous cost-effectiveness study by Chaudhuri et al.[101]

Table 72: Costs used for the different treatment management components.

Component	Unit cost (£)	Source
Full blood count	2.53	NHS National Cost Collection data, code DAPS05,[134]
Coombs test	2.53	Same as full blood count
Liver function tests	6.00	NHS National Cost Collection data, code DAPS04, 5 tests,[134]
Consultant led follow-up visit	187.17	NHS National Cost Collection data, Consultant led WF01A,[134]
Non-Consultant led follow-up visit	147.08	NHS National Cost Collection data, Non-consultant led WF01A,[134]
PEG tube removal	718.09	NHS National Cost Collection data, code FE12A,[134]

Abbreviations: NHS: National Health Service; PEG: percutaneous endoscopic gastrostomy.

Table 73: Frequencies of treatment management usage

	Foslevodopa-foscarbidopa			BMT			LCIG		
	Year 1	Year 2+	Source	Year 1	Year 2+	Source	Year 1	Year 2+	Source
Full blood count	2	2	Wirral University Teaching Hospital NHS[135]	2	2	Assumption	2	2	Wirral University Teaching Hospital NHS[135]
Coombs test	2	2	Wirral University Teaching Hospital NHS[135]	2	2	Assumption	2	2	Wirral University Teaching Hospital NHS[135]
Liver function tests	2	2	Wirral University Teaching Hospital NHS[135]	2	2	Assumption	2	2	Wirral University Teaching Hospital NHS[135]
Consultant led follow-up visit	5	1	Chaudhuri et al. (2022)[101]	5	1	Chaudhuri et al. (2022)[101]	5	1	Chaudhuri et al. (2022)[101]
Non-Consultant led follow-up visit	1	1	Chaudhuri et al. (2022)[101]	1	1	Chaudhuri et al. (2022)[101]	1	1	Chaudhuri et al. (2022)[101]
PEG tube removal	N/A			N/A			Depending on treatment discontinuation: it is assumed that all patients who discontinue LCIG will have their PEG tube removed. For example, in Cycle 1, the discontinuation rate is 2%, therefore 2% of patients will have their PEG tube removed. See Table 59 for the full LCIG discontinuation rates.		

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; N/A: not applicable; NHS: National Health Service; PEG: percutaneous endoscopic gastrostomy.

Table 74: Total management costs

Drug	Year 1: Costs per three months (£)	Year 2+: Costs per three months (£)
Foslevodopa-foscarbidopa	276.27	89.10
BMT	276.27	89.10
LCIG	276.27	89.10

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel.

Health state related costs

The model also accounts for costs associated with health care resource utilisation. The health care resource utilisation depends on the 'OFF' state. Unit costs are shown in Table 75.

Table 75: Unit cost of health care resource utilisation.

Unit[a]	Unit cost (£)	Source
Hospitalisation	3,197.80	NHS National Cost Collection data [134], weighted average based on attendances: AA25C, AA25D, AA25E, AA25F, AA25G
A&E	205.90	NHS National Cost Collection data [134], weighted average based on attendances: VB01Z, VB02Z, VB03Z, VB04Z, VB05Z, VB06Z, VB07Z, VB08Z, VB09Z
GP	39	Unit Costs of Health & Social Care 2020 [136], per surgery consultation (9.22 minutes)
Consultant	59.50	Unit Costs of Health & Social Care 2020 [136], assuming half an hour consultation
PD nurse	44.50	Unit Costs of Health & Social Care 2020 [136], assuming half an hour consultation
Scan	390.23	NHS National Cost Collection data [134], weighted average based on scans in the 2017-2019 Adelphi data: MRI: RD01A, RD02A, RD03Z CT: RD20A, RD21A, RD22Z SPECT: RN08A fMRI: RD07Z DaT: RN11Z PET: RN07A
Respite care	4579.78	NHS National Cost Collection data [134], weighted average based on length of stay in 2017-2019 Adelphi data: WH20A, WH20B, WH20C
Professional care, per hour	12.72	Unit Costs of Health & Social Care 2020 [136], weighted average based on hours of professional care in 2017-2019 Adelphi data: Nursing home staff, Physiotherapist, Social worker and Home help

[a]Units are per visit, unless otherwise specified
Abbreviations: A&E: accident and emergency; CT: computerised tomography; fMRI: functional magnetic resonance imaging; GP: general practitioner; MRI: magnetic resonance imaging; NHS: National Health Service; PET: positron emission tomography; PD: Parkinson's disease; single photon emission computed tomography.

To estimate health state specific resource utilisation, regression models were fitted to Adelphi 2017–2019 data.[21] As some of the scans [e.g. SPECT, fMRI, DaT] had very low patients numbers, all scans were grouped for the regression, in which the total number of scans was estimated. To derive the cost per scan, a weighted average of the different types of scans was applied (Table 75). By this approach, the type of scans received by PD patients is assumed to be independent of disease severity. Likewise, some types of professional care (physiotherapist, social worker) were rarely provided to PD patients. Therefore, all hours of professional care were summed, and regression models were fitted to the total hours of professional care. To derive the cost per hour of professional care, a weighted average was calculated based on the number of hours patients received every type of professional care (Table 75). This implicitly assumes that the amount of professional care PD patients receive is dependent on disease severity, but the type of professional care is not. Whilst there are some limitations with this calculation approach, this was the only appropriate method given the low patient numbers for several scans and types of professional health care provider.

For all units (Hospitalisation, A&E etc.), except for consultations, analyses were performed in two steps:

- Estimating health state specific proportion of patients using that resource unit
- Among users, estimating the number of health care visits or hours

The first step was not used to estimate the number of consultations, as the number of patients with no consultations was very small. Therefore, the health state specific number of consultations was estimated in a single step.

For step 1, binary probit models and binary logit models were fitted (see Appendix P). Based on statistical fit, the probit model was selected for all units. Estimated coefficients are presented in Appendix P. The resulting estimates of the health state specific proportion of patients using that unit are provided in Table 76, Table 77, and Table 78.

For step 2, generalised linear models were fitted with an identity link. Models assuming a log link were also explored, but resulted in unrealistic cost estimates, especially for the health states with a high number of 'OFF' hours. For health care units in which the number of visits was estimated (hospitalisation, A&E, GP, PD nurse, scan, respite care), Poisson and negative binomial models were fitted, of which the Poisson models provided the best statistical fit (Appendix P). For others (consultations, hours of professional care), normal, gamma, Poisson, inverse Gaussian, and negative binomial models were fitted, of which the inverse Gaussian provided the best statistical fit (Appendix P). Estimated coefficients are presented in Appendix P. The resulting health state specific estimates of the number of visits/hours are presented in Table 76, Table 77, and Table 78.

Table 76: Health state specific resource utilisation: A&E, GP and Respite care

Health state	A&E		GP		Respite care	
	Fraction with usage (%)	Number of visits/hours when using	Fraction with usage (%)	Number of visits/hours when using	Fraction with usage (%)	Number of visits/hours when using
OFF 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OFF 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A&E: accident and emergency; GP: general practitioner.

Table 77: Health state specific resource utilisation: Hospitalisation, Scan and PD nurse

Health state	Hospitalisation		Scan		PD nurse	
	Fraction with usage (%)	Number of visits when using	Fraction with usage (%)	Number of visits when using	Fraction with usage (%)	Number of visits when using
OFF 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Abbreviations: PD: Parkinson's disease.

Table 78: Health state specific resource utilisation: Professional care and Consultation

Health state	Professional care (hours per week)		Consultation	
	Fraction with usage (%)	Number of hours when using	Fraction with usage (%)	Number of visits when using
OFF 0	[redacted]	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]	[redacted]	[redacted]
OFF2	[redacted]	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]	[redacted]	[redacted]
OFF 8	[redacted]	[redacted]	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]	[redacted]	[redacted]
OFF 11	[redacted]	[redacted]	[redacted]	[redacted]
OFF 12	[redacted]	[redacted]	[redacted]	[redacted]
OFF 13	[redacted]	[redacted]	[redacted]	[redacted]
OFF 14	[redacted]	[redacted]	[redacted]	[redacted]
OFF 15	[redacted]	[redacted]	[redacted]	[redacted]
OFF 16	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: N/A: not applicable.

Multiplying the results from step 1 with the results from step 2 (Table 76, Table 77, and Table 78) and the unit specific cost (Table 75) results in the total health state specific costs for health care resource utilisation (Table 79). Total health state specific health care resource utilisation costs different substantially between the different health states, ranging from £3,519 for OFF 0 to £101,819 for OFF 16.

Table 79: Total health state specific costs included in the model

Health state	Total yearly costs (£)
OFF 0	3,518.55
OFF 1	6,316.85
OFF2	10,540.89
OFF 3	16,292.02
OFF 4	23,382.50
OFF 5	31,350.12
OFF 6	39,595.97
OFF 7	47,581.66
OFF 8	54,983.69
OFF 9	61,734.50
OFF 10	67,954.70
OFF 11	73,837.48
OFF 12	79,551.89
OFF 13	85,197.27
OFF 14	90,803.64
OFF 15	96,355.57
OFF 16	101,818.88

B.3.5.3 Adverse reaction unit costs and resource use

Table 80: Costs assumed for AEs

AE	Costs per episode (£)	Source
Infusion site erythema	119.40	TA720[125]
Infusion site nodule	4.93	BNF – Hydrocortisone butyrate
Infusion site cellulitis	1.37	BNF – Amoxicillin
Infusion site pain	2.78	BNF – Paracetamol
Infusion site reaction	119.40	TA720[125]
Dizziness	147.50	CG173[137]
Hallucination	148.99	BNF (1.49) + 2 GP visits [137]
Depression	52.60	TA226[138]
Anxiety	52.60	Same as depression

Nausea	154.70	CG173[137]
Falls (hospitalisation)	791.70	Fundament et al. (2016)[139]
Diarrhea	1.77	BNF – Lopermide
Dyskinesia	28.00	Pack of amantadine: £140. 140/150(number of pills)*30(duration of AE)
Replace/reposition tube with surgery	1,095.65	NHS National Cost Collection data DRG code FE12A – Non-elective short stay,[108, 134]
Replace/reposition tube without surgery	738.24	NHS National Cost Collection data, weighted average of DRG codes AA25C-G – Non-elective short stay,[108, 134]

Abbreviations: AE: adverse events; BNF: British National Formulary; NHS: National Health Service.

B.3.5.4 Miscellaneous unit costs and resource use

No further costs were included as part of this submission's cost-effectiveness analysis.

B.3.6 *Severity*

Use of a severity modifier is not applicable for foslevodopa-foscarbidopa,

Whilst foslevodopa-foscarbidopa does not meet the criteria for the severity modifier, advanced PD has a substantial impact on patients' ability to perform everyday tasks, their mental wellbeing and general quality of life, as has been described throughout this submission. Current treatment is primarily aimed at controlling symptoms, with no curative or disease-modifying medicines existing, and the symptoms associated with advanced PD have a great burden on patients (as discussed in Section B.1.3.1). A study comparing QoL between patients with PD and healthy controls found QoL to be significantly poorer overall and in most domains, especially in physical function and mental health.[15] Basic tasks such as walking or handling objects become increasingly difficult as symptoms worsen with disease progression. On top of physical severity, psychological symptoms such as depression and anxiety have significant impacts on patients' mental health.[32] The burden of PD extends beyond patients to carers also; carers experience lower QoL than the general population, high rates of depression, social isolation, and loneliness.[17, 41]

As detailed further in Section B.3.13, aspects of PD most relevant to patients may not be adequately captured in the modelling of the disease, meaning the true severity of the disease may not be captured in the QALY shortfall calculations which now determine NICE's newly introduced definition of severity.

B.3.7 *Uncertainty*

There are a number of factors inherent to the condition of interest, advanced PD, which necessitated a number of assumptions to be made, introducing uncertainty in the cost-effectiveness carried out.

Advanced PD is a highly heterogenous disease, with no clearly established definition of advanced PD; lack of adequate symptom control can look different from patient to patient and relies on clinician and patient judgement. Symptoms can also vary widely from patient-to-patient

and from day-to-day. This presents a number of challenges with regards to modelling a clearly defined patient population, and choosing appropriate outcomes to model treatment effect and disease progression.

The cost-effectiveness analysis was further limited by the limited availability of literature in advanced PD, with few data sources available to explore uncertainty associated with the choice of data source for a number of inputs.

The complexity of the model and the lack of precedent in terms of previously accepted models should be taken into account. The model presented is a *de-novo* design that attempts to explain and capture the relevant components of PD. In order to navigate the above challenges, assumptions and decisions made as part of this submission's cost-effectiveness analysis have been validated by clinical experts in order to ensure they appropriately model the condition, and have been tested by a number of scenario analyses in order to alleviate uncertainty surrounding them.

However, it is important to note that foslevodopa-foscarbidopa represents the first PD treatment to be assessed by NICE's technology assessment process. This means that precedents in the modelling of PD are yet to be established, unlike many other disease areas evaluated by NICE. This additionally means that the comparator treatments for foslevodopa-foscarbidopa have not been evaluated by the same rigorous methods in England (note that LCIG has gone through technology assessment in Scotland).[140]

B.3.8 *Managed access proposal*

A managed access proposal is not applicable for foslevodopa-foscarbidopa.

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

Table 81 provides a summary of the base case cost-effectiveness analysis inputs, and how the uncertainty associated with these has been explored as part of sensitivity analyses.

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results are robust to those variations. A Monte-Carlo simulation with 1,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions.

Where a standard error or CI was not available for a selected parameter, variation of 20% of the mean was applied.

Table 81: Summary of base-case analysis inputs

Variable	Inputs	Measurement of uncertainty and distribution	Cross-reference
Model settings			
Cycle length	Cycles 1–2: 3 months;	Fixed	

	Cycles 3+: 6 months		Section B.3.2.2
Half cycle correction	Included	Fixed	
Discount rate for costs and benefits, %	3.5	Fixed	
Time horizon	Lifetime (20 years)	Scenario analyses: 10, 15, 30 years	
Perspective	NHS and PSS	Fixed	
Patient characteristics			
Baseline patient age, years (SD)	[redacted]	Fixed	Section B.3.3.2
Proportion female	[redacted]	Fixed	
Daily OFF time (hours)	[redacted]	Scenario analysis: 3–16	
Clinical inputs			
Within trial transitions – foslevodopa-foscarbidopa	Values based on M15-736 RCT[63]	**PSA:** Dirichlet distribution **DSA:** ±SE	Section B.3.3.4
Within trial transitions – LCIG	Values based on relative risk to foslevodopa-foscarbidopa, derived from NMA outputs	**PSA:** Dirichlet distribution **DSA:** ±SE	Section B.3.3.4
Beyond trial transitions – foslevodopa-foscarbidopa	• Months 3–33: LOCF • Months 33+: Natural disease progression, derived from Palmer et al.[113]	**PSA:** Dirichlet distribution **DSA:** ±SE **Scenario analysis:** • Months 3–24: LOCF Months 24+: Natural disease progression, derived from Palmer et al.[113]	Section B.3.3.5
Beyond trial transitions – LCIG	• Months 3–33: LOCF • Months 33+: Natural disease progression, derived from Palmer et al.[113]	**PSA:** Dirichlet distribution **DSA:** ±SE **Scenario analysis:** • Months 3–24: LOCF Months 24+: Natural disease progression, derived from Palmer et al.[113]	
Utility inputs			
OFF 0	[redacted]	**PSA:** Beta distribution **DSA:** ±SE	Section B.3.4.1
OFF 1	[redacted]		
OFF2	[redacted]		
OFF 3	[redacted]		
OFF 4	[redacted]		
OFF 5	[redacted]		
OFF 6	[redacted]		
OFF 7	[redacted]		
OFF 8	[redacted]		
OFF 9	[redacted]		

OFF 10	[redacted]		
OFF 11	[redacted]		
OFF 12	[redacted]		
OFF 13	[redacted]		
OFF 14	[redacted]		
OFF 15	[redacted]		
OFF 16	[redacted]		
AEs			
Infusion site erythema	[redacted]	**PSA:** Beta distribution **DSA:** ±SE	Section B.3.4.3
Infusion site nodule	[redacted]		
Infusion site cellulitis	[redacted]		
Infusion site pain	[redacted]		
Infusion site reaction	[redacted]		
Dizziness	[redacted]		
Hallucination	[redacted]		
Depression	[redacted]		
Anxiety	[redacted]		
Nausea	[redacted]		
Falls (hospitalisation)	[redacted]		
Diarrhoea	[redacted]		
Dyskinesia	[redacted]		
Replace/repositio n tube with surgery	[redacted]		
Replace/repositio n tube without surgery	[redacted]		
Cost inputs (£)			
Intervention and comparator acquisition costs per 3 months			Section B.3.5.1
Foslevodopa-foscarbidopa	List: 7,734.17 Net: [redacted]	Fixed	
LCIG	List: 7,031.06 Net: [redacted]		
BMT	428.26		
Administration costs (one-off)			
Foslevodopa-foscarbidopa	3,026.64	Fixed	
LCIG	5,959.94		
BMT	N/A		

Management costs	Year 1	Year 2+		
Foslevodopa-foscarbidopa	276.27	89.10	Fixed	
LCIG	276.27	89.10		
BMT	276.27	89.10		
Health state costs per cycle, mean (£)				
OFF 0	[redacted]		**PSA:** Beta distribution **DSA:** ±SE	Section B.3.5.2
OFF 1	[redacted]			
OFF2	[redacted]			
OFF 3	[redacted]			
OFF 4	[redacted]			
OFF 5	[redacted]			
OFF 6	[redacted]			
OFF 7	[redacted]			
OFF 8	[redacted]			
OFF 9	[redacted]			
OFF 10	[redacted]			
OFF 11	[redacted]			
OFF 12	[redacted]			
OFF 13	[redacted]			
OFF 14	[redacted]			
OFF 15	[redacted]			
OFF 16	[redacted]			

Abbreviations: AE: adverse event; BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; LOCF: last observation carried forward; N/A: not applicable; NHS: National Health Service; PSS: Personal Social Services; RCT: randomised controlled trial; SD: standard deviation.

B.3.9.2 Assumptions

The assumptions used in the base case analysis are described in Table 82.

Table 82: List of assumptions made in the base case cost-effectiveness analysis

Model input	Assumption and justification
Health states based on 'OFF' time	• Treatment efficacy and disease progression are modelled using health states based on increasing daily 'OFF' time • Eighteen health states were included, representing 0–16 hours of daily 'OFF' time experienced by patients, based on one-hour increments in 'OFF' time and an absorbing 'death' state • 'OFF' time was chosen as it reflects patients' experience of their disease, and the ability of treatments to adequately control motor symptoms, a highly important clinical outcome • One-hour increments in 'OFF' time were chosen in order to align with the minimal clinically meaningful reduction in 'OFF' time[64] • 'OFF' time was favoured instead of 'ON' time without troublesome dyskinesia, as clinical experts indicated that 'OFF' time is more intuitive and widely assessed in clinical practice; it is the relevant outcome clinicians treat for, and is easier for patients to report compared with 'ON' time (for example, 'ON' time without troublesome dyskinesia could potentially be confused with 'ON' time with troublesome dyskinesia)
'OFF' time distribution	• 'OFF' times of 1.5, 2.5, 3.5 etc at baseline were rounded to the nearest full 'OFF' time state at the start of the model • Later transitions can only occur for 'OFF' time rounded to a full hour
'OFF' state transitions	• During the within trial and LOCF periods, patients are able to transition from each health state to any other health state, as informed by data from the M15-736 trial • Beyond the within trial and LOCF periods, the transition probabilities change to those of natural disease progression, at which point patients can only move to more severe health states, one health state at a time • Clinical experts indicated that patients may initially experience a jump in 'OFF' time at the start of treatment as they experience a response, whilst M15-741 trial data indicate that foslevodopa-foscarbidopa efficacy is maintained in the long-term, which is captured through the use of LOCF
Comparative efficacy	• Efficacy for LCIG is informed by the NMA • As the population of relevance is those whose symptoms are not sufficiently controlled by their current therapy, it is assumed that BMT imparts no efficacy benefit. Efficacy for BMT is therefore assumed to align with natural disease progression
Treatment discontinuation	• Discontinuation from foslevodopa-foscarbidopa is informed by the M15-741 trial, sample 2 population (which utilised the new infusion set that will be used in clinical practice, see below) • A number of patients in M15-741 discontinued prematurely, which was attributed to difficulties using the drug delivery system and to infusion site skin AEs. Following steps taken to mitigate these issues (effective on the 8th July 2020),

	including the introduction of a new infusion set that is now the only intended commercial infusion set for delivery of foslevodopa-foscarbidopa, a much lower number of discontinuations was observed (see Section B.2.3.1.3). Given that this new delivery system is reflective of that which would be used in UK clinical practice, the cohort of patients using this delivery system in the M15-741 trial (sample 2) was considered the most appropriate source to model treatment discontinuation in the base case
Adverse events	• AEs are included as one-off AEs in terms of costs, whilst utility decrements applied for the duration of the event • Given the lack of data relating to certain AEs associated with LCIG, and its similar pharmacological profile to foslevodopa-foscarbidopa, the rate of two AEs (dizziness and diarrhoea) for LCIG were assumed to be equal to those of foslevodopa-foscarbidopa • Given the lack of reliable data relating to the duration of events, a number of AE durations had to be assumed • When data on duration was not available, duration for AEs was assumed to be four weeks, a period that would allow for potential hospitalisation and a recovery period afterwards
Adjunctive therapies	• As no data were available for patients receiving foslevodopa-foscarbidopa in real-world practice, an assumption was made that no adjunctive therapies would be given • Patients receiving LCIG may receive adjective treatments during the night to control symptoms while the pump is turned off, however it is assumed that as foslevodopa-foscarbidopa is administered continuously, adjunctive therapies will not be required.
Mortality	• In the base case analysis, disease specific mortality was applied, by applying a factor of 2.51 to general population mortality to each health state, derived from published literature by Okunoye et al.[118] • Whilst the precise impact of advanced PD on mortality is uncertain, it is reasonable to assume that such a severe disease would impact patients' survival outcomes • The assumption of disease-specific mortality was tested in a scenario analysis in which mortality was modelled using general population mortality, derived from data published by the ONS[117]

Abbreviations: AE: adverse events; BMT: best medical therapy; ITT: intention-to-treat; LCIG: levodopa-carbidopa intestinal gel; LOCF: last observation carried forward; NMA: network meta-analysis; ONS: Office for National Statistics; PD: Parkinson's disease; UK: United Kingdom.

B.3.10 *Base-case results*

B.3.10.1 Base-case incremental cost-effectiveness analysis results

Table 83 (list price) and Table 84 (with-PAS) present the base case pairwise and fully incremental results of the economic evaluation of foslevodopa-foscarbidopa versus comparators. Net health benefit (NHB) results at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 are presented in Table 85 (list price) and Table 86 (with-PAS).

The base-case fully incremental analysis showed foslevodopa-foscarbidopa to be the most cost-effective treatment option. The results are comparable at both list price and with-PAS:

- Foslevodopa-foscarbidopa was found to be cost-effective against LCIG, yielding a south-west (SW) quadrant ICER of £192,741 (list price) and [redacted] (with-PAS) per QALY forgone, with an NHB of 0.87 (list price) and [redacted] (with-PAS) QALYs at a WTP of £20,000 and 0.55 (list price) and [redacted] (with-PAS) QALYs at a WTP of £30,000.
- Foslevodopa-foscarbidopa dominated BMT at both list price and with-PAS, yielding NHBs of 6.58 (list price) and [redacted] (with-PAS) QALYs at a WTP of £20,000 and 4.62 (list price) and [redacted] (with-PAS) QALYs at a WTP of £30,000.

Foslevodopa-foscarbidopa incurs fewer costs compared with both BMT and LCIG. In comparison, foslevodopa-foscarbidopa yields more QALYs compared with BMT, but fewer compared with LCIG (incremental difference of 0.10 at list price, 0.10 with-PAS). Despite the non-significant, but positive point estimate from the NMA in favour of foslevodopa-foscarbidopa, this difference in QALYs is primarily driven by the higher rates of discontinuations, and patients therefore transitioning onto the less effective BMT. Higher than anticipated discontinuation rates are common across advanced PD therapies; clinical experts have indicated that high initial discontinuation rates are typical for treatments administered by continuous infusion.[61] Furthermore, after using mitigating strategies in M15-741 (see Section B.2.4.1.1), the discontinuation rates considerably dropped, which indicates a capacity in clinical practice to mitigate discontinuations. A number of key areas of value for foslevodopa-foscarbidopa are unable to be captured within the cost-effectiveness model (such as sleep/early morning benefits due to 24-hour continuous administration, and non-quantifiable benefits of the lack of need for surgery; see Section B.3.13 for further details), indicating that the QALY estimates likely underestimate the true value foslevodopa-foscarbidopa can bring to patients and the NHS relative to LCIG.

Clinical outcomes from the cost-effectiveness model, the proportion of the cohort in each health state over time (Markov trace), and the disaggregated results of the base case incremental cost-effectiveness analysis are reported in Appendix J.

Table 83: Base-case cost-effectiveness results, list price (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]	5.30 (5.09, 5.52)	-	-	-	-
LCIG	[redacted]	5.41 (5.19, 5.64)	-£19,432	-0.10	£192,741[a]	£192,741[a]
BMT	[redacted]	4.60 (4.31, 4.89)	-£117,495	0.71	Foslevodopa-foscarbidopa dominant	Foslevodopa-foscarbidopa dominant

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

Table 84: Base-case cost-effectiveness results, 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]	5.31 (5.12, 5.51)	-	-	-	-
LCIG	[redacted]	5.41 (5.18, 5.63)	[redacted]	-0.10	[redacted]	[redacted]
BMT	[redacted]	4.61 (4.31, 4.88)	[redacted]	0.70	Foslevodopa-foscarbidopa dominant	Foslevodopa-foscarbidopa dominant

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

Table 85: Net health benefit, list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB of foslevodopa-foscarbidopa	
					WTP of £20,000	WTP of £30,000
Foslevodopa-foscarbidopa	[redacted]	5.30	-	-	-	-
LCIG	[redacted]	5.41	-£19,432	-0.10	0.87	0.55
BMT	[redacted]	4.60	-£117,495	0.71	6.58	4.62

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; LYG: life years gained; NHB: net health benefit; QALY: quality-adjusted life year.

Table 86: Net health benefit, with-PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB of foslevodopa-foscarbidopa	
					WTP of £20,000	WTP of £30,000
Foslevodopa-foscarbidopa	[redacted]	5.31	-	-	-	-
LCIG	[redacted]	5.41	[redacted]	-0.10	[redacted]	[redacted]
BMT	[redacted]	4.61	[redacted]	0.70	[redacted]	[redacted]

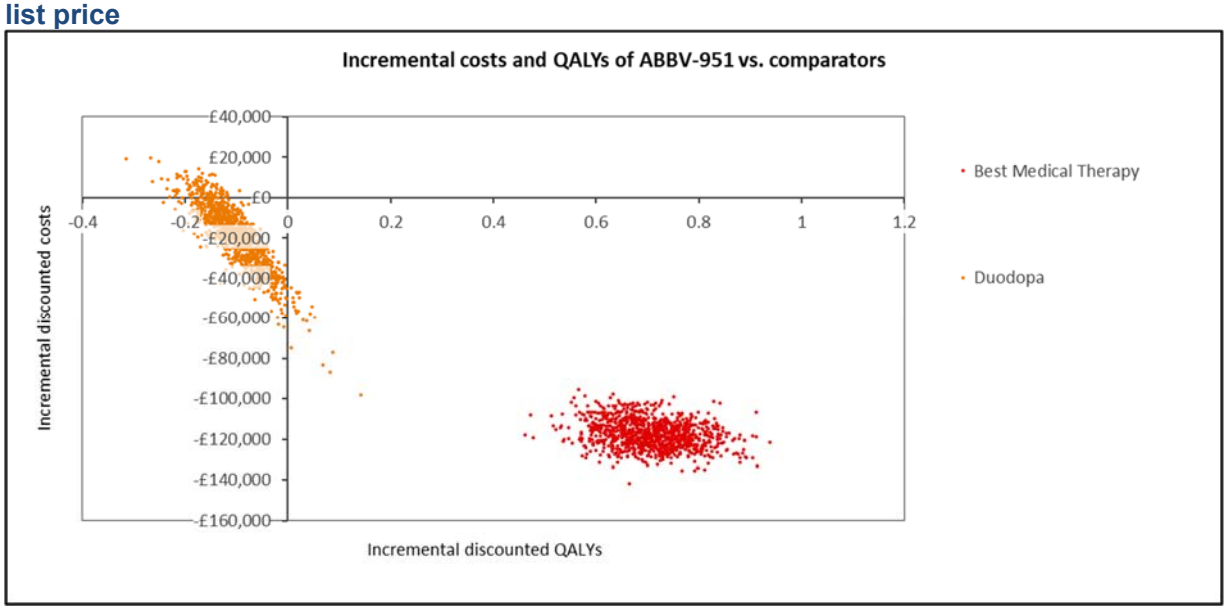
Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year.

B.3.11 *Exploring uncertainty*

B.3.11.1 Probabilistic sensitivity analysis

The cost-effectiveness planes from the PSA are presented in Figure 29 (list price) and Figure 30 (with-PAS). The cost-effectiveness acceptability curves are presented in Figure 31 (list price) and Figure 32 (with-PAS).

Figure 29: Cost-effectiveness plane for foslevodopa-foscarbidopa versus comparators, list price



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

Figure 30: Cost-effectiveness plane for foslevodopa-foscarbidopa versus comparators, with-PAS

[redacted]

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

Figure 31: Cost-effectiveness acceptability curve for foslevodopa-foscarbidopa versus comparators, list price

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

Figure 32: Cost-effectiveness acceptability curve for foslevodopa-foscarbidopa versus comparators, with-PAS

[redacted]

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

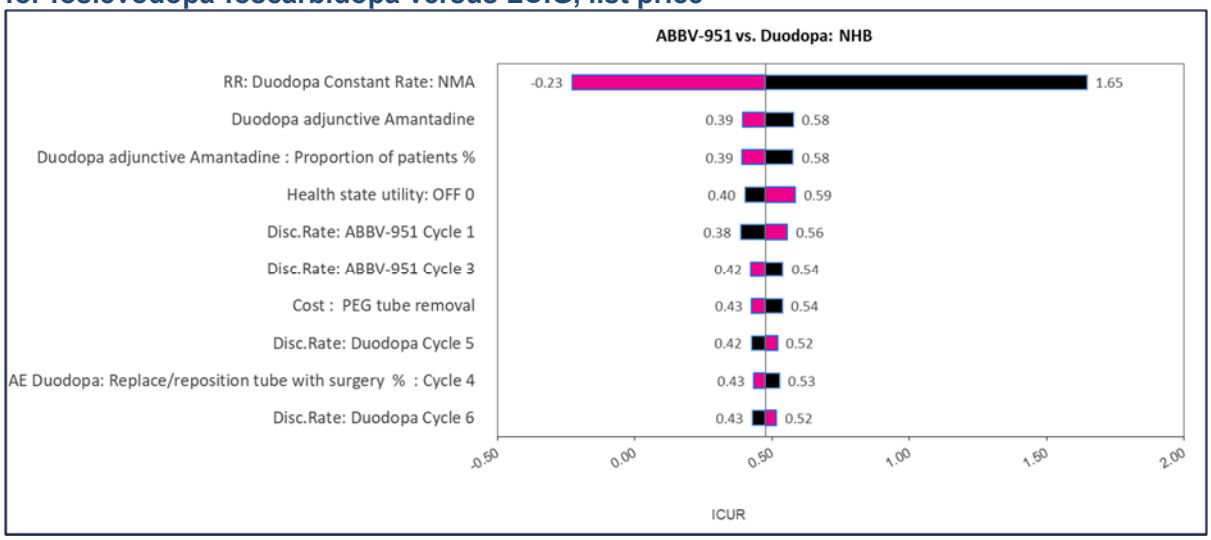
B.3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, deterministic sensitivity analyses (DSA) were conducted by varying the input for each parameter in the model by ±20% of their mean value, whilst keeping all other inputs the same. For certain parameters where standard errors of the mean were available, the lower and upper limits were defined by the 95% CI around the mean.

NHBs calculated at the upper and lower bounds for the 10 most influential parameters are shown graphically in tornado plots in Figure 33 (versus LCIG, list price), Figure 34 (versus LCIG, with-PAS), Figure 35 (versus BMT, list price) and Figure 36 (versus BMT, with-PAS).

As shown in Figure 33, the parameter with the greatest impact on the NHB in the comparison between foslevodopa-foscarbidopa and LCIG was the relative risk output derived from the NMA (see Section B.3.3.4.2). Foslevodopa-foscarbidopa remained cost-effective versus LCIG for all parameters, remained dominant against BMT in all upper and lower bound input variations conducted as part of the DSA (Figure 33 and Figure 34). This indicates that the comparison between foslevodopa-foscarbidopa and BMT is robust to variation of the inputs informing it.

Figure 33: Tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus LCIG, list price



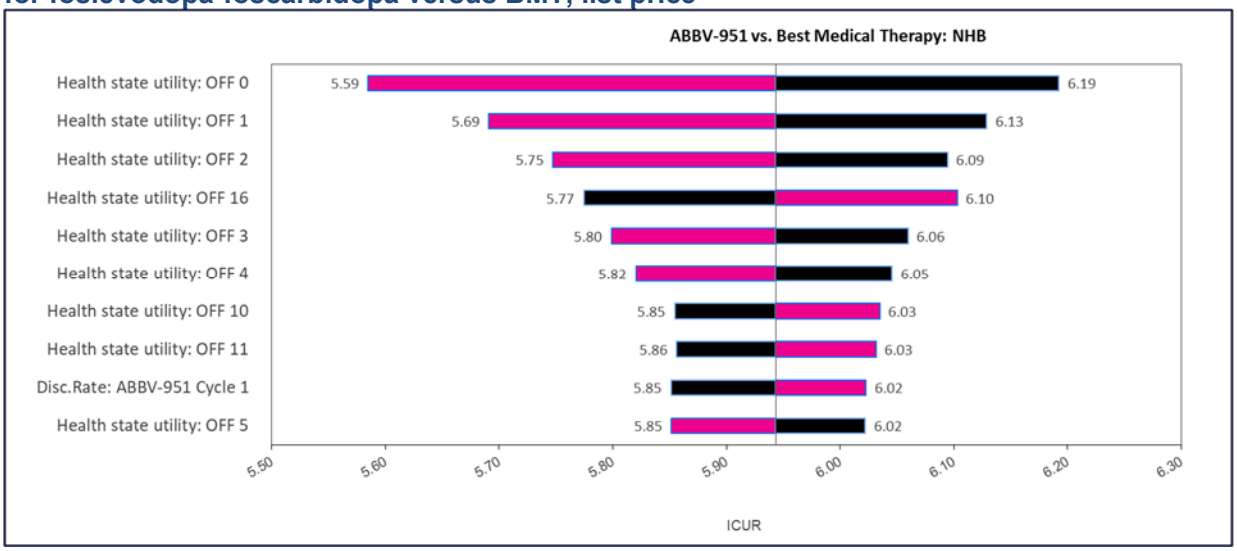
ABBV-951 = foslevodopa-foscarbidopa. Duodopa = LCIG
Abbreviations: AE: adverse event; LCIG: levodopa-carbidopa intestinal gel; NHB: net health benefit; NMA: network meta-analysis; PEG: percutaneous endoscopic gastrostomy; RR: relative risk.

Figure 34: 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: AE: adverse event; LCIG: levodopa-carbidopa intestinal gel; NHB: net health benefit; NMA: network meta-analysis; PAS: patient access scheme; PEG: percutaneous endoscopic gastrostomy; RR: relative risk.

Figure 35: Tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus BMT, list price



ABBV-951 = foslevodopa-foscarbidopa

Abbreviations: BMT: best medical therapy; NHB: net health benefit.

Figure 36: 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.

B.3.11.3 Scenario analysis

As described in Sections B.3.2–B.3.4, several scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the cost-effectiveness model. As per the NICE methods guide,[98] all scenario analyses were run probabilistically, as described in Section B.3.11.1 above. The results of the scenario analyses are presented in Table 87 below.

Overall, the results of the scenario analyses were very similar to the results of the base case analysis, demonstrating the results to be robust to uncertainties in the model inputs and assumptions. In all scenarios analyses, foslevodopa-foscarbidopa remained cost-effective in the SW quadrant when compared to LCIG and dominant against BMT.

Table 87: Results of the scenario analyses, list price

#	Description	Foslevodopa-foscarbidopa		LCIG				BMT			
		Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHB[a] (QALY)	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHB[a] (QALY)
Base case (probabilistic)		[redacted]	[redacted]	[redacted]	[redacted]	£192,741[b]	0.55	[redacted]	[redacted]	Dominant	4.62
Model time horizon											
1	10 years	[redacted]	[redacted]	[redacted]	[redacted]	£168,445[b]	0.39	[redacted]	[redacted]	Dominant	3.98
2	15 years	[redacted]	[redacted]	[redacted]	[redacted]	£183,469[b]	0.49	[redacted]	[redacted]	Dominant	4.55
3	30 years	[redacted]	[redacted]	[redacted]	[redacted]	£237,424[b]	0.65	[redacted]	[redacted]	Dominant	4.60
Wastage											
4	5% standard wastage for LCIG	[redacted]	[redacted]	[redacted]	[redacted]	£300,766[b]	0.87	[redacted]	[redacted]	Dominant	4.62
5	10% standard wastage for LCIG	[redacted]	[redacted]	[redacted]	[redacted]	£401,761[b]	1.18	[redacted]	[redacted]	Dominant	4.61
Foslevodopa-foscarbidopa and LCIG efficacy estimates											
6	Months 3–24: LOCF Months 24+: Natural history	[redacted]	[redacted]	[redacted]	[redacted]	£508,958[b]	1.00	[redacted]	[redacted]	Dominant	3.72
Foslevodopa-foscarbidopa discontinuation rates											
7	Months 0–3: M15-736 Months 3–24: M15-741 and M15-737 (Full cohort) Months 24+: "standard rate"	[redacted]	[redacted]	[redacted]	[redacted]	£103,866[b]	0.45	[redacted]	[redacted]	Dominant	4.50
8	Months 0–12: M15-741 (sample 1) Months 12–24: M15-737 Months 24+: "standard rate"	[redacted]	[redacted]	[redacted]	[redacted]	£109,803[b]	0.48	[redacted]	[redacted]	Dominant	4.53
9	Months 0–12: M15—741 (full cohort) Months 12–24: M15-737 Months 24+: "standard rate"	[redacted]	[redacted]	[redacted]	[redacted]	£130,839[b]	0.51	[redacted]	[redacted]	Dominant	4.55

Mortality rate											
10	Standard mortality rate	[redacted]	[redacted]	[redacted]	[redacted]	£187,786[b]	0.63	[redacted]	[redacted]	Dominant	5.47
Baseline characteristics											
11	Baseline age 61.4 years (-5 from baseline)	[redacted]	[redacted]	[redacted]	[redacted]	£191,372[b]	0.59	[redacted]	[redacted]	Dominant	5.11
12	Baseline age 71.4 years (+5 from baseline)	[redacted]	[redacted]	[redacted]	[redacted]	£267,185[b]	0.57	[redacted]	[redacted]	Dominant	3.85
Carer disutilities											
13	Include carer disutilities	[redacted]	[redacted]	[redacted]	[redacted]	£158,423[b]	0.56	[redacted]	[redacted]	Dominant	4.85

[a]NHB at a WTP threshold of £30,000
[b]SW quadrant ICER; costs saved per QALY forgone
Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; LCIG: levodopa-carbidopa intestinal gel; LOCF: last observation carried forward; NHB: net health benefit; NMA: network meta-analysis; QALY: quality-adjusted life year.; SW: south-west

B.3.12 *Subgroup analysis*

N/A – No subgroup analyses have been conducted as part of this submission's cost-effectiveness analysis.

B.3.13 *Benefits not captured in the QALY calculation*

As per the NICE reference case, QALYs were derived from EQ-5D data derived from the pivotal trial for foslevodopa-foscarbidopa.[121] However, clinician feedback received as part of an advisory board indicating that the EQ-5D is a simplistic measure of HRQoL, which may not accurately reflect the complex nature of PD, and improvements in patients' control of symptoms may therefore not accurately be reflected in the final calculations of QALYs for each treatment.[61]

Advanced PD is a highly debilitating disease associated with a number of both motor and non-motor symptoms, which vary from patient-to-patient and day-to-day. Physical symptoms can impair basic tasks such as walking or handling objects, whilst non-motor symptoms such as constipation and weight change can limit the wellbeing, independence and social life of people with PD.[14] An important set of symptoms reported by patients with PD is their experience of sleep disturbances, and waking with poor symptom control, a symptom commonly referred to as early morning 'Off' time. These have been linked to overnight decline in dopaminergic levels, as patients are unable to receive treatment during sleep.

The 24-hour subcutaneous method of administration of foslevodopa-foscarbidopa is able to maintain overnight dopaminergic levels, and has shown to greatly reduce early morning 'Off' time as compared with BMT (see Section B.2.3.4). Additionally, patients in the M15-736 trial reported large reductions in PDSS-2 scores for foslevodopa-foscarbidopa compared with oral CD/LD, indicating fewer symptoms during sleep. The results of the NMA also indicated that use of foslevodopa-foscarbidopa leads to a [redacted] reduction in PDSS-2 scores compared with LCIG; this outcome is not captured within the model.

Compared with LCIG, foslevodopa-foscarbidopa provides patients with a less invasive treatment option through the avoidance of surgery. Whilst the costs and adverse events of surgery are captured in the model for LCIG, the additional disutility of patients' anxiety in the build up to such surgery is not fully captured.

The QALY calculations reported as part of this submission do not effectively capture some important disease symptoms, and potential additional QALYs associated with, for example, improved sleep symptoms demonstrated by foslevodopa-foscarbidopa.

B.3.14 *Validation*

B.3.14.1 Validation of cost-effectiveness analysis

The model methodology was designed to align with NICE's preferred methods. The model was built to align with the NICE reference case, and used an NHS and PSS perspective and discount rates for cost and benefits of 3.5%.[98] The model used a lifetime time horizon in order to capture all costs and QALY gains associated with the interventions.

Economic model verification

Quality-control procedures were undertaken to ensure the programming and physical implementation of the conceptual model was completed correctly. An independent modelling team undertook a cell-by-cell verification process facilitating a check of all input calculations, formulae and Visual Basic code. Any discrepancies were identified, discussed and corrected as required.

Validation of economic model against clinical expert opinion

The overall model structure has also been validated through iterative discussions with UK clinical and health economic experts throughout the development of the model and drafting of the submission dossier. Additionally, further UK clinical input was sought at an advisory board with six clinical expert and two health economic expert attendees, held virtually via Microsoft Teams in February 2022.

Input from the experts has been highlighted throughout the dossier where relevant. Examples of their influence on the model include the following:

- Experts agreed that the exclusion of H&Y states from the model was appropriate, both from a clinical and modelling standpoint
- Clinicians disagreed with inclusion of treatment waning, indicating that it did not reflect the true nature of disease progression observed in patients with advanced PD

B.3.15 *Interpretation and conclusions of economic evidence*

Summary of cost-effectiveness evidence

Owing to the chronic and progressive nature of disease, for patients who progress to an advanced disease phase, both device-aided and surgical interventions may be considered when oral combinations become less suitable for maintaining good symptom control and stable plasma dopamine levels. However, only a small number of options are available for patients with advanced PD.

The innovative, unique administration of foslevodopa-foscarbidopa that simplifies treatment procedures compared to all available options is reflected in the results as foslevodopa-foscarbidopa is cost-effective at a WTP threshold of £30,000 per QALY in the relevant population (see Section B.1.3.2).

In the base case analysis against LCIG, foslevodopa-foscarbidopa yielded a SW quadrant ICER of £192,741 (list price) and [redacted] (with-PAS) per QALY foregone. Foslevodopa-foscarbidopa incurs fewer costs than LCIG, however yields fewer QALYs (incremental difference of –0.10) compared with LCIG.

A number of key areas of value for foslevodopa-foscarbidopa are unable to be captured within the cost-effectiveness model (see Section B.3.13), indicating that the QALY estimates likely underestimate the true value foslevodopa-foscarbidopa can bring to patients and the NHS relative to LCIG.

Moreover, foslevodopa-foscarbidopa was found to be the most cost-effective treatment option for patients with advanced PD, with symptoms not adequately controlled by their current medical therapy and for whom apomorphine or DBS are unsuitable or no longer providing adequate

symptom control. The NHB for foslevodopa-foscarbidopa versus LCIG was 0.55 at list price and [redacted] with-PAS, and versus BMT was 4.62 at list price and 5.66 with-PAS, at a WTP of £30,000 per QALY gained, with foslevodopa-foscarbidopa found to be dominant against BMT.

The PSA analyses demonstrated that the probability that foslevodopa-foscarbidopa is the most cost-effective treatment option is estimated to be 83% at list price and [redacted] with-PAS% at a WTP threshold of £30,000 per QALY.

The DSA results identified a small number of key influential parameters (RR from the NMA, utility values in the lower 'OFF' health states and discontinuation rates for foslevodopa-foscarbidopa) with the model being largely robust to uncertainty in the majority of parameters. Scenario analyses conducted to address sources of uncertainty in the model such as the model time horizon and treatment efficacy estimates, demonstrated that whilst there was variation in the NHB, the cost-effectiveness conclusions remain the same, with foslevodopa-foscarbidopa remaining cost-effective at a WTP threshold of £30,000 per QALY across all scenarios.

Overall, the base case ICERs for all comparisons demonstrated foslevodopa-foscarbidopa to be cost-effective at a WTP threshold of £30,000 per QALY and thus foslevodopa-foscarbidopa can be considered a cost-effective use of NHS resources as a treatment for advanced PD.

Strengths

The clinical effectiveness evidence presented in this submission has been derived from an SLR of clinical trials investigating the efficacy and safety of a variety of treatment options, including foslevodopa-foscarbidopa, for the treatment of advanced PD. Results from the M15-736 trial have demonstrated that foslevodopa-foscarbidopa was associated with statistically significant decreased daily 'OFF' time compared to oral therapies. Efficacy for foslevodopa-foscarbidopa in the model was based on the daily 'OFF' time outcomes in M15-736, which represents the primary source of evidence for foslevodopa-foscarbidopa in this indication. The baseline characteristics of patients in the M15-736 trial were considered to be reflective of patients with advanced PD in the UK and therefore the outcomes of the M15-736 trial were considered generalisable to UK clinical practice.

An NMA was conducted to compare foslevodopa-foscarbidopa to relevant comparators in clinical practice, which found foslevodopa-foscarbidopa to have similar efficacy to LCIG, with significantly improved outcomes as compared with BMT (Section B.2.7.4). A cost-utility analysis was selected to assess the cost-effectiveness of foslevodopa-foscarbidopa in this indication. The model was built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizon to capture fully all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5%.[121] The *de-novo* model was based on extensive secondary research and all possible existing models for PD were assessed (see Section B.3.2.2). As such a new model structure was designed to better reflect the symptomatology of PD and potential gains of a controlled PD.

Limitations

A key limitation of the clinical evidence base was the lack of head-to-head evidence for foslevodopa-foscarbidopa versus relevant comparators for this appraisal (LCIG and BMT). An NMA was conducted in order to obtain relative efficacy estimates to inform the economic analysis, however these were subject to data availability. The impossibility to test further models due to the very limited sample size is also an important limitation.

An important limitation of this cost-effectiveness model is the relatively large number of transitions (17 x 17) that were estimated based on a relatively small number of patients (e.g., 73 patients in the foslevodopa-foscarbidopa arm of M15-736 used in the base case analysis). This resulted in many transitions having a 0% or a 100% probability of occurring, however this level of granularity provides the most complete use of data from the clinical trial.

Another limitation arises from the limited data available to inform long-term effectiveness of both foslevodopa-foscarbidopa and LCIG. For foslevodopa-foscarbidopa, the RCT conducted to determine its efficacy versus BMT was only three months (M15-736). As such, only the first three months of the model were informed by RCT data for foslevodopa-foscarbidopa. Relative risks, derived from NMA efficacy data, were applied to LCIG, which was used to model transitions in the first three months of the model, and subsequently as part of the LOCF period from Months 3–36, in the absence of long-term comparative data. Natural disease progression was assumed to take place following this model period.

Conclusion

There remains a considerably high unmet need amongst patients with advanced PD for non-surgical treatment options which effectively control symptoms. Foslevodopa-foscarbidopa has demonstrated significantly greater efficacy to BMT, and comparable efficacy to LCIG, at reducing 'Off' time, and significantly greater efficacy to BMT and LCIG at reducing PDSS-2 (Section B.2.7.4) which, as demonstrated in the M15-736 trial, is associated with improved patient HRQoL. Foslevodopa-foscarbidopa, with its novel, 24-hour and non-invasive subcutaneous method of administration of the gold standard PD therapy, could offer a much-needed additional treatment option for patients with advanced PD. Overall, the cost-effectiveness analysis for all comparisons demonstrated foslevodopa-foscarbidopa to be a cost-effective option for the NHS at list and net price at a willingness-to-pay threshold £30,000 per QALY for patients with advanced PD.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

August 2022

File name	Version	Contains confidential information	Date
ID3876_Foslevodopa-Foscarbidopa_NICE SIP_Final_16Aug22	Final	Yes	16th August 2022

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Foslevodopa-foscarbidopa

Brand name: The brand name for foslevodopa-foscarbidopa has not yet been approved by the Medicines and Healthcare products Regulatory Agency (MHRA). The brand name will be known in Q4 2022.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Foslevodopa-foscarbidopa is anticipated to be available for patients with advanced Parkinson's disease with symptoms not adequately controlled by their current medical therapy, and for whom apomorphine or deep brain stimulation (DBS) are unsuitable or no longer providing adequate symptom control.

Apomorphine and DBS are two different types of treatments available for advanced Parkinson's disease. Apomorphine is a medicine, and DBS is a surgical procedure where a device is implanted into the brain. Further details on apomorphine and DBS can be found under section 2c below.

There are different terminologies used by individuals with Parkinson's disease and support groups to refer to the condition. Throughout the Appraisal document submission and this Summary of Information for Patients document the term Parkinson's disease is used as this aligns with terminology used on NHS materials, and the term patient is used to help distinguish between individuals with the condition and others, such as carers, affected. It is recognised that individuals have different experiences of the condition and refer to it in differing ways and therefore the terminology adopted for this document in no way seeks to diminish that.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation from the MHRA for foslevodopa-foscarbidopa is pending approval. Please refer to Section B.1.2 of the submission for further details on the anticipated dates for approval.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AbbVie collaborates with a range of stakeholders with an interest in Parkinson's Disease.

This includes collaboration with Parkinson's UK to support improvements in health and care for individuals with Parkinson's Disease.

Where this includes any Transfer of Value, for example to support the development of information for patients and their families, this is declared on an annual basis and is available at: https://www.abbvie.co.uk/our-company/policies-disclosures.html

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Condition that the medicine plans to treat:

Parkinson's disease is a progressive, neurological condition, where nerve cells in the brain gradually deteriorate over time. As a result, patients with Parkinson's disease do not have enough of the chemical dopamine. Dopamine acts as a chemical messenger in the brain, and having less of it reduces the ability of the nerve cells to communicate.

There is currently an estimated 120,000 people living with Parkinson's disease in England, with the disease most common in people over 60 years old and in males.[1-3] People with Parkinson's disease also have a higher rate of mortality (i.e. risk of death) compared with the general population, which gradually increases as the disease advances.[4]

Symptoms:

The symptoms of Parkinson's disease vary between individual patients and from day-to-day. The most well-known symptoms of Parkinson's disease relate to difficulty in controlling movement of the body (motor symptoms). These include unintentional shaking (tremors), stiffness, and slowness or absence of movement.[5, 6]

Patients may also experience symptoms unrelated to movement (non-motor symptoms), which can include physical symptoms such as loss of the sense of smell, constipation, rapid eye movement sleep behaviour disorder, other sleep disorders as well as psychological symptoms such as, depression, anxiety, pain, cognitive impairment (memory and thinking problems), and psychosis (hallucinations or delusions). [7, 8] Over time, these symptoms can become worse, whilst becoming more difficult for some patients to manage with treatment, which can include medication.[9, 10]

Patients on medication may also experience changes in dopamine levels in between doses of medication throughout their day. Patients will often experience good symptom control immediately after taking treatment, followed by poor symptom control as the medication wears off.[11] This variation between poor and good symptom control is known as 'motor fluctuations'. This creates a requirement for higher and/or more frequent doses of treatment to control patients' motor symptoms in the more advanced stages of Parkinson's disease.[9] Adding to the complexity is the high probability of uncontrolled movements, dyskinesia, as peak drug doses are reached.

As both the symptoms and progression of Parkinson's disease varies between individuals, the treatment of this disease should be tailored to each patient.[12]

Impact on patients:

Motor symptoms can make it difficult for patients to carry out basic tasks such as walking, eating or handling objects. Non-motor symptoms, such as sleep disorders, cognitive impairment, fatigue and speech changes can limit the wellbeing, independence and social life of people living with Parkinson's disease.[13]

The most commonly reported psychological symptoms are depression and anxiety. All of these symptoms can have a significant impact on patients' mental health and the physical impact of Parkinson's disease.[14] For example, patients with Parkinson's disease tend to get tired more easily due to the extra challenges in carrying out daily activities, with sleep disturbances, as well as other sleep disorders, leading to patients being less well rested.[15] These sleep-related symptoms are particularly important for patients taking oral medication, as there will be periods of time where their motor symptoms are less well controlled, for example in the early morning after not receiving medication overnight.[16] This wearing off of medication can create both physical challenges and emotional distress for patients living with Parkinson's disease.[17] These symptoms can reduce the quality of life for patients with Parkinson's disease compared with the general population.[18]

Impact on carers:

As the ability of patients with Parkinson's disease to carry out daily activities is limited by the motor symptoms they experience there can be a greater reliance on carers, who are needed to help with everyday tasks such as taking medication, getting dressed, walking and eating.[19] This assistance means Parkinson's disease also affects the carers and families of patients, resulting in them experiencing a lower quality of life than the general population, with high rates of depression, social isolation, and loneliness.[19, 20]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Parkinson's disease is typically diagnosed by a specialist and an individual with Parkinson's disease will typically be under the care supervision of a specialist healthcare team.

The diagnosis of advanced Parkinson's disease is based on the judgement of doctors and patients. The '5-2-1' motor criteria are commonly used to help identify patients with advanced Parkinson's disease. These criteria define advanced Parkinson's disease as being when patients experience at least one hour of troublesome involuntary movements, at least two hours of 'Off' symptoms, or at least five doses of levodopa containing tablets a day.[21]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The National Institute for Health and Care Excellence (NICE) have published a guideline (NG71: 'Parkinson's disease in adults') which recommends using medication to manage the motor symptoms associated with Parkinson's disease.[22] Elements of this guideline are outlined below. It is also recommended in other NICE and NHS guidance that the relevant advantages and disadvantages of commencing treatment or choosing between different treatments should be discussed openly and frequently between healthcare teams and individuals with Parkinson's disease to support a shared decision making approach.

Initial treatment:

Most commonly, patients are initially treated with an oral medicine called levodopa, which is given once their motor symptoms become disabling.[23, 24] Levodopa aims to replenish the reduced supply of dopamine in the brain.[24] Levodopa is often taken as a tablet which also contains another medicine, carbidopa, which helps to prevent levodopa being changed to dopamine in the blood. This means that more levodopa is able to reach the brain before being converted to dopamine, and reduces the dose needed to be taken.[24, 25]

As the disease progresses, other oral medicines are often taken alongside levodopa to help with the management of motor symptoms, and manage the side effects caused by long-term use of levodopa. These include monoamine oxidase type B (MAO-B) inhibitors, dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors and amantadine.[22] These treatments tend to be tablets or capsules, and are collectively referred to as best medical therapy (BMT). The exact combination of treatments used as part of BMT is tailored to the needs of each individual patient.

Advanced treatment:

Device-aided therapies (DATs) are offered to patients once the disease progresses to the advanced phase, and oral treatments are no longer able to maintain good symptom control and stable levels of dopamine in the brain.

These treatments aim to reduce the amount of time patients' motor symptoms are not well controlled ('Off' time), whilst increasing the amount of time with good symptom control ('On' time), without uncontrolled, involuntary movements (known as dyskinesia), which may occur with long-term levodopa use.

The NICE guideline NG71 recommends patients with advanced Parkinson's disease are offered BMT, which may include apomorphine, delivered as either a continuous subcutaneous (under the skin) infusion or injection at irregular intervals.[22] Apomorphine has been shown to reduce 'Off' time by 50%,[26] however the associated unwanted effects of the medicine include hallucinations, psychosis and impulse control disorder, as well as poor control of dyskinesia (involuntary movements). This can lead some patients to stopping this treatment.[26-29] Apomorphine is therefore suitable for patients waiting for alternative currently available advanced Parkinson's disease therapies, but not necessarily for long-term use in all patients.[27]

DBS is a treatment option that involves surgery A pulse generator (a device like a heart pacemaker) is placed under the skin around the chest or stomach area. It is connected to one or two fine wires that are inserted into specific areas of your brain. When the pulse generator is switched on, the electrodes deliver high frequency stimulation to the targeted area. This stimulation changes some of the electrical signals in the brain that cause the symptoms of Parkinson's disease.

Another treatment, levodopa and carbidopa intestinal gel (LCIG; Duodopa®) is available for patients with advanced Parkinson's disease who respond to levodopa treatment, and when apomorphine or DBS are not suitable.[31] This treatment requires surgery to place a tube, through the skin, into the small intestine. This tube is connected to a pump and cartridge system containing levodopa-carbidopa gel, allowing a continuous supply of levodopa to be provided throughout the waking day.[22]

Some patients in the advanced stage of disease may not be able, or willing, to receive advanced treatments, and may therefore continue receiving optimised doses of BMT, despite their symptoms remaining uncontrolled.

Until now, there has not been an evaluation of a Parkinson's disease treatment by NICE. When a medicine is approved by NICE, the recommendation comes with a funding mandate that seeks to ensure that funding is made available for individuals with the condition to be able to access the medicine if it is clinically appropriate for them. AbbVie is keen therefore for this medicine to be appraised by NICE in this way to ensure the best chance for equitable patient access to the medicine, if it is approved.

Foslevodopa-foscarbidopa

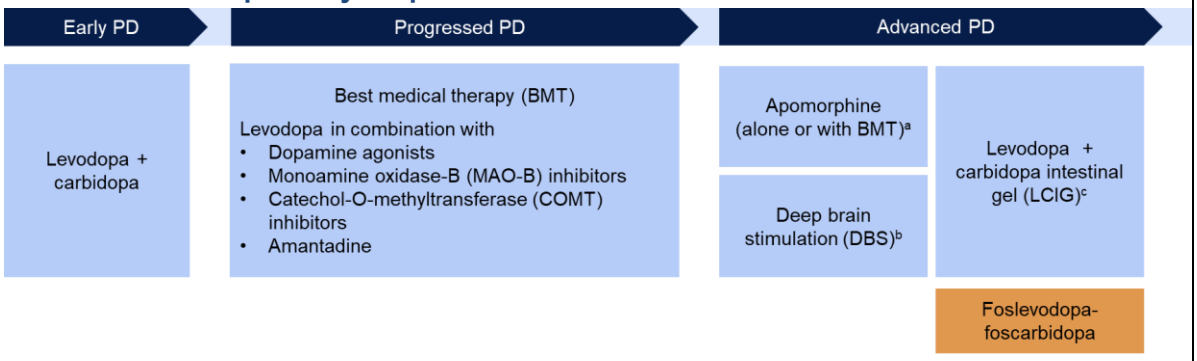
Given that currently available treatments have not been critically appraised through the NICE technology appraisal route, this understandably introduces an element of uncertainty regarding the clinical, pathway and economic assumptions that can be agreed upon and there are challenges in building the economic case of foslevodopa-foscarbidopa versus apomorphine

and DBS, in particular when considering the length of time these interventions have been on the market, and where DBS is a surgical procedure rather than a medicinal product. With the currently available evidence, using LCIG and current medical therapy (BMT) as comparators in this NICE submission allows best cost-effectiveness comparisons.

Ultimately, if successfully appraised, AbbVie expects clinicians to be able to prescribe foslevodopa-foscarbidopa for a group of patients with advanced Parkinson's disease, whose symptoms are not adequately controlled by their current medical therapy.

They will also be unsuitable for apomorphine or DBS or their symptoms will no longer be adequately controlled by these therapies. It must be acknowledged that treatment choice throughout all stages of Parkinson's disease is specific to the individual patient.

Figure 1: Anticipated positioning of foslevodopa-foscarbidopa with respect to the current treatment pathway for patients with Parkinson's disease



[a]Apomorphine may be given as an intermittent injection in the earlier stages of PD, but is predominantly used as a continuous infusion under the skin in patients with advanced PD.
[b]If symptoms are inadequately controlled by BMT.
[c]LCIG is only used in patients who are unsuitable for DBS or apomorphine.
Abbreviations: BMT: best medical therapy; COMT: catechol-O-methyltransferase; CSCI: continuous subcutaneous infusion; DBS: deep brain stimulation; LCIG: levodopa-carbidopa intestinal gel; PD: Parkinson's disease.
Source: Adapted from NICE NG71.[22]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

A recent study of 2,707 patients with Parkinson's disease and 150,661 members of the general population investigated the quality of life of patients with Parkinson's disease as compared with people without the disease.[32] Researchers reviewed the published evidence of patient responses to questionnaires about their quality of life.

The study found that patients with Parkinson's disease had significantly lower quality of life compared with the general population in most aspects of quality of life. The difference was particularly large when considering physical functions and mental health.[32]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Levodopa and carbidopa are currently available to patients with advanced Parkinson's disease either as oral tablets, as they are unsuitable to receive any advanced medicines, or through an intestinal gel (LCIG). LCIG requires surgery to place a tube, through the skin, into the small intestine. This tube is connected to a pump and cartridge system containing levodopa-carbidopa gel, allowing a continuous supply of levodopa to be provided throughout the waking day.[22]

How foslevodopa-foscarbidopa works:

Foslevodopa-foscarbidopa is a new form of levodopa and carbidopa that allows the drugs to be administered continuously without the need for surgery.

It is a combination medicine of two inactive forms of levodopa and carbidopa, known as prodrugs. These prodrugs dissolve in water, enabling them to be administered subcutaneously (under the skin) via an external pump.[33]

Once in the endothelial capillaries (small blood vessels under the skin), these inactive prodrugs are converted by the body into the active forms of levodopa and carbidopa. Levodopa aims to replenish the reduced supply of dopamine in patients' brains.[24]

The active carbidopa remains in the bloodstream, where it prevents levodopa being changed into dopamine prior to entering the brain. This increases levodopa's absorption into the brain, where it is transformed to dopamine.[24, 25] This dopamine replenishment aids the nerve cells' ability to communicate with each other, and helps to control Parkinson's disease symptoms.

Innovation of treatment:

As foslevodopa-foscarbidopa is administered subcutaneously, it is less invasive than LCIG as it does not require surgery to allow it to be used.

Additionally, in comparison to LCIG that must be detached during sleep, foslevodopa-foscarbidopa can be given continuously throughout the night, due to the subcutaneous administration of the medicine.

Foslevodopa-foscarbidopa could be administered in an outpatient setting, and as such patients are not required to stay overnight in hospital.

Foslevodopa-foscarbidopa is the first and only 24-hour subcutaneous infusion of levodopa. This continuous administration of treatment to patients enables greater symptom control during sleep and during the day.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, it is not used in combination with other medicines. However, patients may receive additional therapies to further support control of their symptoms.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Foslevodopa-foscarbidopa is administered continuously for 24 hours each day, via subcutaneous infusion (under the skin), using a small external pump.

The pump can be independently managed by patients or caregivers at home once an optimal dose is established. Due to the subcutaneous administration of the medicine, foslevodopa-foscarbidopa could be administered in an outpatient setting, as such patients are not required to stay overnight in hospital.

The recommended starting infusion rate is established by working out the amount of oral levodopa the patient is taking in the day time, and increasing this to account for a 24-hour subcutaneous administration. Some notable differences as a result of this administration and dosing include:

- It allows for sustained and predictable symptom control.
- The dose can be tailored to individual patients which seeks to ensure the amount of ‘On’ time is maximised, and number and duration of ‘Off’ episodes and ‘On’ episodes with uncontrolled movements are minimised.
- Foslevodopa-foscarbidopa does not require an invasive surgical procedure, as is the case with certain treatments available for advanced Parkinson’s disease.

Patients will need to see their specialist to adjust the optimum dose if this is required.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Foslevodopa-foscarbidopa has been investigated in a number of different clinical trials. The primary trials that provide the evidence for this appraisal are known as M15-736 and M15-741. Both trials were followed by longer-term extension trials.

M15-736

M15-736 evaluated the efficacy, safety and tolerability of foslevodopa-foscarbidopa versus oral carbidopa/levodopa in patients with advanced Parkinson's disease whose motor fluctuations were inadequately controlled by their current medication. This trial took place across 57 clinical trial sites in the United States and Australia.

The trial consisted of three separate periods. Firstly was a screening period (6 to 60 days), followed by an oral carbidopa/levodopa stabilisation period (14 to 21 days) in which the appropriate daily dose of levodopa-equivalent medication was determined for each patient. Finally, there was a 12-week treatment period when patients received either foslevodopa-foscarbidopa or oral levodopa and carbidopa.

The screening period determined whether eligible patient volunteers qualified for the trial. The key eligibility criteria for the trial included:

- Male or female patients, 30 years of age or older at the time of screening, with a diagnosis of Parkinson's disease which had an unknown cause and responded to levodopa.
- Patients had to be taking a minimum of 400 mg per day of levodopa equivalents and be judged by the investigator to have motor symptoms inadequately controlled by current therapy.
- Patients also had to have identifiable fluctuations between 'Off' and 'On' periods and have had an average 'Off' time of at least 2.5 hours each day over three consecutive days, with a minimum of two hours each day.
- Patient (or caregiver, if applicable) had to have demonstrated understanding and correct use of the delivery system, including the insertion of the cannula into the patient's abdomen, as assessed by the investigator or designee during the Screening Period.

Patients were randomly and evenly assigned to receive either foslevodopa-foscarbidopa or oral carbidopa/levodopa during the 12-week treatment period. This period was double-blind, double-dummy which means that neither the patient nor the researchers knew which treatment they were receiving.

In total, 174 patients were enrolled into the study and 141 took part in the randomised treatment period. Seventy-four patients received foslevodopa-foscarbidopa and 67 receiving oral levodopa and carbidopa.

Further information can be found on the ClinicalTrials.gov entry for M15-736: https://clinicaltrials.gov/ct2/show/study/NCT04380142

M20-098 (ongoing)

Eligible patients who completed the 12-week double-blind treatment period in M15-736 could enter M20-098. This is an extension study where all patients receive foslevodopa-foscarbidopa treatment for up to 96 weeks.

Further information can be found on the ClinicalTrials.gov entry for M20-098: https://clinicaltrials.gov/ct2/show/NCT04750226

M15-741

M15-741 evaluated the efficacy, safety, and tolerability of foslevodopa-foscarbidopa in patients with advanced Parkinson's disease whose motor fluctuations were not adequately controlled by their current medication. The trial was primarily designed to evaluate the safety of foslevodopa-foscarbidopa, but did also assess its efficacy as a secondary objective. This trial took place at 60 clinical trial sites across Australia, Belgium, Canada, Denmark, Germany, Italy, Japan, Netherlands, United States and United Kingdom.

The trial consisted of two separate periods. Firstly, there was a four-week optimisation period, where the optimal dosage of foslevodopa-foscarbidopa was determined for each patient. This was followed by a 48-week maintenance period in which all patients received foslevodopa-foscarbidopa.

The screening period determined whether eligible patient volunteers qualified for the M15-741 clinical trial. The key eligibility criteria for the trial included:

- Male or female patients, 30 years of age or older at the time of screening, with a diagnosis Parkinson's disease which had an unknown cause and responded to levodopa.
- Patients whose oral medication included levodopa and had remained unchanged for at least 30 days prior to commencing treatment with foslevodopa-foscarbidopa . These patients must also have had identifiable fluctuations between 'Off' and 'On' states.
- Patient (or caregiver, if applicable) had to have demonstrated the understanding and correct use of the delivery system, including the insertion of the cannula into the patient's abdomen, as assessed by the investigator or designee during the Screening Period.

During the optimisation period, patients' foslevodopa-foscarbidopa dose was adjusted to achieve optimal symptom control, as determined by a study investigator. Patients were then continued on this optimal dose during the maintenance period. A total of 244 patients took part in the trial.

M15-737:

Eligible patients who completed the 52-week M15-741 trial were able to continue treatment as part of a 144-week extension study called M15-737.

Further information can be found on the ClinicalTrials.gov entry for M15-737: https://clinicaltrials.gov/ct2/show/NCT04379050

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

M15-736 was the pivotal trial evaluating the efficacy, safety and tolerability of foslevodopa-foscarbidopa in advanced Parkinson's disease patients whose motor fluctuations were inadequately controlled by their current medication. The trial compared foslevodopa-foscarbidopa with oral carbidopa/levodopa.

The trial's primary objective was to measure the amount of time patients reported having good control of their symptoms each day ('On' time) without suffering any dyskinesia, and to compare this to the amount of 'On' time without dyskinesia reported prior to starting the trial. This is an important measure of how well treatments improve patients' experience of their symptoms.

At the end of the 12-week treatment period, foslevodopa-foscarbidopa was shown to significantly increase patients' daily 'On' time without dyskinesia compared with oral levodopa and carbidopa. Additionally, foslevodopa-foscarbidopa significantly reduced the time patients' symptoms were not well controlled ('Off' time) compared to the oral levodopa and carbidopa group.

The number of patients who experienced impaired movement (akinesia) in the morning greatly decreased following 12-weeks of treatment with foslevodopa-foscarbidopa compared with before the study started. The same decrease was not observed in the oral levodopa and carbidopa group, indicating that the 24-hour administration of foslevodopa-foscarbidopa positively impacted patients' quality of sleep.

The efficacy of foslevodopa-foscarbidopa demonstrated by M15-736 was supported by the M15-741 clinical trial. M15-741 showed similar 'On' time to M15-736, demonstrating that the control of motor symptoms that foslevodopa-foscarbidopa provides is maintained over 52 weeks. M15-741 also showed patients had a clinically meaningful improvement in motor symptoms, early morning non-sleep symptoms and Parkinson's disease symptoms with foslevodopa-foscarbidopa. Significant improvements in patients' health-related quality of life were also observed.

Although it has not been measured within the clinical studies, it is also worth noting that foslevodopa-foscarbidopa may have a potential impact on carers of individuals with Parkinson's disease also. The continuous administration of foslevodopa-foscarbidopa means that carers do not have to take responsibility for the correct administering of oral medicines and organising the timings of meals. Carers may also share the experience of improved sleep, as there is less need to wake up and attend to an immobile patient. These redcued burdens can positively impact carers' quality of life.

The M15-736 trial provided evidence for foslevodopa-foscarbidopa against oral medicines for Parkinson's disease, i.e. BMT. However, neither of the M15-736 and M15-741 studies directly compared foslevodopa-foscarbidopa to LCIG. Therefore, an indirect comparison method called a network meta-analysis (NMA) had to be used to compare the efficacy of foslevodopa-

foscarbidopa and LCIG. An NMA allows different treatments to be compared indirectly (i.e. not within the same clinical trial) using clinical trial data and statistical methods.

The NMA compared the rates of 'Off' time and 'On' time without troublesome dyskinesia that were achieved by patients receiving foslevodopa-foscarbidopa with patients who received LCIG in other clinical trials. The NMA also assessed the different scores on the Parkinson's disease sleep scale (PDSS) reported by patients receiving foslevodopa-foscarbidopa and LCIG.

The results of the NMA showed foslevodopa-foscarbidopa to be comparably effective in improving symptom control as LCIG, with similar changes in 'Off' time and 'On' time without troublesome dyskinesia associated with both treatments. Foslevodopa-foscarbidopa was shown to result in greater improvements in patients' sleep and early morning symptoms as compared to LCIG, with lower scores reported on the PDSS questionnaire, which indicates patients experiencing better sleep.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The M15-736 and M15-741 trials assessed patients' quality of life using two validated patient questionnaires.

The 39-item Parkinson's Disease Questionnaire (PDQ-39) assesses the impact of Parkinson's disease across eight different areas of physical function and well-being, including relationships, social situations and communication, as well as specific dimensions of functioning and wellbeing.

The EuroQoL EQ-5D-5L is a more general measure of patients' quality of life across five areas of health-related quality of life, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. EQ-5D-5L is applicable for all diseases, rather than Parkinson's disease specifically.

The results of both PDQ-39 and EQ-5D-5L in M15-736 showed that foslevodopa-foscarbidopa resulted in greater improvements in patients' quality of life compared with oral levodopa and carbidopa. Patients receiving foslevodopa-foscarbidopa over 52 weeks in the M15-741 trial showed similar improvements to their quality of life, indicating these improvements in quality of life persist over longer-term treatment durations.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk

assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The negative or unwanted effects of foslevodopa-foscarbidopa treatment outlined in this section are based on the M15-736 and M15-741 clinical trial data. The M15-736 study enabled comparison to the safety profile of oral carbidopa/levodopa. Both clinical trials observed the side effects associated with foslevodopa-foscarbidopa to be manageable, however these side effects led to some patients stopping treatment in the M15-736 trial.

In the M15-741 study, the most common side-effects that were reported by patients were reactions at the site of the infusion, hallucination, fall, anxiety, and dizziness. In the M15-736 study, the most common side-effects of foslevodopa-foscarbidopa are shown in Table 1. These side-effects were experienced by more than 10% of patients receiving foslevodopa-foscarbidopa.

Table 1: Most common side effects experienced by patients treated with foslevodopa-foscarbidopa in the M15-736 trial

Side effect	Symptoms
Infusion site erythema	Reddening of the skin around the injection site
Infusion site pain	An unpleasant sensation at the injection site
Infusion site cellulitis	A bacterial infection at the injection site
Infusion site oedema	Swelling, due to accumulation of fluid at the injection site
Dyskinesia	Uncontrolled, involuntary movements
Fall	

In the M15-736 trial, more patients experienced infusion site infections in the foslevodopa-foscarbidopa treatment group compared with the oral carbidopa/levodopa group, but the majority were non-serious, were mild or moderate in severity, and resolved.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Foslevodopa-foscarbidopa represents a novel administration method for the well-established Parkinson's disease treatment combination, levodopa and carbidopa, in their prodrug form (inactive medicine). This enables continuous subcutaneous infusion of the treatment, leading to stable and predictable levels of dopamine in the brain, which results in good symptom control throughout the day.

Foslevodopa-foscarbidopa represents the first levodopa-based treatment for Parkinson's disease to be administered over a continuous 24-hour subcutaneous infusion, which results in patients experiencing better sleep and fewer symptoms when they wake up, having received

treatment overnight. This is an important innovation in the treatment of Parkinson's disease, as poor sleep and poor control of symptoms when waking are commonly reported by patients, and can be highly debilitating to the individuals affected, their carers and families.[16]

In contrast to other treatment options available to patients with advanced Parkinson's disease, foslevodopa-foscarbidopa does not require a surgical procedure to be administered to patients. Foslevodopa-foscarbidopa is administered via a small external device, which can be simply worn by patients, and independently managed by patients or caregivers following dose optimisation.

Due to the subcutaneous administration of the medicine, foslevodopa-foscarbidopa could be administered in an outpatient setting, as such patients are not required to stay overnight in hospital. Foslevodopa-foscarbidopa therefore represents a more convenient treatment option than what is currently available to patients with advanced Parkinson's disease.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Foslevodopa-foscarbidopa is administered by infusion under the skin, which can result in side effects to the skin close to where the infusion needle is inserted. Infusion-site infections, swelling, and adverse reactions were the most commonly reported side effects of treatment with foslevodopa-foscarbidopa.

Prior to commencing treatment, either the patient or administrating carer must be trained in how to use foslevodopa-foscarbidopa and the delivery system. This includes patients needing to change the infusion set, including the cannula containing the needle, every three days. This can be inconvenient for patients, in particular those uncomfortable with needles.

As is common with other levodopa-based treatments, dyskinesia was also reported by patients to be associated with treatment with foslevodopa-foscarbidopa.

The medication also has temperature storage requirements (i.e. needs to be stored in a fridge) that will likely need to be considered by patients and their carers.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

In the economic analysis, patients were modelled as having a number of daily 'Off' hours, ranging from 0–16, with a higher number of 'Off' hours indicating lower quality of life. The quality and quantity of life experienced by patients is reported in quality-adjusted life years (QALYs).

QALYs are a health outcome measure that take into account both the length and the quality of life provided by a treatment. A year spent in perfect health (i.e. a utility score of 1) represents one QALY. Side effects were taken into account by lowering patients' utility scores, and therefore QALYs, when they experienced a side effect.

The results from the M15-736 trial and the NMA were used to model how effective foslevodopa-foscarbidopa and LCIG are as treatments.

These data informed how patients moved between different 'Off' times in the model for the first 36 months. This timeframe was chosen based on published literature for 'Off' time reported in patients with advanced disease. For the effectiveness of BMT, data on the natural progression of the disease was used for the whole length of the model.

The efficacy of each treatment and their associated costs were modelled over a 20-year period. The resulting accumulation of costs and QALYs associated with each treatment, and the ratio between these values, indicates whether they are cost effective or not. A ratio of £30,000 per QALY is considered cost-effective for a new treatment to be adopted by the NHS.

Foslevodopa-foscarbidopa was found to result in patients experiencing a greater number of QALYs and lower total costs to the NHS, as compared with BMT.

Whilst foslevodopa-foscarbidopa is more expensive than BMT, it is much more effective at controlling the symptoms of Parkinson's disease and therefore overall costs the NHS less. This is because treating the more frequent and severe symptoms experienced by patients who receive BMT, for example being admitted to hospital after a fall, is very costly to the NHS. Foslevodopa-foscarbidopa therefore ends up being both less expensive and more effective at improving patients' quality of life than BMT.

Foslevodopa-foscarbidopa and LCIG were associated with similar clinical benefits and therefore similar total QALYs, with foslevodopa-foscarbidopa resulting in marginally fewer QALYs (5.40 QALYs for LCIG and 5.30 QALYs for foslevodopa-foscarbidopa). However, in terms of costs, LCIG is associated with higher treatment and administration costs to the NHS than foslevodopa-foscarbidopa, for example the costs associated with the surgical procedure necessary with the medicine.

Given that a number of assumptions had to be made when developing the cost-effectiveness model, a number of additional analyses were conducted to assess the impact of these assumptions on the results of the economic analysis. In other words, further analyses were undertaken to "pressure test" the validity of the models' outputs. For example, one of the additional analyses includes the impact that Parkinson's disease has on the quality of life of carers. The results of these additional analyses showed very similar results to the initial analysis, indicating that these assumptions had a limited impact on the final results of the analysis, meaning the assumptions could be made with greater confidence. Explained another way, the different modelling that was conducted did not have any significant impact on the original output, which provides confidence it is an accurate model.

Whilst the QALYs calculated within the economic model aim to capture all the benefits to patients' health-related quality of life associated with new treatments, it is not always possible to do so. In particular, 'Off' time only measures patients' control of their symptoms during their waking hours, and therefore does not take into account patients' sleep related symptoms. The improvements to patients' sleep and early morning symptoms associated with foslevodopa-foscarbidopa may therefore not be captured in the QALYs reported for the treatments. This represents some of the limitations and challenges of an economic assessment such as this, but the various modelling conducted demonstrates there can be confidence in the results regardless.

Additionally, the model used the EQ-5D questionnaire to measure patients' health-related quality of life. This questionnaire is not specific to Parkinson's disease, and may therefore not accurately capture the complex nature of the condition and its impact on patients' quality of life.

Overall, the results of the economic analysis shows that for the proposed group of patients to receive foslevodopa-foscarbidopa, it offers the best value for money to the NHS when compared with current available treatments.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Foslevodopa-foscarbidopa represents an important addition to the treatment options available to patients in the advanced stage of Parkinson's disease. Currently, patients with advanced Parkinson's disease face limited options. Two of these options, DBS and LCIG, require invasive surgical procedures which may be off-putting to many patients and have associated surgery-related adverse events.

Foslevodopa-foscarbidopa offers a non-invasive and reversible treatment method of delivering constant and stable concentrations of levodopa, a well-known and understood medicine that the patient can manage at home. Due to the subcutaneous administration of the medicine, Foslevodopa-foscarbidopa could be administered in an outpatient setting, as such patients are not required to stay overnight in hospital.

An important innovation of foslevodopa-foscarbidopa is its continuous, 24-hour delivery, which allows for control of symptoms overnight. Sleep disturbances and poor control of symptoms are commonly reported symptoms of Parkinson's disease, which have a highly detrimental impact on patients' quality of life and also that of their carer.

Current treatment options inadequately address these symptoms, as they are unable to maintain constant levels of dopamine in the brain overnight. Foslevodopa-foscarbidopa's novel method of both day and night-time administration allows for good control of motor symptoms continuously, including during sleep and the early-morning.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

No equality issues are expected in this appraisal.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

The following websites provide useful information relating to Parkinson's disease:

- Parkinson's UK. Available at: https://www.parkinsons.org.uk/
- European Parkinson's Disease Association at: https://www.epda.eu.com/
- Parkinson's foundation. Available at https://www.parkinson.org/
- NICE clinical guidelines for the treatment of Parkinson's disease in adults. Available at: https://www.nice.org.uk/guidance/ng71
- NHS overview of Parkinson's disease. Available at https://www.nhs.uk/conditions/parkinsons-disease/

Further information on NICE and the role of patients can be found at the following links:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE

- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Akinesia:** A temporary loss of the ability to move muscles voluntarily.
- **Amantadine:** A medicine typically used to treat side effects related to taking levodopa, in particular dyskinesia.
- **Apomorphine:** A medicine used to treat severe Parkinson's symptoms. It is a form of morphine that can increase the amount of dopamine available in the brain, which then decreases symptoms of Parkinson's disease.
- **Carbidopa:** A medicine that is usually given in combination with levodopa. Carbidopa improves the effectiveness of levodopa by inhibiting its conversion to dopamine before entering the brain. It can also be used to reduce the side effects of levodopa.
- **Catechol-O-methyltransferase (COMT):** An enzyme in the body which can block the action of levodopa. By blocking this enzyme, certain medications known as COMT inhibitors are able to improve the efficacy of levodopa.
- **Deep brain stimulation (DBS):** A surgical procedure used to treat Parkinson's disease. The surgery involves the implantation of permanent electrodes in various parts of the brain through which continuous pulses of electricity are given to control the symptoms of Parkinson's disease.
- **Dopamine:** A chemical produced by the brain that assists in the effective transmission of messages from one nerve cell to the next. People with Parkinson's disease have decreased amounts of the chemical in the brain. Dopamine coordinates the actions of movement, balance, and walking.
- **Dyskinesia:** Uncontrolled and involuntary movement that often occurs with long-term use of levodopa and longer time with Parkinson's disease.

- **EQ-5D-5L:** A self-assessed, health related, quality of life questionnaire. The scale measures quality of life on a five-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- **Foslevodopa-foscarbidopa:** A combination of two inactive forms of levodopa and carbidopa, known as prodrugs, which can be administered continuously by subcutaneous infusion. Once in the blood, the prodrugs are rapidly converted to levodopa and carbidopa.
- **Levodopa:** A medicine which contains a precursor form of the chemical dopamine. It is the most commonly used treatment to control symptoms of Parkinson's disease.
- **Levodopa-carbidopa intestinal gel (LCIG):** A combination of levodopa and carbidopa administered continuously via a gastric tube which is implanted by surgical insertion.
- **Monoamine oxidase type B (MAO-B):** An enzyme in the body that breaks down dopamine in the brain. By blocking this enzyme, certain treatments can increase dopamine levels in the brain, allowing for better symptom control.
- **Network meta-analysis (NMA):** A statistical method used to indirectly compare the effectiveness of multiple treatments by combining multiple clinical studies.
- **'On' time:** Time spent by patients with Parkinson's disease when symptoms are well controlled.
- **'Off' time:** Time spent by patients with Parkinson's disease when symptoms are poorly controlled.
- **PDQ-39:** A 39 item questionnaire which assesses how often patients with Parkinson's disease experience difficulties across eight dimensions of daily living including relationships, social situations and communication, as well as specific dimensions of functioning and wellbeing.
- **Subcutaneous infusion:** Infusion of fluids through a needle placed under the skin.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

September 2022

File name	Version	Contains confidential information	Date
ID3876 fos-dopa EAG Clarification letter_Final_30Sept22 [Fully redacted]	Final	No	30th September 2022

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

Population

A1. Priority question. Please provide baseline characteristics of prior deep brain stimulation (DBS) and apomorphine use for patients in M15-736 and M15-741.

Patients who received prior DBS were excluded from the M15-736 trial. Patients recruited into M15-741 were eligible to receive foslevodopa-foscarbidopa after DBS, provided that the patients were considered stable and were still levodopa-responsive and met all other eligibility criteria; of the 244 patients in the M15-741 safety analysis set, [redacted] received a DBS procedure.

Patients recruited in M15-736 could receive apomorphine intermittent injection as a rescue medication during the screening period [redacted] though it had to be discontinued prior to starting oral carbidopa/levodopa (CD/LD). Patients who received previous continuous subcutaneous infusion (CSCI) apomorphine were eligible for recruitment into M15-741 though must have discontinued within 30 days of commencing foslevodopa-foscarbidopa. A total of [redacted] received prior CSCI apomorphine.

Table 1 presents the demographics and baseline characteristics of patients who previously received either CSCI apomorphine or DBS in the M15-741 study. Demographic and baseline characteristics for patients who previously received either CSCI apomorphine or DBS closely matches the baseline characteristics from the trial population (see Table 18, Document B). Patients are similarly matched for age, sex, race, and weight. Differences in geographic region for patients who previously received either CSCI apomorphine or DBS could reflect differences in treatment patterns in these respective areas.

Table 1: Demographics and Baseline Characteristics of Patients Taking Continuous Apomorphine or DBS as Prior Anti-Parkinson's Disease Medications in M15-741 (SAS)

	Prior DBS (N = [redacted])	Prior CSCI Apomorphine (N = [redacted])
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Age category, n (%)		
<65 years	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]
Multiple	[redacted]	[redacted]
Weight, kg		
Mean (SD)	[redacted]	[redacted]
BMI (kg/m^2), n (%)		
Mean (SD)	[redacted]	[redacted]
Geographic Region, n (%)		
North America	[redacted]	[redacted]
Europe and Australia	[redacted]	[redacted]
Japan	[redacted]	[redacted]
Mini-Mental State Examination Total Score		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Brief Neurological Examination, n (%)		
Mental Status, Normal	[redacted]	[redacted]
Cranial Nerves, Normal	[redacted]	[redacted]
Motor System, Normal	[redacted]	[redacted]
Sensory System, Normal	[redacted]	[redacted]
Reflexes, Normal	[redacted]	[redacted]
Coordination, Normal	[redacted]	[redacted]

	Prior DBS (N = [redacted])	Prior CSCI Apomorphine (N = [redacted])
Gait, Normal	[redacted]	[redacted]
Station, Normal	[redacted][a]	[redacted][a]

[a]Missing data for one patient.
Abbreviations: BMI: body mass index; CSCI: continuous subcutaneous infusion; DBS: deep brain stimulation; SAS: safety analysis set; SD: standard deviation.
Source: AbbVie Data on File. M15-741 Clinical Study Report (IA3).[1]

A2. Please provide a discussion around the potential impact on the clinical efficacy of foslevodopa compared with best medical therapy (BMT) and levodopa-carbidopa intestinal gel (LCIG), of the inclusion of patients in the M15-736 and M15-741 trials for whom apomorphine or DBS was suitable, i.e. a broader population than that addressed in the submission.

In the CS (Document B), foslevodopa-foscarbidopa is positioned for use in patients with advanced PD with symptoms not adequately controlled by their current medical therapy (i.e. BMT), or for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control.

There is expected to be no impact on the clinical efficacy of foslevodopa-foscarbidopa compared with BMT and LCIG regarding the inclusion of patients in the M15-736 and M15-741 trials for whom apomorphine or DBS was suitable. Further, based on clinical expert opinion, prior use of apomorphine is not expected to affect efficacy. As can be seen in Table 1 above 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 CSCI apomorphine or DBS in M15-741 were similarly matched to the full trial populations who were enrolled in M15-736 and M15-741 study. Accordingly, outcomes for these patients are not expected to be different from the broader trial populations.

SLR

A3. Please provide the reason for exclusion for each of the studies included in the systematic literature review which subsequently did not contribute to the submission (33 clinical trials and 118 non-comparative studies).

The full list of excluded studies and reason for exclusion is available in the Excel file provided in the reference pack of the CS ('AbbVie Data on File_Clinical SLR_Excluded studies').

Trial design

A4. Priority question. The external assessment group (EAG) considers that the differences between treatment arms in terms of adverse effects (AEs) and OFF time in the morning may have caused blinding to fail in the M15-736 trial. As

such, please can the company comment on the likely impact of this on the different outcomes assessed.

It is not expected that blinding failed in the M15-736 trial. Patients (and caregivers, if applicable) remained blinded to the treatment throughout the study. CD/LD immediate release (IR) tablets were over-encapsulated and identical in appearance to the placebo capsules. The over-encapsulated CD/LD IR tablets and placebo capsules were packaged identically. Foslevodopa-foscarbidopa solution for infusion and the placebo solution for infusion were packaged identically.

AbbVie would like to highlight that the risk of potential unblinding of participants is inherent to all double-blind randomised controlled trials and is not specific to this trial; i.e., differences between arms for health-related quality of life (HRQoL), mobility, functionality, and AEs could give patients reason to “predict” the treatment that they are receiving. This may be even more apparent in placebo-controlled trials. As such, the possibility of inadvertently unmasking blinded participants based on the observed AEs or effect on symptoms cannot be entirely ruled out. However, all requirements of good clinical practice were implemented into the study protocol and statistical analysis plan to ensure stringent blinding of treatment allocation for the investigators and their site staff, the study participants, and the clinical team. Despite differences between treatment arms in M15-736 for AEs and “Off” time in the morning, it could be speculative to draw conclusions on blinding.

A5. Priority question. Please confirm if patients in M15-736 trial were unblinded after treatment discontinuation.

AbbVie can confirm that patients were not unblinded after treatment discontinuation.

A6. Priority question. Please clarify if patients’ Parkinson's disease (PD) diary entries were continued to be captured at each treatment visit after treatment discontinuation until the end of the M15-736 trial?

AbbVie can confirm that PD diary entries were continued to be captured at each treatment visit after discontinuation where possible, except if the reason for discontinuation was due to lack of entries.

A7. Please clarify the choice of 6mm and 9mm Neria guard infusion set for patients in M15-736. Please specify if both widths are intended for delivery of foslevodopa in clinical practice.

Investigators in the M15-736 and M15-741 trials selected the length of the cannula from the two provided standard options (6mm and 9mm) considering individual patient characteristics such as thickness of the abdominal subcutaneous fat tissue. The appropriate cannula was one deemed long enough to deliver the study drug solution to the subcutaneous tissue without infiltrating the muscle wall. The 6mm and 9mm cannula lengths accommodate the range of needs for the target population and are the intended lengths for delivery of foslevodopa-foscarbidopa in clinical practice.

A8. Please provide data on concomitant therapies used during the stabilisation and double-blind period of M15-736, in each treatment arm.

Following a 6- to 60-day Screening Period, patients entered a 14- to 21-day Oral CD/LD Stabilisation Period, during which all LD-containing medications, regardless of formulation, as well as those containing catechol-O-methyltransferase (COMT) inhibitors, were converted to an equivalent amount of CD/LD IR. All other concomitant PD medications, although allowed, were required to remain unchanged until study completion, unless specific safety conditions dictated their modification. Concomitant medications during stabilisation and the double-blind period are presented in Table 2.

Table 2: Concomitant Parkinson's Disease Medication in the M15-736 Trial (SAS)

Medication	Foslevodopa-foscarbidopa (N = [redacted])	Oral CD/LD (N = [redacted])
Any concomitant medications, n (%)	[redacted]	[redacted]
Anticholinergic agents, n (%)	[redacted]	[redacted]
Derivatives benzatropine, n (%)	[redacted]	[redacted]
Trihexyphenidyl, n (%)	[redacted]	[redacted]
Dopaminergic agents, n (%)	[redacted]	[redacted]
Amantadine, n (%)	[redacted]	[redacted]
Amantadine hydorchloride, n (%)	[redacted]	[redacted]
Carbidopa monohydrate; levodopa, n (%)	[redacted]	[redacted]
Pramipexole, n (%)	[redacted]	[redacted]
Pramipexole dihydrochlroide monohydrate, n (%)	[redacted]	[redacted]
Ropinirole, n (%)	[redacted]	[redacted]
Rotigotine, n (%)	[redacted]	[redacted]
Rasagiline, n (%)	[redacted]	[redacted]
Rasagiline mesylate, n (%)	[redacted]	[redacted]
Safinamide, n (%)	[redacted]	[redacted]
Safinamdie mesylate, n (%)	[redacted]	[redacted]
Selegiline, n (%)	[redacted]	[redacted]
Other PD drugs, n (%)	[redacted]	[redacted]
Istradefylline, n (%)	[redacted]	[redacted]

Abbreviations: CD/LD: carbidopa/levodopa; PD: Parkinson's disease; SAS: safety analysis set.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[2]

A9. Please clarify what days were PD diary recording days in M15-736. For example, was the patient's PD diary to be filled in over (at least) three consecutive days within seven days prior to each clinical visit?

A valid diary day is one with no more than two hours of missing data (four or fewer missing 30-minute entries) for the entire 24-hour diary and the entry must be within the 7 days preceding the day of the clinical visit. Additionally:

- If more than three valid diary days were available for Baseline or post-baseline visits, the three days closest to the clinical visit were used.
- If only two valid diary days were available prior to a clinic visit, data from the two days were used to calculate the average daily normalised "Off" or "On" times.
- If only one valid diary day was available, the value from the one valid diary day was the visit value.
- If no valid diary day was available for a visit, the average daily normalised "Off" or "On" times were missing for that visit.

An invalid PD Diary day was not used in the calculation of the average daily normalised or absolute "Off" or "On" times for the visit with which it was associated.

A10. Please provide the average daily normalised 'ON' time without troublesome dyskinesia responder criteria used in M15-736, which are mentioned in the description of the statistical analysis (company submission [CS], Table 7).

Given that there is no well-accepted responder definition for average daily normalised "On" time without troublesome dyskinesia, the percentage of patients with at least a given percentage of improvement (from ≥ 0% to 100% in 5% increments) in average daily normalised "On" time without troublesome dyskinesia at Final Visit was summarised, which demonstrated consistently greater improvement in the foslevodopa-foscarbidopa group than in the Oral CD/LD group at each threshold (Figure 1). Here, 'Dyskinesia' is from the PD diary that was used in the M15-736 and M15-741 studies, which is the 'Hauser Parkinson's Disease Diary'.

Figure 1: Percentage of Patients who Achieved at Least a Certain Percentage of Improvement in Average Daily Normalised "On" Time Without Troublesome Dyskinesia at Final Visit in the M15-736 Trial (FAS)

ABBV-951 = foslevodopa-foscarbidopa.
Abbreviations: CD/LD: carbidopa/levodopa; FAS: full analysis set.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[2]

Clinical effectiveness

A11. Priority question. Please provide data on the number of patients with 0 to 16 hours of OFF time at baseline, 4 weeks, 8 weeks and 12 weeks in each treatment arm of M15-736. Please provide the data in a table format as well as visually represented in a figure equivalent to Figure 28 of the CS.

Table 3 and Table 4 present the number of patients and patient distribution of foslevodopa-foscarbidopa in M15-736 by health state at Days 29, 57 and 85. Table 4 and Figure 3 show the same data for the oral comparator arm in M15-736. The tables and graphs clearly show that the number of patients in the lower OFF states increase more following administration of foslevodopa-foscarbidopa versus oral therapy.

Table 3: Number of patients receiving foslevodopa-foscarbidopa with 0 to 16 hours of OFF time at baseline, 4 weeks, 8 weeks, and 12 weeks in M15-736

NROFF	BASELINE	DAY 29	DAY 57	DAY 85	Total
OFF 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NROFF	BASELINE	DAY 29	DAY 57	DAY 85	Total
OFF 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4. Number of patients receiving oral treatment with 0 to 16 hours of OFF time at baseline, 4 weeks, 8 weeks, and 12 weeks in M15-736

NROFF	BASELINE	DAY 29	DAY 57	DAY 85	Total
OFF 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 2: Distribution of patients receiving foslevodopa-foscarbidopa with 0 to 16 hours of OFF time at baseline, 4 weeks, 8 weeks, and 12 weeks in M15-736

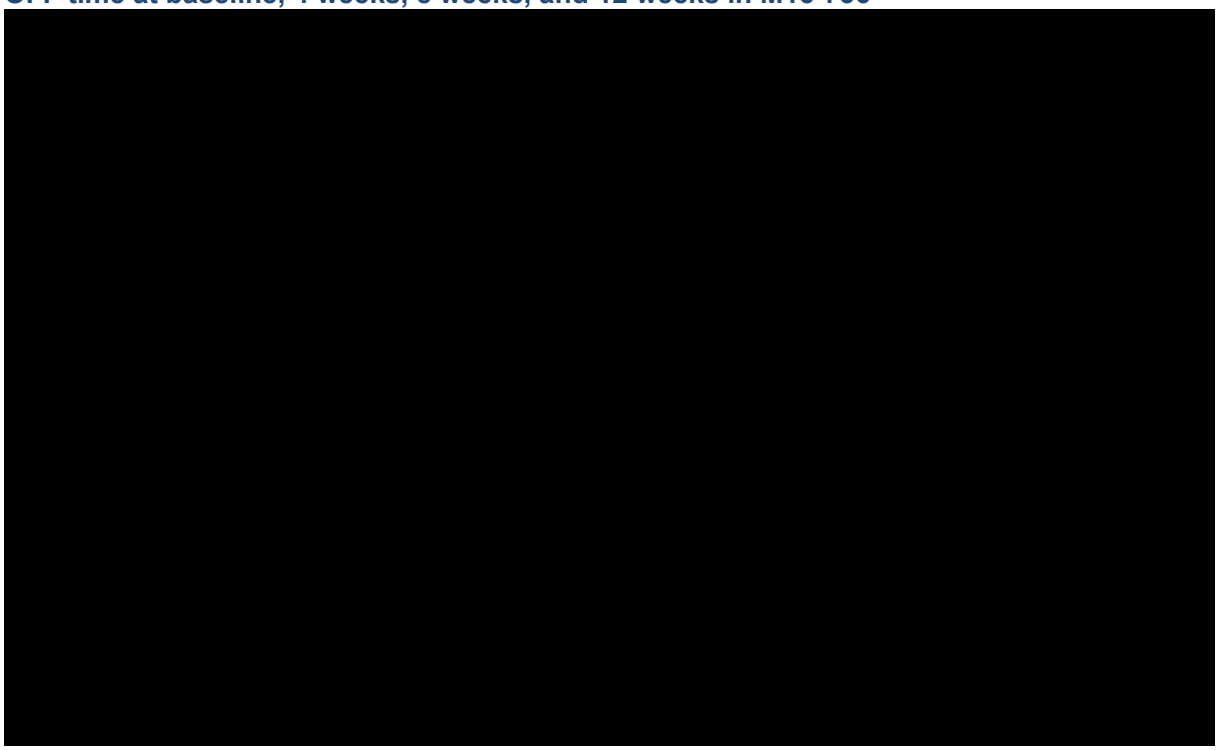


Figure 3: Distribution of patients receiving oral treatment with 0 to 16 hours of OFF time at baseline, 4 weeks, 8 weeks, and 12 weeks in M15-736

A12. Priority question. Please provide the number of patients who had missing data due to treatment discontinuation or due to missing valid PD diary data or

other reasons, at each visit for ON time without troublesome dyskinesia and for OFF time in M15-736 and M15-741. Please also provide the mean time to treatment discontinuation in each arm of M15-736 and in M15-741.

The number of patients who had missing data due to treatment discontinuation or due to missing valid PD diary data or other reasons in M15-736 are presented in Table 5. The corresponding data are presented in Table 6 for the M15-741 trial. All data are presented by each visit. The mean time to treatment discontinuation in each arm of M15-736 and in M15-741 is presented in Table 7 and Table 8 respectively.

Table 5: Summary of Patients Not Included in the Analysis of Parkinson's Disease Diary by Visit in the M15-736 Trial (FAS)

	Treatment	N	Patients Not Included Due To…		
			Treatment Discontinuation	No Valid PD Diary Day	Any Other Reason
Baseline	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]
Day 8	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]
Day 15	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]
Day 22	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]
Day 29	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]
Day 57	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]

	Treatment	N	Patients Not Included Due To…		
			Treatment Discontinuation	No Valid PD Diary Day	Any Other Reason
Day 85	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CD/ LD: Carbidopa/ Levodopa; FAS: Full Analysis Set; FosL-FosC: Foslevidopa-Foscarbidopa; PD: Parkinson's Disease.
Source: AbbVie Data on File. M15-736 Clinical Study Report.2

Table 6: Summary of Patients Not Included in the Analysis of Parkinson's Disease Diary by Visit in the M15-741 Trial (FAS)

	N	Patients Not Included Due To…		
		Treatment Discontinuation	No Valid PD Diary Day	Any Other Reason
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 1	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]
Week 39	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS: Full Analysis Set.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[2]

Table 7: Summary of Time (Days) to Treatment Premature Discontinuation (M15-736 Trial FAS)

	N	Mean (SD)	Median	Min, Max
FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CD/ LD: Carbidopa/ Levodopa; FAS: Full Analysis Set; FosL-FosC: Foslevidopa-Foscarbidopa; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[2]

Table 8: Summary of Time (Days) to Treatment Premature Discontinuation (M15-741 Trial FAS)

	N	Mean (SD)	Median	Min, Max
FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS: Full Analysis Set; FosL-FosC: Foslevidopa-Foscarbidopa; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[2]

A13. Priority question. Overall discontinuations in M15-741 are reported as 103 patients out of 244 who initiated treatment (CS, table 40). However, in CS Table 44 overall treatment discontinuations are reported as 66/244. Please explain this discrepancy in the data.

Tables 40 and 44 of the CS report rates of discontinuation from the M15-741 study at different cut-off dates. Table 40 reflects a 52-week cut-off, while Table 44 reflects a 12-week cut-off. In Table 44, discontinuation is referred to as “premature discontinuation” to reflect the shorter follow-up.

A14. Priority question. Please provide efficacy results available from the ongoing M15-737 trial, the long-term follow up study of M15-741. Please confirm when any planned interim and final analyses for this study are expected.

Study M15-737 is an open-label, single-arm, multicentre extension study to continue assessing the local and systemic safety and tolerability of foslevidopa-foscarbidopa administered as a CSCI for 24 hours daily. Approximately 130 adult subjects who completed the parent study (Study M15-741) are expected to enrol in this study.

The most recent interim analysis available for M15-737 has a data cut-off date of 2nd March 2022; the next interim database lock is planned for [redacted], whereby the outcomes of analyses will be available in late [redacted] and Last Subject Last Visit (LSLV) for Week 96. The last Primary Study Visit for study M15-737 is projected for [redacted] after which, final analyses will be produced. The efficacy results for the M15-737 trial are presented in Table 9.

As of the data cutoff date for this interim report (2nd March 2022), the [redacted] subjects enrolled in this study were exposed to study drug for a mean of [redacted]. A total of [redacted] subjects were exposed to foslevidopa-foscarbidopa for ≥ [redacted] days. The mean changes from Study M15-737 baseline (the last assessment in parent Study M15-741) in "Off" time, "On" time with non-troublesome dyskinesia, and "On" time with troublesome dyskinesia were small. These results demonstrate the sustained efficacy over time after the subjects had received 12 months of treatment with foslevidopa-foscarbidopa in Study M15-741.

Table 9: A Summary of Key Efficacy Outcomes at Week 48 from the M15-737 Study

	Foslevidopa-foscarbidopa
Change from baseline to Week 48 in hours of average daily normalised 'On' time without troublesome dyskinesia	
Baseline, N	[redacted]
Baseline, Mean average daily normalised 'On' time without troublesome dyskinesia	[redacted]
Week 48, Mean average daily normalised 'On' time without troublesome dyskinesia (SD)	[redacted]
Mean change from baseline (SD)	[redacted]
p-value	[redacted]
Change from baseline to Week 48 in hours of average daily normalised 'Off'	
Baseline, N	[redacted]
Baseline, Mean average daily normalised 'Off' time (SD)	[redacted]
Week 48, Mean average daily normalised 'Off' time (SD)	[redacted]
Mean change from baseline (SD)	[redacted]
p-value	[redacted]
Change from Baseline to Week 48 in MDS-UPDRS Part II Score	
N	[redacted]
Baseline, Mean MDS-UPDRS Part II Score	[redacted]
Week 48, Mean MDS-UPDRS Part II Score (SD)	[redacted]
Mean change from baseline (SD)	[redacted]
p-value	[redacted]

* A total of [redacted] patients had outcomes reported at baseline. [redacted] of these had follow-up to Week 48.
** A total of [redacted] patients had outcomes reported at baseline. [redacted] of these had follow-up to Week 48.
Abbreviations: MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SD: standard deviation.
Source: AbbVie Data on File. M15-737 Clinical Study Report.

A15. Priority question. Please provide efficacy and safety results available from the ongoing M20-098 trial, the long-term follow up study of M15-736. Please confirm when any interim and final analyses are expected.

A summary of efficacy outcomes from the most recent interim analysis (first interim analysis; data cut-off on 29th September 2021) for the M20-098 trial are presented in Table 10. A total of 103 patients who completed the parent study (Study M15-736) have been enrolled in this ongoing extension study.

As of the data cut-off date (29th September 2021), the sample size for Week 24 assessments was [redacted] patients. Therefore, outcomes at Week 4 are presented. There was little change from Study M20-098 baseline in "Off" time and in "On" times for the [redacted] patients with PD Diary assessments at Week 4 in the foslevodopa-foscarbidopa / foslevodopa-foscarbidopa group, which suggests that efficacy was maintained. Improvements in "Off" time and in "On" times were observed for the [redacted] patients with PD Diary assessments at Week 4 in the Oral CD/LD /foslevodopa-foscarbidopa group. Results were similar for MDS-UPDRS Part II scores.

Table 10: A Summary of Key Efficacy Outcomes at Week 4 from the M20-098 Study

	Foslevodopa-foscarbidopa/ Foslevodopa-foscarbidopa	Oral CD/LD/ Foslevodopa-foscarbidopa
Change from baseline to Week 4 in hours of average daily normalised 'On' time without troublesome dyskinesia		
Baseline, N	[redacted]	[redacted]
Baseline, Mean average daily normalised 'On' time without troublesome dyskinesia	[redacted]	[redacted]
Week 4, Mean average daily normalised 'On' time without troublesome dyskinesia (SD)	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Change from baseline to Week 4 in hours of average daily normalised 'Off'		
Baseline, N	[redacted]	[redacted]
Baseline, Mean average daily normalised 'Off' time	[redacted]	[redacted]
Week 4, Mean average daily normalised 'Off' time	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Change from Baseline to Week 4 in MDS-UPDRS Part II Score		
N	[redacted]	[redacted]
Baseline, Mean MDS-UPDRS Part II Score	[redacted]	[redacted]

	Foslevodopa-foscarbidopa/ Foslevodopa-foscarbidopa	Oral CD/LD/ Foslevodopa-foscarbidopa
Week 4, Mean MDS-UPDRS Part II Score (SD)	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]

Abbreviations: CD/LD: carbidopa/levodopa; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SD: standard deviation.
Source: AbbVie Data on File. M20-098 Clinical Study Report.

Foslevodopa-foscarbidopa was generally safe and well tolerated. As of the data cut-off date for this interim report (29th September 2021), AEs had been reported for [redacted] patients ([redacted]%). The majority of AEs were nonserious and were mild or moderate in severity. AEs reported for ≥ 5% of patients were infusion site cellulitis, infusion site erythema, infusion site pain, and fall. SAEs were reported for [redacted] patients ([redacted]%). The only SAE that was reported for more than 1 patient was infusion site cellulitis ([redacted] patients, [redacted]%). [redacted] patients had SAEs that led to premature discontinuation of study drug. The treatment discontinuation rate was higher in the Oral CD/LD /foslevodopa-foscarbidopa group ([redacted]%) compared to the foslevodopa-foscarbidopa/ foslevodopa-foscarbidopa group ([redacted]%). The overall incidence and nature of AEs was consistent with what was observed in the parent study (Study M15-736). Analysis of AEs did not show any clinically meaningful differences by subgroup for age, sex, race, country, concomitant dopamine agonist use, BMI, or duration of PD.

Infusion site reactions were reported for [redacted] patients ([redacted]%), and infusion site infections were reported for [redacted] patients ([redacted]%). In the majority of patients, infusion site AEs were nonserious, were mild or moderate in severity, and resolved with some requiring treatment.

No deaths were reported. No clinically meaningful changes from Baseline in clinical laboratory measurements, vital signs and weight, or ECG were observed. There was no evidence of increased suicidality with foslevodopa-foscarbidopa based on review of the C-SSRS data. No clinically meaningful changes from Baseline were observed in QUIP-RS scores.

The next interim database lock for M20-098 is planned for [redacted] and LSLV for Week 96. The last Primary Study Visit for M20-098 is currently projected for [redacted]. Final analyses will be produced following LSLV for Week 96 when the last Primary Study Visit occurs.

A16. Please provide the results for the secondary outcome of M15-736: change from Baseline to Week 12 in median bradykinesia score (BK50) as assessed by the Parkinson's KinetiGraph™/Personal KinetiGraph™ (PKG) wearable device.

Outcomes for change from Baseline to Week 12 in median bradykinesia as assessed by the PKG wearable device are presented in Table 11. While there was an apparent treatment effect in favour of the oral CD/LD group, it is likely a result of the analysis being conducted at a group level rather than stratifying patients according to their baseline bradykinesia and dyskinesia scores.

Table 11: Change from Baseline to Week 12 in median bradykinesia as assessed by the PKG wearable device (FAS)

Treatment group	Baseline, N	Baseline, mean (SD)	Mean change (SD)	LS Mean change (SE)	LS Mean difference (SE)	p value
Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Foslevodopa-foscarbidopa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CD/LD: carbidopa/levodopa; FAS: full analysis set; LS: least squares; PKG: Parkinson's KinetiGraph; SD: standard deviation; SE: standard error
Source: AbbVie Data on File. M15-736 Clinical Study Report.[2]

Network meta-analysis (NMA)

A17. Priority question. Please re-run the NMA for ON time without troublesome dyskinesia and the NMA for OFF time, excluding the Weaver 2009 and TOLEDO trials. The exclusion of these trials may affect the convergence of the random effects model. However, please run both fixed effect and random effects model for both outcomes. Please present the results for foslevodopa and LCIG versus BMT as well as for foslevodopa versus LCIG.

Results of the NMA excluding the Weaver 2009 and TOLEDO trials for 'On' time without troublesome dyskinesia and 'Off' time are presented in Table 12 and Table 13, respectively. The network is provided in Figure 4.

Figure 4: Network of studies included in the 'On' and 'Off' time analysis

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel.

Table 12: Difference in mean 'On' time without troublesome dyskinesia change from baseline (95% CrI)

Treatment	RE (DIC = 16.36)	FE (DIC = 15.79)
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]

Abbreviations: BMT: best medical therapy; CrI: credible interval; DIC: deviance information criteria; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.

Table 13: Difference in mean 'Off' time change from baseline (95% CrI)

Treatment	RE (DIC = 16.36)	FE (DIC= 15.79)
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]

Treatment	RE (DIC = 16.36)	FE (DIC= 15.79)
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]

Abbreviations: BMT: best medical therapy; CrI: credible interval; DIC: deviance information criteria; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.

Please note that fixed effects (FE) and random effects (RE) models were fitted and compared on deviance information criteria (DIC) to determine the better fitting model (lower DIC values indicate better fit to the data). When DIC differences are small (i.e., less than 3 to 5 points) across different fitted models, common practice is to choose the simplest model because the additional complexity does not result in better model fit. For both outcomes, FE provided the better model fit.

A18. Priority question. Please provide an NMA of foslevodopa versus LCIG and BMT for treatment discontinuations including all relevant trials.

AbbVie believe that an NMA for treatment discontinuation between foslevodopa-foscarbidopa, LCIG and BMT is not appropriate. While both therapies continuously deliver levodopa-based therapy for the treatment of motor fluctuations in advanced PD, the modalities are different.

The administration of LCIG requires the surgical placement of a percutaneous endoscopic gastrojejustomy (PEG-J) tube in the small intestine, whereas the administration of foslevodopa-foscarbidopa does not require surgical placement and is infused subcutaneously via a cannula placed by the patient every 1 to 3 days.

Foslevodopa-foscarbidopa is a minimally invasiveness procedure, which makes it easier for a patient to start therapy but equally easy to interrupt or stop therapy at the first challenge. Education around the use of the infusion set has proved to be essential for the success of this therapy, as demonstrated in the M15-741 trial.[3]

Discontinuation of LCIG requires the HCP to remove the tubing, whereas foslevodopa-foscarbidopa can be discontinued at any time by the patient. Accordingly, AbbVie believe that an NMA for treatment discontinuation between foslevodopa-foscarbidopa, LCIG and BMT is not appropriate.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user-selectable options in the economic model so that these can be combined.

Furthermore, if the company chooses to update its base case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses

incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

Model structure

B1. Priority question. The last observation carried forward (LOCF) period is stated to last up to month 36 based on supportive evidence from M15-741 demonstrating sustained effect. However, this trial lasted 12 months and Kalabina *et al.* 2019, which uses the same method/source for determining natural disease progression assumes this period starts at cycle 3 (year 1.5). What is the origin of the assumed 36 month cut-off point?

The 36 month cut-off point for the LOCF assumption was based on expert clinical opinion solicited as part of the development of the CS. Consulted clinicians were asked to estimate the long-term efficacy profile they would expect to see for device-aided therapies (DATs), based on their experience in clinical practice. They indicated that patients receiving DATs would typically be expected to see a decrease in OFF time in the weeks following treatment initiation, which would then be maintained as long as patients were still receiving treatment. Clinicians indicated that they had experience of patients receiving DATs for five years; this was therefore considered an upper bound for the LOCF cut-off point. Given that clinical evidence exists for treatment efficacy lasting over two years, this was chosen as a lower bound.[4] The 36 month cut-off point was therefore chosen as a plausible conservative estimate for the time patients would be expected to maintain treatment benefit whilst still receiving treatment with foslevodopa-foscarbidopa or LCIG.

B2. Previous models which used OFF time, including the Canadian Agency for Drugs and Technologies in Health (CADTH) submission for apomorphine, Kalabina *et al.* 2019, Walter and Odin 2015, Chaundhuri *et al.* 2022, Lowin *et al.* 2011 and Lowin *et al.* 2017, all represented OFF time with 4 health states. Furthermore, the Adelphi real-world evidence (RWE) data used for costs, also presented OFF time in this 4-state form. Please explain the rationale for requiring increased granularity provided by one hour increments compared to previous models?

The modelling approach was based on secondary research conducted to evaluate potential model structures based on previous cost-effectiveness models in advanced PD; this is presented in Table 50, Section B.3.2.2 of the CS.

The model structure was developed such as to appropriately reflect improvements in symptom control experienced by patients receiving treatment. A clinically meaningful change of one hour,[5] which was validated by an expert, was used to achieve this. Overall, this model structure was therefore considered to better align to the assessment of advanced PD observed in clinical practice compared with earlier models.

B3. As a scenario, please provide the option for patients to discontinue from foslevodopa to LCIG.

The rationale for not considering patients to discontinue from foselvedopa-foscarbidopa to LCIG is that this was not considered an adequate reflection of what might be expected in clinical practice. For example, introducing a new infusion set (in M15-741) that is now the only intended commercial infusion set resulted in numerically lower rates of discontinuation compared with the original set ([redacted]% and [redacted]% due to AEs by Week 12 respectively; see Table 44 of Document B). Clinical expert opinion suggested that LCIG follow-on treatment may then only be a realistic treatment option in those who might discontinue foselvedopa-foscarbidopa due to severe subcutaneous reaction such that it could not be treated by antibiotics, who are responsive to levodopa, and who are willing to undergo required surgery to receive LCIG. Given that this could be a minority of patients and that there are no data from clinical practice for this, outcomes from such a scenario analysis could be speculative and AbbVie have opted not to conduct this.

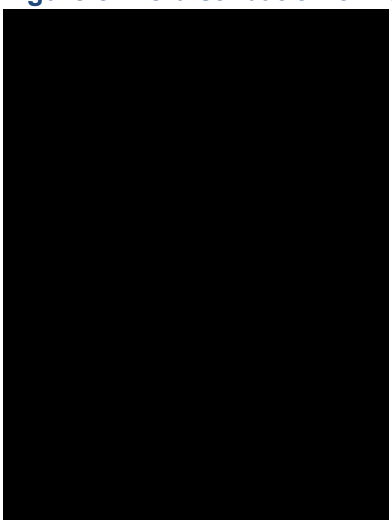
Baseline patient characteristics

B4. Please provide a scenario with the initial distribution of OFF states fit to a model (i.e. zero-inflated negative binomial, beta-binomial, negative binomial, poisson).

AbbVie have fit several models on the baseline patient distribution. The graph (Figure 5) below shows the initial trial distribution at the far left, followed by a zero-inflated Poisson (ZIP) model, a negative binomial model, and a zero-inflated negative binomial model (ZINB). The ZIP, negative binomial and ZINB models are relatively similar in terms of distribution but also show similarity with the trial distribution. The trial shows a slightly higher proportion of patients for OFF state 7, and lacks patients in some of the higher OFF states; the models that were fit come with a slightly more symmetrical shape. Nevertheless, all models place the vast majority of patients in middle (and lower) health states; and all show that only few patients reside in the higher OFF states.

Overall, we can conclude that the models that were fit show a similar patient distribution as the trial. As such, applying a model to estimate the initial patient distribution will likely have limited impact on the outcomes. Hence, AbbVie suggests applying the trial-based distribution, to prevent deliberate manipulation of the source data and preventing non-required bias that could affect all subsequent transitions.

Figure 5: Re-distribution of Patients by OFF State



Abbreviations: ZINB: zero-inflated negative binomial model; ZIP: zero-inflated Poisson.

Treatment effectiveness within the model

B5. Priority question. Figure 5 in the company submission demonstrates the majority of the reduction in mean OFF hours is achieved by day 8 and only minor changes occur between day 29 and day 85. Therefore, the LOCF assumption that change from baseline to 3 months continues for 3 years is an over extrapolation of the data. Please can you:

a) **Decrease the cycle length during the trial period to 1 month and use the month to month data to inform the transition matrices. In this case the LOCF would be the transition between month 2 and month 3 in the trial, adjusted to match the longer cycle length. Apply these changes to the scenario requested in B8.**

AbbVie believe that applying the treatment effect between the end of month 2 and end of month 3 would not be clinically realistic. In the CS (Document B), Figure 5 shows that there is a slight increase in the "Off" time between these time points for foslevodopa-foscarbidopa. This is only a minor increase in the short-term and could be explained by clinical variance. By extrapolating this transition, there would be a poorer disease progression for foslevodopa-foscarbidopa compared to BMT (which shows a constant "Off" time between months 1 to 3) during the LOCF period. Further, the M15-741 trial shows that foslevodopa-foscarbidopa lowers the "Off" time for up to a year compared with baseline (Table 23, Document B). Hence, the original approach – that extrapolates the 3-month foslevodopa-foscarbidopa treatment effect – is the most appropriate.

b) Provide an option to fix health states for the LOCF period. This would mean patients are assumed to experience no improvement or decline in off-time over the 3 years after the trial.

As per above, the M15-741 trial shows that foslevodopa-foscarbidopa lowers the "Off" time for up to a year compared with baseline (Table 23, Document B). Hence, AbbVie believe that the original approach – that extrapolates the 3-month foslevodopa-foscarbidopa treatment effect – is the most appropriate.

B6. Priority question. Transition matrices appear to remain the same each cycle regardless of cycle length for duodopa and ABBV treatment. In order to maintain the LOCF assumption, please adjust these rates to 6 monthly probabilities, as has been done with natural disease progression.

The changes to the foslevodopa-foscarbidopa and LCIG transitions requested by the EAG have been implemented as a scenario analysis, the results of which are presented in Table 14 below.

Please note that results of all scenarios are presented as probabilistic results.

Table 14: Results of the scenario analysis assuming fixed health states during the LOCF period for foslevodopa-foscarbidopa and LCIG, PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.22	-	-	-
LCIG	[redacted]	5.31	[redacted]	−0.09	[redacted]
BMT	[redacted]	4.52	[redacted]	0.69	Foslevodopa-foscarbidopa dominant

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

B7. Priority question. The relative risk figure used in the model (worksheet "ITC Input" cell E100) is 1.096 yet the relative risk calculated in table 54 of the company submission is 1.04. Please confirm which value is correct?

AbbVie can confirm that there was a typographical error in the submission document; the correct value for the relative risk is 1.096. This is due to typographic errors in Table 29 of Document B. Results for the FE model (Mean Reduction in "Off" Time Relative to BMT), should be [redacted] for foslevodopa-foscarbidopa and [redacted] for LCIG compared with BMT respectively. This yields a relative risk calculation of [redacted] which equals a relative risk ratio of 1.096, as reported in the model calculation.

a) According to the NMA results displayed in table 29 of the company submission the difference between change in mean off time between LCIG and foslevodopa does not appear to be statistically significant. Please provide a scenario assuming no difference in efficacy.

In the base case analysis, mean change from baseline in 'Off' time relative to BMT was the largest for [redacted] (Table 29 of Document B). Further, [redacted] also demonstrated the highest likelihood of ranking as the top treatment as given by the highest SUCRA amongst all treatment options (vs. LCIG and BMT). These results did not achieve statistical significance however.

Despite this, foslevodopa-foscarbidopa would provide the first and only treatment option that would be administered as a continuous subcutaneous infusion (CSCI), 24 hours/day, in contrast with LCIG, whereby treatment is usually administered during the patient's awake period. This could confer other efficacy benefits for foslevodopa-foscarbidopa, such as consistent overnight dosing and improved sleep symptoms and early morning "Off" status. Indeed in the FE model, foslevodopa-foscarbidopa was estimated to have a [redacted] in PDSS-2 compared with LCIG at 3 months.

AbbVie believe that it is unlikely that there is no difference in efficacy between foslevodopa-foscarbidopa and LCIG, however have conducted a scenario analysis to test the impact that this could have.

To implement a scenario of equal efficacy, the relative risk for LCIG versus foslevodopa-foscarbidopa was assumed to be equal to 1. The results of this scenario are shown in Table 15.

Table 15: Results of the scenario analysis assuming equal efficacy between foslevodopa-foscarbidopa and LCIG , PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.23	-	-	-
LCIG	[redacted]	5.34	[redacted]	–0.11	[redacted]
BMT	[redacted]	4.53	[redacted]	0.70	Foslevodopa-foscarbidopa dominant

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

b) The average OFF time in the model is 3.07 for foslevodopa and 3.43 for duodopa following one cycle of treatment. Why does the model produce notably bigger differences in change from baseline between treatment arms, than can be found in table 29?

This difference results from the way the relative risk is applied in the model to capture the average effect considering both improving and worsening health states. As detailed in the CS, the relative risk was implemented by multiplying the foslevodopa-foscarbidopa transition probabilities by the relative risk for worsening transitions (e.g., OFF 1 to OFF 2) and by 1/relative risk for improving transitions (e.g., OFF 2 to OFF 1). Given that there was a greater number of patients making improving transitions than worsening transitions in the foslevodopa-foscarbidopa arm of the M15-736 trial, this resulted in the higher "Off" time as seen in cost-effectiveness results in comparison with those from the NMA results in Table 29 of the CS.

c) Please validate this relative risk approach in the model against real data for LCIG.

To assess the comparability of LCIG's real-world longer-term (i.e. 24 months) effectiveness versus the model outcomes, the GLORIA study was considered.[6] In this 24-month, multi-national, non-interventional, observational registry, 258 patients with advanced PD completed the study. Table 16 presents a comparison of the cycle-specific "Off" time in the model and in the GLORIA registry.

Table 16: OFF time in the company cost-effectiveness model versus the GLORIA real-world registry

Time point	LCIG OFF time cost-effectiveness model (hours)	LCIG OFF time GLORIA registry (hours)	Difference (hours)
Baseline	[redacted]	6.0	[redacted]
6 months	[redacted]	1.8	[redacted]
12 months	[redacted]	2.0	[redacted]
18 months	[redacted]	1.9	[redacted]
24 months	[redacted]	2.0	[redacted]

Abbreviations: LCIG: levodopa-carbidopa intestinal gel.

In both the model and the GLORIA registry, the baseline "Off" time was around [redacted] hours. Based on the NMA outcomes, the LCIG "Off" time decreases to [redacted] hours (decrease of [redacted] hours) after six months, which is similar to the decline seen in GLORIA (decrease of 4.3 hours, leading to 1.8 hours of "Off" time at six months). At subsequent time points, the "Off" time in GLORIA stabilises, while the decline continues somewhat in the model population. Nevertheless, the "Off" time at months 12–24 is relatively comparable between the model and the GLORIA registry.

B8. Priority question. Can you explain why the model applies natural disease progression immediately to the BMT arm and does not take into account the benefit of BMT experienced during the trial?

In the M15-736 trial, patients in the oral LD/CD were stabilised on oral treatment. Due to being in a trial setting with increased exposure to the healthcare system, efficacy and safety outcomes could be improved over outcomes in clinical practice. Hence, outcomes from the BMT arm in the model did not take into account the benefit of BMT experienced during M15-736.

The base-case model that had been submitted applied natural disease progression data to the BMT arm. This was applied to better-reflect clinical practice, whereby it is expected that "re-challenging" (versus prescribing foslevodopa-foscarbidopa) a patient who had previously failed BMT will likely not change the outcome of their treatment as the patient might experience increasingly more motor fluctuations at an advanced stage with oral therapy. Based on clinical expert opinion, the disease trajectory of patients who had previously failed BMT could more-closely reflect natural disease progression.

a) **Please add a scenario which applies the trial transition probabilities for BMT in the first three months of the model and uses the LOCF assumption for the following two cycles. This should be done in line with the reduced cycle length requested in B5.**

As per above, it is not expected that non-responders who are "re-challenged" with BMT will experience any change in outcome given previous failure (non-response) on therapy. Accordingly, AbbVie believes that using natural disease progression data remains appropriate given the proposed positioning in the clinical pathway.

B9. Priority question. Please expand in more detail as to how data from Palmer *et al.* 2002 was used to model natural disease progression.

a) The data related to off-time transition probabilities contained in Palmer relates to changing between the two states (≤25% and >25% off-time), where in the Palmer paper was the data extracted to model hour by hour off-time with an exponential model?

The Palmer study does not provide transition probabilities per OFF hours; instead it details that the average duration of levodopa therapy in patients who had >25% OFF time per day was 11.38 years, while the average duration of levodopa therapy in patients with ≤25% OFF time was 5.53 years. To estimate transition probabilities for each one OFF hour, quartiles were taken and populated with these values (Table 17). An exponential distribution was fitted to the points and used to estimate the duration of levodopa before each one hour OFF change. In line with the approach by Palmer, the calculation of the annual rate was based on the reciprocal of the time to

proceed from each of these one hour OFF states (e.g. OFF 2 to OFF 3), adjusted to the model cycle length.

Table 17: Fitted duration of levodopa (exponential)

Quartile	No. of hours	OFF state	Mid-point in OFF time	Duration of levodopa, years	Fitted duration of levodopa (exponential)
0%	0	OFF 0	0.005	5.53	5.518
1–25%	1	OFF 1	0.5	5.53	5.743
	2	OFF 2	1.5	5.53	6.225
	3	OFF 3	2.5	5.53	6.748
	4	OFF 4	3.5	5.53	7.316
26–50%	5	OFF 5	4.5	11.38	7.930
	6	OFF 6	5.5	11.38	8.597
	7	OFF 7	6.5	11.38	9.320
	8	OFF 8	7.5	11.38	10.103
51–75%	9	OFF 9	8.5	11.38	10.952
	10	OFF 10	9.5	11.38	11.872
	11	OFF 11	10.5	11.38	12.870
	12	OFF 12	11.5	11.38	13.952
76–100%	13	OFF 13	12.5	-	15.124
	14	OFF 14	13.5	-	16.396
	15	OFF 15	14.5	-	17.774
	16	OFF 16	15.5	-	19.267

[a]No patients with >75% OFF time were included in the original study by Palmer et al.[7] As such, model fitting was conducted with data up to OFF 12, and then extrapolated to OFF 16.

b) Please provide all the calculations undertaken to transform the Palmer data into the transition probabilities (reported in table 55 in the CS) used in the model.

Table 18 is a continuation of Table 17 provided in response to question B9a. An Excel file detailing the calculations has also been provided as part of the reference pack accompanying these responses.

Table 18: Transition probability for standard of care

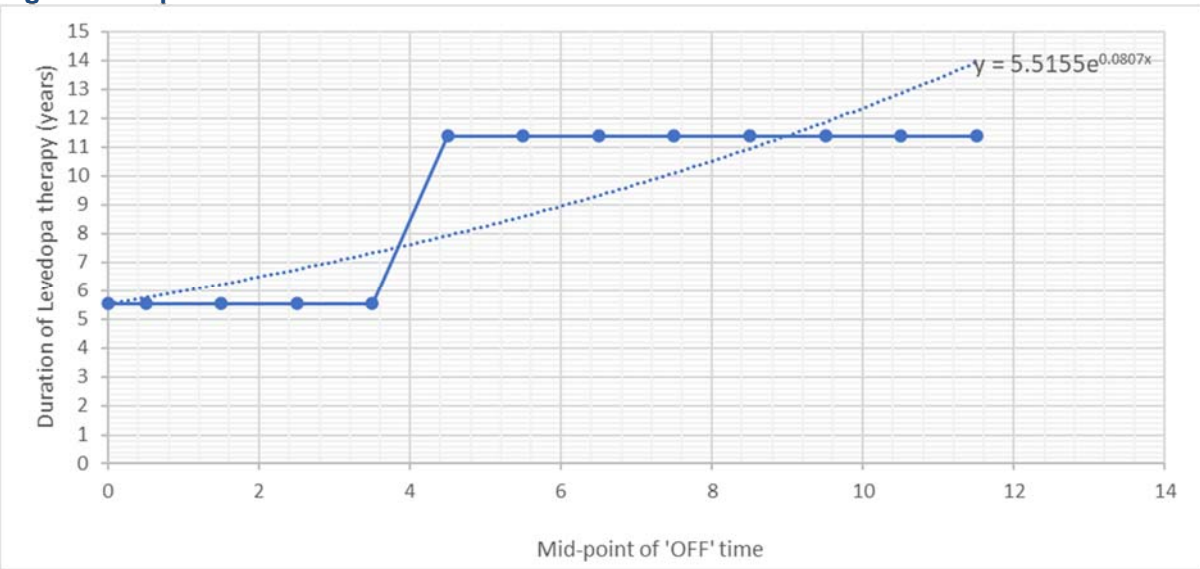
OFF health state	Fitted duration of levodopa	1/diff in mean	Transition probability for 6 months
0	5.518	4.446906439	0.8918
1	5.743	2.071935209	0.6451
2	6.225	1.911298883	0.6154
3	6.748	1.763116628	0.5859
4	7.316	1.626422885	0.5566
5	7.930	1.500326955	0.5277

OFF health state	Fitted duration of levodopa	1/diff in mean	Transition probability for 6 months
6	8.597	1.384007193	0.4994
7	9.320	1.276705656	0.4718
8	10.103	1.177723166	0.4450
9	10.952	1.08641475	0.4191
10	11.872	1.002185439	0.3941
11	12.870	0.924486394	0.3701
12	13.952	0.852811325	0.3471
13	15.124	0.786693197	0.3252
14	16.396	0.725701181	0.3043
15	17.774	0.669437852	0.2845
16	19.267	-	-

c) Please provide further details on the exponential model fitted and display how well it fits the data visually.

Figure 6 presents a visualisation of the exponential model which was fitted in Excel. Given that there were only two data points provided in the Palmer study, visually comparing the data with the predicted data is of limited use. The exponential model served to offer a means to estimate 1 hour OFF transitions in patients who were DAT naïve.

Figure 6: Exponential model fitted



d) Were alternative models besides linear and exponential considered? If so, please provide details and an explanation of why the preferred model was chosen.

Given that there were only two data points in the Palmer study, fitting more complex and flexible models such as generalised linear models or even higher order non-linear models was not

deemed appropriate as these would most likely result in obscure results due to the lack of data. As the linear model would result in the same transition probability for each OFF-time transition, this was not deemed plausible as it would be expected that patients in lower OFF states are more likely to move to the next OFF state than a patient in higher OFF states moving to their next respective OFF state.

e) What was the makeup of 'standard treatment' in the Palmer paper and does it differ from the treatments used BMT in the model?

AbbVie acknowledge that there are differences between standard treatment in the Palmer paper and the treatments used for BMT in the model. BMT in this model comprises a number of different treatments used in UK clinical practice whereas standard treatment in the Palmer study is levodopa without entacapone. However, the natural disease progression that is informed by the Palmer paper applies similarly to all treatments. As such, if long-term disease progression would be (slightly) different in clinical practice, the impact on incremental results would likely be limited.

B10. Please compare the trial results of mean OFF hours for foslevodopa-foscarbidopa at 12 weeks in M15-736 with the mean OFF hours predicted in the model at 12 weeks for the treatment.

The mean OFF time reported by patients who received at least one dose of foslevodopa-foscarbidopa at Week 12 in M15-736 was [redacted] hours. The mean number of OFF hours for patients receiving foslevodopa-foscarbidopa in the first 12 weeks of the model is predicted to be [redacted] hours, which includes patients modelled as discontinuing foslevodopa-foscarbidopa in the first 12 weeks of the model.

As per above (Question 7b), this small difference results from the way the relative risk is applied in the model to capture the average effect considering both improving and worsening health states. As detailed in the CS, the relative risk was implemented by multiplying the foslevodopa-foscarbidopa transition probabilities by the relative risk for worsening transitions (e.g., OFF 1 to OFF 2) and by 1/relative risk for improving transitions (e.g., OFF 2 to OFF 1). Given that there was a greater number of patients making improving transitions than worsening transitions in the foslevodopa-foscarbidopa arm of the M15-736 trial, this resulted in the higher "Off" time as seen in cost-effectiveness results in comparison with those from the NMA results in Table 29 of the CS.

Adverse events

B11. Priority question. The EAG's clinical experts have confirmed that the AEs included would be expected to continue throughout treatment, though some like "infusion site cellulitis" and "nausea" can be managed with medication. What is the company's justification for only applying costs and utilities as a one-off within the first cycle?

The company did consider these AEs continuing throughout treatment. The decision was made not to include nausea as an AE throughout treatment as this is often expected at the onset of treatment; accordingly, it abates with oral levodopa. Clinical expert opinion noted that infusion-site cellulitis and similar reactions may occur over the duration of treatment, though can be mitigated with appropriate education on hygiene and rotation of the subcutaneous site. Accordingly, infusion site cellulitis was omitted from subsequent cycles.

a) Please add an option to the model to continue to apply AE costs and disutilities for the model time horizon and run this as a scenario.

AbbVie recognise that AEs can occur throughout the duration of treatment, though believe that the approach taken to capture AEs as a one-off within the first cycle remains appropriate. AEs can fluctuate over time and will be complex to accurately reflect in the model. Further, the make-up of AEs will likely change over time, as patients still receiving treatment may experience different AEs than those who might discontinue. Therefore the simplest approach would be to assume a one-time capture. This is a typical assumption made in economic models across a range of disease areas.

b) Experts have advised the EAG that some of the one-off AEs (infusion site nodule, infusion site erythema, infusion site pain, infusion site reaction, dizziness, falls and dyskinesia) may progress over time with the disease, was any consideration given for this?

The above one-off AEs were considered during the development of the company model. Many one-off AEs can be managed and may not progress over time. For example, AEs associated with existing infusion therapies, such as infusion site nodules, erythema and pain, are managed by appropriate education on hygiene and rotating sites where possible; if sites are not rotated, these AEs may be more evident.

As noted by a clinical expert, among the other AEs listed above, dizziness and falls may alternatively be features of disease progression rather than treatment-related AEs. Additionally in clinical practice, it could be challenging to discern dyskinesia as an AE or as a function of “On” time symptoms (such as “On” time with non-troublesome dyskinesia). For example, dyskinesia could indicate that patients are overmedicated and would prompt adjustment to doses, particularly if they are troublesome. Such issues are often related to the use of concomitant medication; accordingly, the company expect that the use of adjunctive therapies in clinical practice to decline after initiation of foslevodopa-foscarbidopa, matching treatment patterns observed following LCIG initiation.[8]

Sensitivity analyses were conducted to assess the robustness and sensitivity of results. As shown in the CS (Document B, Section 3.11), the cost-effectiveness results were not sensitive to AEs. Foslevodopa-foscarbidopa remained cost-effective versus LCIG for all parameters and remained dominant against BMT in all upper and lower bound input variations conducted as part of the deterministic sensitivity analysis (DSA).

B12. Priority question. AEs were recorded throughout the trial duration and have time to onset of the AE and how long it took to resolve. For example,

infusion site infections had a median time to onset of 32 days, and most events resolved with a median duration of 16.5 days. Why was this data not used in the model for duration of AEs?

The mean duration of adverse events from the trial was used, given that the trial captures AE duration for the duration of the trial (3 months, aligning with the Cycle 1 duration), and these were applied as a one-off cost in the model. The AE durations for several of the AEs were assumed to be 28 days to capture the potential of any recurrence. AE duration values based on the M15-736 trial are provided in Table 18. The duration for infusion site AEs were only categorised into infusion site related infections and infusion site related non-infections. As such, infusion site erythema, infusion site nodule, infusion site pain and infusion site reaction were categorised as infusion site related non-infections. Infusion site cellulitis was classified as infusion site related infections.

AbbVie agree that using trial data may be a more appropriate method of estimating AE duration in the model and have therefore incorporated these changes as part of the updated base case. Where AE duration was not available from the trial, the same values as those used in the base case model are used in the updated base case. Results from the updated base case are provided in Appendix A.

Table 19: Adverse event duration based on M15-736 trial

AE	AE duration (current base case)		AE duration (Update base case)	
	Estimate (days)	Source	Estimate (days)	Source
Infusion site erythema	7	NICE TA720	[redacted]	M15-736 trial
Infusion site nodule	28	Assumption	[redacted]	M15-736 trial
Infusion site cellulitis	28	Assumption	[redacted]	M15-736 trial
Infusion site pain	7	Walter 2015	[redacted]	M15-736 trial
Infusion site reaction	7	NICE TA720	[redacted]	M15-736 trial
Dizziness	28	Assumption	28	Same as base case model
Hallucination	28	Assumption	28	Same as base case model
Depression	28	Assumption	28	Same as base case model
Anxiety	28	Assumption	28	Same as base case model
Nausea	28	Assumption	28	Same as base case model
Falls (hospitalisation)	42	Assumption based on an average of six weeks in a cast	[redacted]	M15-736 trial

AE	AE duration (current base case)		AE duration (Update base case)	
	Estimate (days)	Source	Estimate (days)	Source
Diarrhoea	15	NICE TA581	15	Same as base case model
Dyskinesia	28	Assumption	28	Same as base case model

Abbreviations: AE: adverse event

B13. Priority question: Please provide the definition of dyskinesia as an adverse event, how this was captured in the trial and how it compares to changes in troublesome dyskinesia as captured in the patient PD diary; i.e. does an incidence of 0.7% for a duration of 28 days mean, on average, patients experience 0.7% of their time in a 28 day period experiencing on time with troublesome dyskinesia?

Dyskinesia as an adverse event was part of the classification by primary system organ, in this case classified as a nervous system disorder. Dyskinesia was not categorised into troublesome or non-troublesome dyskinesia when considered as an adverse event.

AbbVie can confirm that the incidence of 0.7% for a duration of 28 days means, on average, patients experience 0.7% of their time in a 28 day period with any form of dyskinesia.

a) **Within table 14.2__2.4 on page 404 of the M15-736 CSR appears to show Average Daily Normalized 'On' Time With Troublesome dyskinesia appeared to increase more in the ABBV-951 arm (0.21 vs 0.08 increase). However, the incidence of dyskinesia used in the model is 0.7% in the foslevodopa arm and 1.5% in the BMT arm. Please can the company explain this discrepancy and elaborate on how the incidence of dyskinesia was calculated?**

The value of [redacted]% for foslevodopa-foscarbidopa and 1.5% for BMT were derived from Table 14.3__1.8.1 of the M15-736 CSR (page 753) of the M15-736 CSR which provides information on treatment-emergent AEs (TEAEs) associated with product complaints by primary system organ class.[2] This has since been found to be an error; the incidence of [redacted]% applies to all patients in M15-736. [redacted] dyskinesia as a TEAE associated with product complaints was reported for foslevodopa-foscarbidopa, whereas the value remains the same ([redacted]%) for BMT. This has been updated accordingly in the model.

'On' time with troublesome dyskinesia as assessed by the PD diary and dyskinesia as an AE are also not comparable. While the PD diary splits dyskinesia and classifies it as troublesome or non-troublesome, dyskinesia as an AE was not categorised as such. Further, PD diary is patient reported and categorisation of dyskinesia is captured within a patient report of ON-time. Dyskinesia as AE is typically reported by physicians in the trials. Therefore, it would not be

appropriate to use the average daily normalised 'On' time with troublesome dyskinesia to calculate the incidence of dyskinesia.

b) Why was dyskinesia given an AE duration of 28 days (assumed AE duration) when this was recorded at each trial visit and then recorded as number of hours over the 3 preceding days?

Dyskinesia as reported in the PD diary (captured in the 3 preceding days of a visit) was captured differently from dyskinesia reported as an AE (as per above). The mean duration of adverse events from the trial was used, given that the trial only captures AE duration for the duration of the trial at 3 months. The durations for several of the AEs were assumed to be 28 days to capture the potential of any recurrence.

c) Why was the utility related to dyskinesia taken from a schizophrenia model (Graham *et al.* 2012) and not either derived from the trial data or taken from the source for LCIG dyskinesia incidence; e.g. Walter and Odin 2015?

The Walter and Odin 2015 study provided a disutility in percentage terms; it was unclear in the study what the percentage decline is/should be applied to, and the model could not accommodate a disutility in percentage terms. Following the EAG comment, AbbVie have obtained the original source for the disutility used by Walter and Odin 2015. The updated disutility is now based on Farkouh 2012 and estimated by taking the difference in utility for patients on levodopa without dyskinesia as second-line treatment (0.78), and utility for patients on levodopa with dyskinesia (0.71).[9] The difference between these two utilities is 0.07, which is now applied and results of the updated base case are provided in Appendix A.

d) The probability of dyskinesia recorded in Walter and Odin 2015 for LCIG is 0.07 for a 6 month cycle and the incidence over a 3 month cycle period (with duration 28 days) used in the company submission is 0.07%. Is this an error?

AbbVie can confirm that this is an error, and should be 7.00% in the model. This has been updated in the new base case and results are provided in Appendix A.

Discontinuations and mortality

B14. Priority question. Given the transition probabilities were taken from the M15-736 trial, what was the clinical rationale for not including these patients who discontinue treatment of foslevodopa in the base case?

Rates of discontinuation from the M15-741 trial were deemed to be more reflective of discontinuation rates in clinical practice. In particular, discontinuation rates in the model were derived from Sample 2 of the M15-741 trial. As discussed in Section B.3.3.8 of the CS, high initial

discontinuation rates, due in part to the steep learning curve of patients and physicians to manage the delivery system and managing the infusion site skin events, were mitigated by the introduction of the new infusion set. Patients in Sample 2 of the M15-741 trial received the new infusion set that is now the only intended commercial infusion set for delivery of foslevodopa-foscarbidopa. As such, discontinuation rates from this cohort could better reflect those in clinical practice whereby patients would receive the same infusion set.

Additionally, the follow-up (three months) of M15-736 would require making an assumption at an early-stage for discontinuation beyond three months. An option (which is presented as a scenario in the CS), is to use M15-736 data for the first three months followed by M15-741. However, it was deemed more robust to use the longer-term M15-741 discontinuation rates as the base case to provide discontinuation data from a continuous source and to reflect the infusion set that will be the only intended infusion set for delivery of foslevodopa-foscarbidopa.

Finally, transition probabilities were taken from the M15-736 as this is the considered the pivotal trial for foslevodopa-foscarbidopa. As such, the primary objectives of the trial were to assess the efficacy (and safety) of foslevodopa-foscarbidopa and is powered accordingly. This is opposed to the M15-741 study that sought to evaluate the safety and tolerability of foslevodopa-foscarbidopa.

B15. Why does each health state for each cycle have an individual mortality rate in the "Mortality Cals" worksheet when mortality does not vary by health state?

The "Mortality Cals" worksheet was developed to include individual mortality rates for each health state to allow the flexibility to apply OFF time-specific mortality. However, given the lack of robust data, the decision was made to apply the same mortality rate in any given model cycle, meaning mortality rates do not vary by OFF state. This is reflected in AbbVie's base case analysis.

Quality of life

B16. Priority question. Please provide the (mapped) EQ-5D-3L utility data from M15-736, M15-098, M15-741, and M15-737, separately by study, for the following endpoints and for the entirety of the follow-up period:

The requested data have been provided as part of the reference pack. The data are summarised for each sub-question below.

a) Number of patients at baseline with EQ-5D-3L data available, by OFF state;

Table 20: Number of patients receiving foslevodopa-foscarbidopa at baseline with EQ-5D-3L data available, by OFF state

	M15-736		M20-098		M15-741		M15-737	
	Frequency ([redacted])	%	Frequency ([redacted])	%	Frequency ([redacted])	%	Frequency ([redacted])	%
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	M15-736		M20-098		M15-741		M15-737	
	Frequency ([redacted])	%	Frequency ([redacted])	%	Frequency ([redacted])	%	Frequency ([redacted])	%
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) Mean utility score at baseline, by OFF state;

Table 21: Mean Utility Scores reported by patients receiving foslevodopa-foscarbidopa at Baseline, by OFF state

	M15-736		M20-098		M15-741		M15-737	
	Frequency ([redacted])	Mean (SD)	Frequency ([redacted])	Mean (SD)	Frequency ([redacted])	Mean (SD)	Frequency ([redacted])	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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	M15-736		M20-098		M15-741		M15-737	
	Frequency ([redacted])	Mean (SD)	Frequency ([redacted])	Mean (SD)	Frequency ([redacted])	Mean (SD)	Frequency ([redacted])	Mean (SD)
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SD: standard deviation.

c) Number of patients at the end of follow-up (and specify the follow-up period) with EQ-5D-3L data available, by OFF state;

The number of patients receiving foslevodopa-foscarbidopa at the end of follow-up with EQ-5D-3L data available, by OFF state, is shown in Table 22.

Table 22: Number of patients at the end of follow-up with EQ-5D-3L data available, by OFF state

	M15-736 (3 mos)		M20-098 (3 mos)		M15-741 (12 mos)		M15-737 (24 mos)	
	Frequency ([redacted])	%	Frequency ([redacted])	%	Frequency ([redacted])	%	Frequency ([redacted])	%
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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	M15-736 (3 mos)		M20-098 (3 mos)		M15-741 (12 mos)		M15-737 (24 mos)	
	Frequency ([redacted])	%	Frequency ([redacted])	%	Frequency ([redacted])	%	Frequency ([redacted])	%
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: mos: months.

d) Mean utility score at the end of follow-up period, by OFF state;

The mean utility score of patients receiving foslevodopa-foscarbidopa at the end of the follow up periods in M15-736, M20-098, M15-741 and M15-737 are presented in Table 23, Table 24, Table 25 and Table 26, respectively.

Table 23: M15-736 Mean utility score at the end of follow-up period (Month 3), by OFF state

Off state	N	Mean	Std Dev	Minimum	Maximum
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 24: M20-098 Mean utility score at the end of follow-up period (Month 3), by OFF state

NROFF	N	Mean	Std Dev	Minimum	Maximum
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 25: M15-741 Mean utility score at the end of follow-up period (Month 12), by OFF state

OFF state	N	Mean	Std Dev	Minimum	Maximum
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26: M15-737 Mean utility score at the end of follow-up period (Month 24), by OFF state

OFF State	N	Mean	Std Dev	Minimum	Maximum
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

e) Statistical significance of the change from baseline to end of study period, by OFF state.

The statistical significance of changes in utility scores from baseline for patients receiving foslevodopa-foscarbidopa in M15-736, M15-741, and M15-737 are shown in Table 27, Table 28 and Table 29, respectively. No statistical significance data was available for the M20-098 trial due to limited sample sizes. It should be noted that small sample sizes in each OFF state across all trials limits the interpretability of the results presented below.

Table 27: M15-736 Change from baseline to the end of follow-up period (Month 3) for mean utility score, by OFF state

Obs	Off state	N	Mean	StdDev	Minimum	Maximum	tValue	Probt
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Obs	Off state	N	Mean	StdDev	Minimum	Maximum	tValue	Probt
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 28: M15-741 Change from baseline to the end of follow-up period (Month 12) for mean utility score, by OFF state

Obs	OFF state	N	Mean	StdDev	Minimum	Maximum	tValue	Probt
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 29: M15-737 Change from baseline (Month 12) to the end of follow-up period (Month 24) for mean utility score, by OFF state

Obs	OFF State	N	Mean	StdDev	Minimum	Maximum	tValue	Probt
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B17. Priority question. Please confirm that the study referred to as M15-098 in the CS is actually study M20-098. If it is not please provide this study. Please provide the baseline characteristics of the populations in the M15-736 and M15-741 and discuss their comparability in terms of impacting patients' quality of life (QoL).

AbbVie can confirm that this was a typographical error, and the study referred to as M15-098 is actually M20-098.

The baseline characteristics of the populations in M15-736 and M15-741 are presented in Table 30 and Table 31, respectively. The baseline characteristics were generally well-matched across the two studies, and AbbVie do not anticipate there to be any major impact in terms of QoL resulting from any differences. The majority of patients in both studies were male, and the mean age of patients were [redacted] and [redacted] in M15-736 and M15-741, respectively. While the mean age was slightly higher in M15-736, this may be balanced by the fact that the mean duration since PD diagnosis was lower in M15-736 ([redacted] years versus [redacted] years). In addition, importantly the baseline normalised 'Off' time was well matched between the two populations, with patients experiencing a mean of [redacted] hours in M15-736 and [redacted] hours in M15-741.

Table 30: Baseline characteristics of patients in M15-736 – Document B, B.2.3.1.2, Table 5 (page 36)

Characteristic	Foslevodopa-foscarbidopa (N = [redacted])	Oral CD/LD (N = [redacted])	Total (N = [redacted])
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Age category, n (%)			
< 50 years	[redacted]	[redacted]	[redacted]
50–64 years	[redacted]	[redacted]	[redacted]
65–74 years	[redacted]	[redacted]	[redacted]
≥ 75 years	[redacted]	[redacted]	[redacted]
Weight, kg			
Mean (SD)	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), n (%)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Country, n (%)			
Australia	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]
LED at Baseline, mg/day			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Duration of PD since diagnosis			

Mean (SD), years	[redacted]	[redacted]	[redacted]
< 10 years, n (%)	[redacted]	[redacted]	[redacted]
≥ 10 years, n (%)	[redacted]	[redacted]	[redacted]
Concomitant dopamine agonist use, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Baseline normalised 'Off' time, hours			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body-mass index; LED: levodopa equivalent dose; PD: Parkinson's disease; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[2]

Table 31: Baseline characteristics of patients in M15-741 – Document B, B.2.4.1.2, Table 18 (page 55)

Characteristic	Total (N = [redacted])
Sex, n (%)	
Male	[redacted]
Race, n (%)	
White	[redacted]
Black or African American	[redacted]
Asian	[redacted]
Other	[redacted]
Age, years	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Age category, n (%)	
< 65 years	[redacted]
≥ 65 years	[redacted]
Weight, kg	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Location, n (%)	
Europe and Australia	[redacted]
North America	[redacted]
Japan	[redacted]
LED at baseline,[a] mg/day	
n	[redacted]
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Duration of PD since diagnosis, n (%)	
Mean (SD), years	[redacted]
Median (min, max), years	[redacted]

< 10 years	[redacted]
≥ 10 years	[redacted]
Baseline normalised 'Off' time, hours	
n	[redacted]
Mean (SD)	[redacted]
Median (min, max)	[redacted]

[a] from levodopa containing medications and COM-T inhibitors
Abbreviations: LED: levodopa-equivalent dose; PD: Parkinson's disease; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[3]

B18. Priority question. Please explain if the regression models used to estimate utility data by OFF state were built with a stepwise approach. Please explain if variables such as age, gender, baseline OFF hours, etc. were tested as predictors of patients' quality of life.

a) If the latter analysis was conducted, please provide the results of the stepwise approach and the variable selection process;

b) If the latter analysis was not conducted, please explain why and consider undertaking the analysis.

The following variables were evaluated for inclusion in the linear mixed model:

- NROFF, representing the total number of 'OFF' hours per day, ranging from 0 to 16. This matches the health states of the model.
- PDSSTOS, which represents the PDSS-2 score, ranging from 0 to 60.
- MorningOFF, which captures whether a patient wakes up in an 'OFF' state, which is either yes or no.
- ARM, representing the treatment arm patients were in.
- NROFF*ARM, an interaction term.
- NROFF*PDSSTOS, an interaction term.
- NROFF*MorningOFF, an interaction term.

A stepwise approach was used to evaluate which of these variables were included in the regression model used to estimate utility data. The variables age, gender and baseline OFF hours were not evaluated. An overview of the different models evaluated and their Akaike information criterion (AIC) and Bayesian information criterion (BIC) is provided in Table 32. The lower the AIC/BIC value, the better the statistical fit to the data. Of note, all values in Table 32 are negative. The model with the best statistical fit to the data was the model that only included NROFF as a variable. Including MorningOFF and PDSSTOS did not improve statistical fit. Furthermore, treatment arm did not improve the statistical fit to the data, which suggests that the inclusion of NROFF captures the effect of treatment on a patient's utility. Furthermore, the inclusion of interaction terms also did not improve the performance of the linear mixed model. Based on statistical fit, the model with NROFF was selected as the base case.

Table 32: Overview of statistical fit criteria (AIC & BIC) of different linear mixed models fitted to the combined dataset of four foslevodopa-foscarbidopa studiesa

Model	Variables	AIC	BIC
1	NROFF	[redacted]	[redacted]
2	NROFF ARM	[redacted]	[redacted]
3	NROFF ARM NROFF*ARM	[redacted]	[redacted]
4	NROFF PDSSTOS	[redacted]	[redacted]
5	NROFF PDSSTOS NROFF*PDSSTOS	[redacted]	[redacted]
6	NROFF ARM PDSSTOS	[redacted]	[redacted]
7	NROFF MorningOFF	[redacted]	[redacted]
8	NROFF MorningOFF NROFF*MorningOFF	[redacted]	[redacted]
9	NROFF ARM MorningOFF	[redacted]	[redacted]
10	NROFF PDSSTOS MorningOFF	[redacted]	[redacted]
11	NROFF PDSSTOS MorningOFF ARM	[redacted]	[redacted]

[a]Included studies were M15-736, M15-098, M15,741, and M15-737.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

B19. Priority question. Please justify why the more commonly used source (Ara and Brazier, Value in Health 2010; 13(5): 509–518) was not used to adjust utility values by age and gender, but instead the Janssen *et al.* source was used. Please conduct a scenario analysis to assess if using adjusted utility

values with the Ara and Brazier source has an impact on the final (incremental cost-effectiveness ratio) ICER.

Janssen *et al.* was originally used as it would also be applicable to other countries/regions than the UK. However, as Ara *et al*. (2010) applies to the UK population, the company agrees that this source may be more appropriate; the model has been updated accordingly to include this as a scenario. The results of the scenario analysis are presented below (Table 33).

Table 33: Results of the scenario analysis using Ara and Brazier to adjust utility values by age and gender, PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.15	-	-	-
LCIG	[redacted]	5.24	[redacted]	−0.09	[redacted]
BMT	[redacted]	4.46	[redacted]	0.69	Foslevodopa-foscarbidopa dominant

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

B20. Given the utilities are calculated from a regression on direct trial utility data, does including AE utility decrements on top double count utility decrements, since these AE disutilities would already be accounted for in the utility by off state regression?

The regression models on utility data are not able to appropriately capture the impact of adverse events on quality-of-life due to the limited timepoints of the utility questionnaires. For example, in M15-736, utility questionnaires were taken only at baseline and at Day 85. Given the assumed duration of the AEs (Table 62, Document B of the CS), it is estimated that the timing of the AEs coincided with the timing of the EQ-5D-5L questionnaire for only a small number of patients.

This is further supported by the fact that despite a difference in the incidence of adverse events between foslevodopa-foscarbidopa and BMT (Table 56, Document B of the CS), the inclusion of treatment arm in the regression model for utility did not improve the statistical fit (please refer to Table 32 in clarification question B18 for further details).

Costs and resource use

Treatment and administration costs

B21. Priority question. Please clarify if treatment with foslevodopa-foscarbidopa is intended to be initiated at home by patients, or in the hospital setting.

a) **If treatment initiation with foslevodopa-foscarbidopa takes place in the hospital setting please consider adding the relevant costs associated with the first administration of the treatment in the model.**

Foslevodopa-foscarbidopa is intended to be initiated in the hospital setting. The relevant costs associated with the first administration of the treatment have been included as "Titration and monitoring", which consists of one hospital visit, at a cost of £726.60. Patients initiating treatment with foslevodopa-foscarbidopa are anticipated to require [redacted] such visits upon treatment initiation, equating to a cost of [redacted]. These costs have already been accounted for in the CS model (Treatment Admin tab, cell K40).

This is a conservative estimate and it is plausible that [redacted] visits are sufficient to determine dose optimisation. Further, initiation can be supported in a hospital setting as a day case. This is corroborated in the M15-736 and M15-741 studies, whereby neither trial had an overnight stay for treatment initiation. Finally, it is possible that initiation at home may be feasible in the future, as a day case/outpatient visit, once clinical experience is established.

B22. Priority question. Please provide the cost code used to estimate the cost of the PEG tube removal.

The cost code used to estimate the cost of the PEG tube removal was FE12A (Day Case - endoscopic insertion of gastrostomy tube, 19 years and over) from the 2019/2020 NHS National Cost Collection data.[2]

B23. Priority question. The EAG's clinical experts have advised that adjunctive therapies would be expected to be utilised with foslevodopa. Please include a scenario in the model where the costs of adjunctive therapies are applied to the foslevodopa arm.

While the concomitant use of foslevodopa-foscarbidopa with other levodopa-containing medications or with medicinal products that significantly regulate synaptic dopamine levels (such as catechol-o-methyl-transferase [COMT] inhibitors) has not been studied, they may present complexities in patient care. For example, it is expected COMT inhibitors will increase the bioavailability of levodopa, necessitating a correction factor to be applied to levodopa equivalents (LE) calculations based on the levodopa-containing medications used during the patient's awake time. Furthermore, monoamine oxidase type-B (MAO-B) inhibitors are contraindicated (with the exception of MAO-B selective inhibitors) in patients receiving foslevodopa-foscarbidopa.[10] Furthermore, a monotherapy approach minimises the potential for side effects from long-term

use of other PD medications. Dopamine agonists, for example, were have been linked to impulse control disorders among patients with PD, the risk for which increased with lifetime average daily dose and duration of treatment. These effects resolved over time after patients discontinued treatment with dopamine agonists.[11] Accordingly, AbbVie expect the use of adjunctive therapies in clinical practice to decline after initiation of foslevodopa-foscarbidopa.

B24. Priority question. The EAG's clinical experts have advised that wastage may still occur with foslevodopa use due to changes in individualised treatment patterns which would not match standard dosing. Please add a scenario analysis accounting for wastage of foslevodopa.

The company expects that foslevodopa-foscarbidopa will be self-administered in an optimal manner. As per the draft SmPC, patients will be trained on the proper use of foslevodopa-foscarbidopa and the delivery system prior to initiating treatment with foslevodopa-foscarbidopa and, as necessary, thereafter.[10] If wastage were to occur, it is expected that this will be minimal. Similarly, minimal wastage could also be expected with LCIG. As such, no scenario analyses including foslevodopa-foscarbidopa wastage have been presented.

B25. Please conduct a scenario analysis where nasogastric (NG) tube insertion is removed from the model, given clinical expert opinion provided to the EAG that only percutaneous endoscopic gastrostomy (PEG) tubes are used in UK's clinical practice.

The option to remove NG tube insertion has been added to the revised company model. The results of the scenario analysis where NG tube insertion is not included are provided in Table 34.

Table 34: Results of scenario analysis excluding NG tube insertion, PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.22	-	-	-
LCIG	[redacted]	5.31	[redacted]	−0.09	[redacted]
BMT	[redacted]	4.52	[redacted]	0.70	Foslevodopa-foscarbidopa dominant

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

B26. The company has used British National Formulary (BNF) prices to source treatment costs yet eMIT prices are available for the following BMT therapies: IR Levodopa + carbidopa (e.g sinemet) 110 mg, pramipexole 0.7 mg and rasagiline 1mg. Ropinirole 2mg (84 pack) has eMIT price but the company submission uses 28

pack size which is not on the eMIT list. The EAG requests the company adjust their base case to use eMIT prices for these treatment costs.

The following eMIT prices (Table 35) have replaced the previous BNF prices and have been incorporated into the revised company base case. The updated base case results are presented in Appendix A.

Table 35: eMIT prices updated in the base case

Drug	eMIT price	eMIT price/unit
IR Sinemet 110 mg	£3.86 (100 pack)	£0.04
Pramipexole 0.7 mg	£3.41 (30 pack)	£0.11
Rasagiline 1 mg	£1.57 (28 pack)	£0.06
Ropinirole 2 mg	£32.45 (84 pack)	£0.39

Abbreviations: eMIT: electronic market information tool; IR: immediate release.
Source: eMIT.

Health state-related costs

B27. Priority question. The EAG is concerned with the representativeness of the Adelphi 2017–2019 dataset to UK's clinical practice. Therefore, can the company please:

a) Confirm that only UK data from the Adelphi study (out of the available EU5, USA and Japan data) were used to estimate resource use in the model;

AbbVie can confirm that only the UK data from the Adelphi study were used to estimate resource use.

b) Confirm that the data from the Adelphi study used to estimate resource use in the model was restricted to that collected for patients with advanced PD (i.e., that early stage and intermediate stage patients were not included);

The Adelphi dataset included only UK patients with PD and was not restricted to patients with advanced PD. This decision had been made due to the limited sample size (n=[redacted]) of patients in the Adelphi dataset who presented with APD, in relation to the wider cohort (n=[redacted]).

c) If data from other countries were used to estimate resource use in the model, please conduct a scenario analysis where only UK data are included in the model. Similarly, if patients with milder PD (i.e., not advanced PD) were included in the analysis, please remove these patients from the estimates of resource use;

The resource use and costs in the model were only from the UK cohort from the Adelphi study. Resource use and costs were obtained from the entire PD cohort and not restricted to advanced PD patients due to small sample sizes.

d) Discuss the comparability of patients' characteristics (and disease stage) of the UK patients included in the Adelphi study with the study population in M15-736 (for example, use of DBS, age, etc.).

Descriptive statistics are provided in Table 36. The patients in the Adelphi study were slightly older, with a higher proportion of female patients with a slightly lower BMI. Time since diagnosis was longer in the M15-736 than in the Adelphi study. Most of the patients were in HY2 or HY3 for both the Adelphi and M15-736 trial. 1.4% of patients were only on DBS in the Adelphi study and 0.7% of patients had DBS as a prior procedure in the M15-736 trial. Patients in the Adelphi study are comparable to those in the M15-736 trial in terms of their characteristics, however time since diagnosis does differ between the two studies.

Table 36: Patient characteristics of UK patients included in the Adelphi study and study population in M15-736

Patient characteristics	Adelphi study (UK sample)	M15-736
Age	[redacted]	[redacted]
Female (%)	[redacted]	[redacted]
Patient BMI	[redacted]	[redacted]
Time since diagnosis (years)	[redacted]	[redacted]
H&Y Stage	[redacted]	[redacted]
DBS (%)	[redacted]	[redacted]

Abbreviations: BMI: body mass index; DBS: deep brain stimulation; H&Y: Hoehn and Yahr; UK: United Kingdom.

B28. Priority question. The EAG is unclear why regression models were fitted to the Adelphi 2017–2019 cost data. The study provided by the company reports the proportion of patients utilising resources, together with mean time of visits and/or mean duration of episodes over 1 year. Therefore, can the company please clarify why regression analysis was needed.

Regression models were used for resource utilisation due to a lack of available data for a number of OFF health states to be modelled, as shown in Table 37 below. Due to the lack of data in a number of health states, use of the raw Adelphi data is not feasible.

Table 37: Number of observations by OFF state in Adelphi 2017-2019 data

OFF state	Number of patients
0 OFF hours	[redacted]
1 OFF hours	[redacted]

OFF state	Number of patients
2 OFF hours	[redacted]
3 OFF hours	[redacted]
4 OFF hours	[redacted]
5 OFF hours	[redacted]
6 OFF hours	[redacted]
7 OFF hours	[redacted]
8 OFF hours	[redacted]
9 OFF hours	[redacted]
10 OFF hours	[redacted]
11+ OFF hours	[redacted]

a) Please include a scenario analysis in the model where the raw data from the Adelphi study, for the UK patients with severe PD disease are used in the model (i.e., ensuring that the proportions in the question below (question B29) reflect the proportions of patients in the estimations of resource use in the economic model).

A scenario analysis based on UK patients with severe PD may generate increased uncertainty due to the limited number of patients (n=[redacted]) with severe PD in the Adelphi dataset. As such, AbbVie believe that this scenario analysis is not appropriate and the wider cohort is more suitable (n=[redacted]).

B29. Priority question. Please can the company (for the UK, advanced PD patients in the Adelphi study):

The requested data below reflects responses in the overall PD cohort from the Adelphi study and have been provided as part of the reference pack, in the file "Resource use by OFF time". The data are summarised for each sub-question below.

a) Provide the percentage of patients attending A&E and average number of visits (per OFF state);

Table 38: Percentage of patients in the Adelphi dataset requiring admittance to A&E and average number of visits per OFF state

OFF State	Number of patients in health state included in Adelphi study	Percentage of patients who required admittance to A&E (%)	Average number of visits
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]

OFF State	Number of patients in health state included in Adelphi study	Percentage of patients who required admittance to A&E (%)	Average number of visits
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

Abbreviations: A&E: accident and emergency.

b) For the 19% of patients attending the GP, provide the distribution (and average number of visits) per OFF state;

Table 39: Percentage of patients in the Adelphi dataset attending the GP and average number of visits per OFF state

OFF State	Number of patients in health state included in Adelphi study	Percentage of patients attending the GP (%)	Average number of visits
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

Abbreviations: GP: general practitioner.

c) Provide the percentage of patients requiring hospitalisations for Cerebral Degenerations or Miscellaneous Disorders of Nervous System;

Hospitalisation due to Cerebral Degenerations or Miscellaneous Disorders of Nervous System were not reported in the Adelphi study. As the Adelphi data did not contain information relating to CC Scores, these proportions were instead based on the number of elective hospitalisations in the 2019/2020 National schedule of NHS costs.[12] The derived proportions used to model Cerebral Degenerations or Miscellaneous Disorders of Nervous System can be found in Table 40 below.

Table 40: Proportions used the derive a cost estimate for hospitalisation.

Currency code	Description	Number of elective hospitalisations (%)	National average cost
AA25C	Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC Score 14+	212 (5.8%)	£9,199
AA25D	Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC Score 11-13	262 (7.1%)	£5,798
AA25E	Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC Score 8-10	437 (11.9%)	£4,015
AA25F	Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC Score 5-7	803 (21.8%)	£3,727
AA25G	Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC Score 0-4	1,975 (53.5%)	£1,813

Source: 2019/2020 National schedule of NHS costs.[12]

d) The percentage of patients being hospitalised, and the reason for hospitalisation (if available) and average number of hospitalisations per OFF state;

Table 41: Percentage of patients in the Adelphi dataset requiring hospitalisation and average number of hospitalisation per OFF state

OFF State	Number of patients in health state included in Adelphi study	Percentage of patients requiring hospitalisation (%)	Average number of hospitalisations
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

e) The company mentions that the hospitalisations were weighted based on attendances with CC Score 0 to 14+, therefore, please provide the proportion of patients in the Adelphi study in each severity category;

As detailed in the Company response to clarification question B29 part c, no data were available from the Adelphi study regarding hospitalisations by CC score, which were therefore weighted using usage data from the 2019/2020 National schedule of NHS costs.[12]

f) For the 14% of patients receiving computerised tomography (CT) scans, provide the distribution of patients (and average number of CT scans), per OFF state;

Table 42: Percentage of patients in the Adelphi dataset receiving a CT scan and average number of CT scans per OFF state

OFF State	Number of patients in health state included in Adelphi study	Percentage of patients receiving CT scan (%)	Average number of scans
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

Abbreviations: CT: computed tomography.

g) For the 7% of patients receiving dopamine transporter (DaT) scans, provide the distribution of patients (and average number of DaT scans), per OFF state;

Table 43: Percentage of patients in the Adelphi dataset receiving a DaT scan and average number of DaT scans per OFF state

OFF State	Number of patients in health state included in Adelphi study	Percentage of patients receiving DaT scan (%)	Average number of scans
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

Abbreviations: DaT: dopamine transporter.

h) For the 17% of patients receiving respite care between 5 and 8 days, provide the distribution of patients per OFF state;

Table 44: Percentage of patients in the Adelphi dataset receiving respite care

OFF State	Number of patients in health state included in Adelphi study	Percentage of patients receiving Respite Care (%)	Average number of scans
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

i) Provide the percentage of patients having half an hour consultant appointments, per hour, per OFF state;

Data relating to the duration of consultant visits was not available as part of the Adelphi study. Proportion of patients by number of consultant visit per OFF state is provided in Table 45 instead.

Table 45: Proportion of patients in the Adelphi dataset by number of consultant visits per OFF state

OFF State	Number of Consultant visits											N
	0	1	2	3	4	5	6	7	9	10	12	
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

j) For the 36% of patients having half an hour band-6 nurse, provide the distribution of patients, per OFF state;

Data relating to the duration of nurse visits was not available as part of the Adelphi study. Proportion of patients by number of nurse visits per OFF state is provided in Table 46 instead.

Table 46: Proportion of patients in the Adelphi dataset by number of nurse visits per OFF

state

OFF State	Number of nurse visits					N
	0	1	2	3	4	
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

k) For the 52% of patients requiring professional care, provide the distribution of patients per hour, per OFF state.

Table 47: Proportion of patients in the Adelphi dataset by number of hours per week of professional care per OFF state

Number of hours per week of professional care	OFF state								
	0	1	2	3	4	5	6	7	10
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
143	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
144	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
168	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B30. Priority question. Clinical expert opinion provided to the EAG was that PD patients very rarely (if ever) receive positron emission tomography (PET) or single photon emission computed tomography (SPECT) scans in the UK NHS.

This is confirmed in the Adelphi 2017-2019 dataset for UK patients with advanced PD disease, where 0% of patients received SPECT scans and only 1% of patients received PET scans. Therefore, please remove the cost of these scans from the health-state related costs in the model.

The health state-related costs included in the model have been updated as part of the revised company base case, in which to remove the costs for PET and SPECT scans. This change to the health-state related costs in the updated base case has been made in combination to the change described in question B31. The resultant health state-related costs are presented in Table 48. These have been incorporated in the base case economic analysis, which is presented in Appendix A.

Table 48: Total health state specific costs included in the model, assuming no costs for SPECT and PET, and excluding MRI costs

Health state	Total yearly costs (£)
OFF 0	[redacted]
OFF 1	[redacted]
OFF2	[redacted]
OFF 3	[redacted]
OFF 4	[redacted]
OFF 5	[redacted]
OFF 6	[redacted]
OFF 7	[redacted]
OFF 8	[redacted]
OFF 9	[redacted]
OFF 10	[redacted]
OFF 11	[redacted]
OFF 12	[redacted]
OFF 13	[redacted]
OFF 14	[redacted]
OFF 15	[redacted]
OFF 16	[redacted]

Abbreviations: MRI: magnetic resonance imaging; PET: positron emission tomography; SPECT: single photon emission computed tomography.

B31. Priority question. The clinical experts informing the EAG also noted that magnetic resonance imaging (MRIs) would only be needed before patients undergo DBS. In the Adelphi 2017–2019 dataset for UK patients with advanced PD disease, 18% of patients receive MRIs over 1 year. Given these are likely to

be patients receiving DBS, please remove the cost of these scans from the health-state related costs in the model.

AbbVie agree with the EAG that MRIs would be unlikely to be used by patients considered for treatment with foslevodopa-foscarbidopa. As such, costs associated with MRIs have been removed from the health state-related costs in the model, in combination with the changes described in question B31 above. The resultant health state-related costs are shown in Table 48, and the updated base case results are provided in Appendix A.

B32. Priority question. Clinical expert opinion provided to the EAG was that as patients increase their OFF time, they become less eligible to be admitted to hospital (unless patients are at the end of life). The experts added that PD patients tend to only be admitted to hospital for causes other than increase in OFF hours (such as chest infections or falls). The experts added that respite care for these patients would happen in a non-acute hospital bed (for example in a rehabilitation bed). Therefore, please can the company conduct a scenario analysis where only the 17% of UK patients (per year) with advanced PD in the Adelphi population needing respite care (for a mean of 8.7 days) are costed for respite care, and please ensure that the costs associated with respite care are not for the acute primary care setting.

AbbVie have recalculated the health state specific costs, assuming 17% of patients, regardless of the health state they occupy in the model, require respite care. Per-patient costs were assumed to be £9,830.23, sourced from WH20A from the National schedule of NHS costs, based on a duration of 8.7 days.[12] The updated total annual costs used for a scenario analysis are included in Table 49 below (which also incorporates the revised base case health state costs requested in Questions B30 and B31), and results from the scenario in which these values are used are provided in Table 50.

Table 49: Total health state specific costs included in scenario analysis, assuming 17% of the patients, regardless of health state, require respite care

Health state	Total yearly costs (£)
OFF 0	[redacted]
OFF 1	[redacted]
OFF2	[redacted]
OFF 3	[redacted]
OFF 4	[redacted]
OFF 5	[redacted]
OFF 6	[redacted]
OFF 7	[redacted]

Health state	Total yearly costs (£)
OFF 8	[redacted]
OFF 9	[redacted]
OFF 10	[redacted]
OFF 11	[redacted]
OFF 12	[redacted]
OFF 13	[redacted]
OFF 14	[redacted]
OFF 15	[redacted]
OFF 16	[redacted]

Table 50: Results of the scenario analysis with 17% of patients receive respite care, PAS price

Technologies	Total costs (£)	Total QALYs,	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.23	-	-	-
LCIG	[redacted]	5.31	[redacted]	−0.09	[redacted]
BMT	[redacted]	4.53	[redacted]	0.70	Foslevodopa-foscarbidopa dominant

[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.

B33. Priority question. Please clarify if the A&E admissions costed are independent events than those leading to hospitalisation, as the Adelphi data seems to suggest that A&E visits were captured as the "route" through which patients were hospitalised. If the latter is the case, please ensure that the costs of hospitalisation in the model do not already include the cost of admittance into A&E, and equally that A&E costs reflect this appropriately.

A&E visits were counted and costed separately from hospitalisation; hospitalisation costs do not include cost of admittance into the A&E.

B34. Priority question. The current calculation of health state-related costs lacks transparency. Therefore, can the company please provide the raw calculations (in an excel spreadsheet in the model, as opposed to having hard-

coded costs) used to estimate each of the cost estimates provided in Table 79 of the CS, per OFF state.

An Excel spreadsheet detailing how health state-related costs were calculated has been provided as part of the updated cost-effectiveness model. Please refer to the tab "Cost regression output" within the updated model provided alongside these responses.

B35. Priority question. Despite the CS reporting that health state costs are varied in probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) (CS page 136), the EAG could not verify that health state costs were included in the models' PSA. Please confirm if these were included and if not, please include health state costs in PSA appropriately and provide the standard errors (SE's) associated with health state cost.

The health state costs were mistakenly omitted from the PSA. These have been added to the updated model, with SEs provided within the "Inputs" tab.

B36. Table 78 in the CS does not provide the percentage of patients per OFF state requiring a consultation - does this mean that 100% of patients in each OFF state were assumed to have consultations, respectively, per OFF state as indicated in the table?

As the numbers of patients with no consultations in the Adelphi 2017–2019 data was very small, 100% of patients in each OFF state were assumed to have consultations, and only the number of visits varied between different OFF states.

Economic analysis results

B37. Priority question. Please provide detailed deterministic results so the EAG can confirm the model and CS match.

The original base case deterministic results with PAS are presented in Table 51, which match the submitted model. These were reported in Appendix J.2 of the company submission at list price (Table 52). Updated base case deterministic results from the new company base case are presented in Appendix A.

Table 51: Original deterministic base case cost-effectiveness results, PAS price

Technologies	Total costs (£)	Total QALYs,	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.415	-	-	-

Technologies	Total costs (£)	Total QALYs,	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
LCIG	[redacted]	5.520	[redacted]	−0.106	[redacted]
BMT	[redacted]	4.601	[redacted]	0.814	Foslevodopa-foscarbidopa dominant

[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.

Table 52: Original deterministic base case cost-effectiveness results, list price (Appendix J.2, Table 32, page 159)

Technologies	Total costs (£)	Total QALYs,	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.415	-	-	-
LCIG	[redacted]	5.520	[redacted]	–0.106	[redacted]
BMT	[redacted]	4.601	[redacted]	0.814	Foslevodopa-foscarbidopa dominant

[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.

B38. Why is BMT set to be the “Main comparator” on the “Main board” worksheet? Please alter the model to allow users to select Duodopa as the main comparator.

The model has been adapted and localised to the UK from a Global model that was developed to suit multiple markets; while LCIG is the main comparator in the CS, BMT is noted as the main comparator in the model for this reason. The labelling of the comparators in the model does not impact the outcomes and has therefore been maintained as it is.

Section C: Textual clarification and additional points

Economic model

C1. Please confirm that the company’s deterministic base case results (not reported in the CS) for foslevodopa are [redacted] per quality adjusted life year (QALY) gained

(south-west quadrant) against LCIG; and dominant (incremental costs [redacted] and incremental QALYs [redacted]) vs BMT.

The original deterministic base case with PAS results are shown in Table 3 above (Question B37), which are in agreement with the values reported here by the EAG.

C2. Please confirm if the value in cell BL53, sheet “clinical data sheet” of the model is a mistake. The cell reports that 8 patients were in the OFF 10 state at baseline but other tables in the model and Figure 28 in the CS suggest that this value should be 0.

AbbVie can confirm that this is a typographical error: the cell BL53 in the sheet “clinical data sheet” should in fact report 0 patients in the OFF 10 state at baseline. This has been corrected in the updated model submitted as part of the company responses to the EAG’s clarification questions. Please note that this cell is not involved in the model calculations, and this error therefore does not affect any model outcomes.

C3. Please confirm what is the intended input parameter for the proportion of females at baseline in the model. Cell E41, sheet “main board” of the model reports the proportion to be 44%, whereas Table 52 of the CS reports this value to be 42% and Table 81 of the CS reports this value to be 29.8%.

Tables 52 and 81 of the company submission are both correct (n=[redacted] female patients, giving a proportion of [redacted]% from [redacted]patients). The model, however, incorrectly reports the proportion as [redacted]%. AbbVie apologise for this discrepancy; this has been corrected to [redacted]% in the revised company model submitted alongside these responses.

C4. Please confirm if the mean changes reported in Appendix M.4.1., Table 42 are the means at week 12 rather than mean change from baseline. If so, please provide the mean change from baseline.

The mean changes reported in Appendix M.4.1., Table 42, are the means at week 12 rather than mean change from baseline. The mean change from baseline is presented below.

Table 53: ANCOVA change from Baseline to Final Visit in Average Daily Normalised 'On' Time Without Troublesome Dyskinesia in the M15-736 Trial

	Oral CD/ LD	Foslevodopa-foscarbidopa
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Min	[redacted]	[redacted]

	Oral CD/ LD	Foslevodopa-foscarbidopa
Max	[redacted]	[redacted]
Within Group P-Value	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]
LS Mean of Difference (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Two-Sided P-Value	[redacted]	[redacted]

Abbreviations: ANCOVA: Analysis of co-variance; CD/ LD: carbidopa/levodopa; CI: confidence interval; SD: standard deviation; SE: standard error.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[2]

C5. The tick box for “Unadjusted OFF time” on the “Utilities” worksheet does not function. Please fix if this functionality is required.

This functionality is not required, and has therefore been removed from the model.

Appendix A: Updated cost-effectiveness analysis results

AbbVie have agreed with a number of the EAG's preferred changes to the cost-effectiveness model, which have therefore been incorporated into the updated cost-effectiveness analysis. These are summarised in Table 54, and the updated cost-effectiveness results at PAS prices are shown in Table 55 (probabilistic) and Table 56 (deterministic). An updated cost-effectiveness plane (Figure 7), cost-effectiveness acceptability curve (Figure 8), and tornado plots showing key model drivers of net health benefit (NHB) (Figure 9 and Figure 10) are shown below. Probabilistic results of all original and new EAG-requested scenario analyses are presented in Table 57.

Table 54: Summary of changes to the company base case cost-effectiveness analysis

EAG clarification question	Description of change incorporated in updated base case economic model
B12	Duration of AEs have been updated in line with data from M15-736.
B13	• The incidence of dyskinesia in the foslevodopa-foscarbidopa arm of the model has been corrected from [redacted]% to [redacted]% • The disutility for dyskinesia has been updated from 0.076 to 0.07 • The probability of dyskinesia has been corrected from [redacted]% to [redacted]%
B26	The drug acquisition costs for Levodopa + carbidopa (e.g sinemet) 110 mg, pramipexole 0.7 mg and rasagiline 1mg and ropinirole 2mg (84 pack) have been updated to eMIT prices, as per the EAG's request.
B30, 31	Costs for PET, SPECT and MRI scans have been removed from the health state-related costs, as per the EAG's suggestion.
C3	The proportion of female patients has been corrected from [redacted]% to [redacted]%, in line with the correct value from the M15-736 trial.

Abbreviations: AE: adverse event; EAG: external assessment group; eMIT: electronic market information tool; MRI magnetic resonance imaging; PET: positron emission tomography; SPECT: single-photon emission computed tomography.

Table 55: Updated probabilistic base case cost-effectiveness results, PAS price

Technologies	Total costs (£)	Total QALYs,	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.22	-	-	-
LCIG	[redacted]	5.31	[redacted]	−0.09	[redacted]
BMT	[redacted]	4.53	[redacted]	0.70	Foslevodopa-foscarbidopa dominant

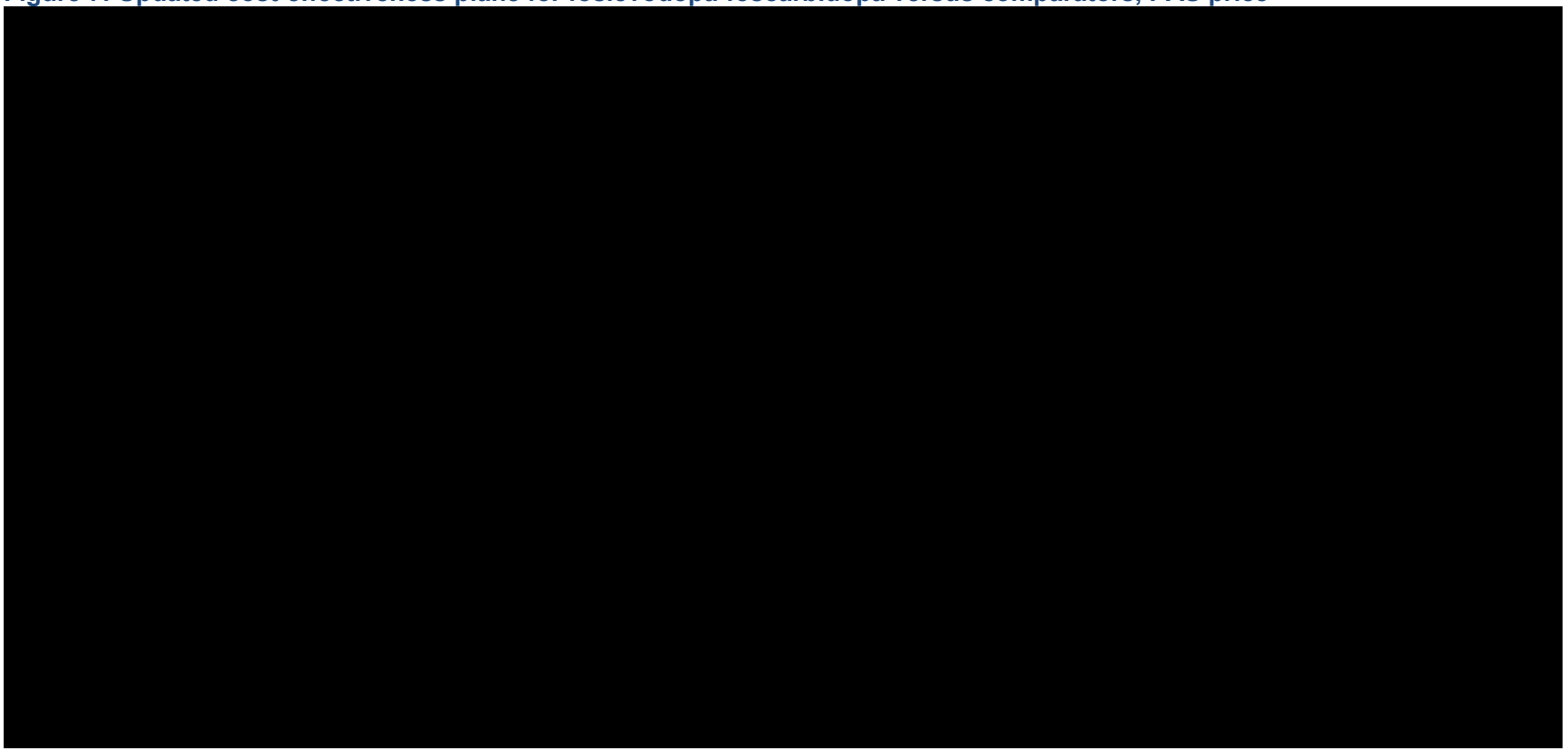
[a]SW quadrant ICER: costs saved per QALY forgone.
Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Table 56: Updated deterministic base case cost-effectiveness results, PAS price

Technologies	Total costs (£)	Total QALYs,	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.327	-	-	-
LCIG	[redacted]	5.430	[redacted]	−0.10	[redacted]
BMT	[redacted]	4.527	[redacted]	0.80	Foslevodopa-foscarbidopa dominant

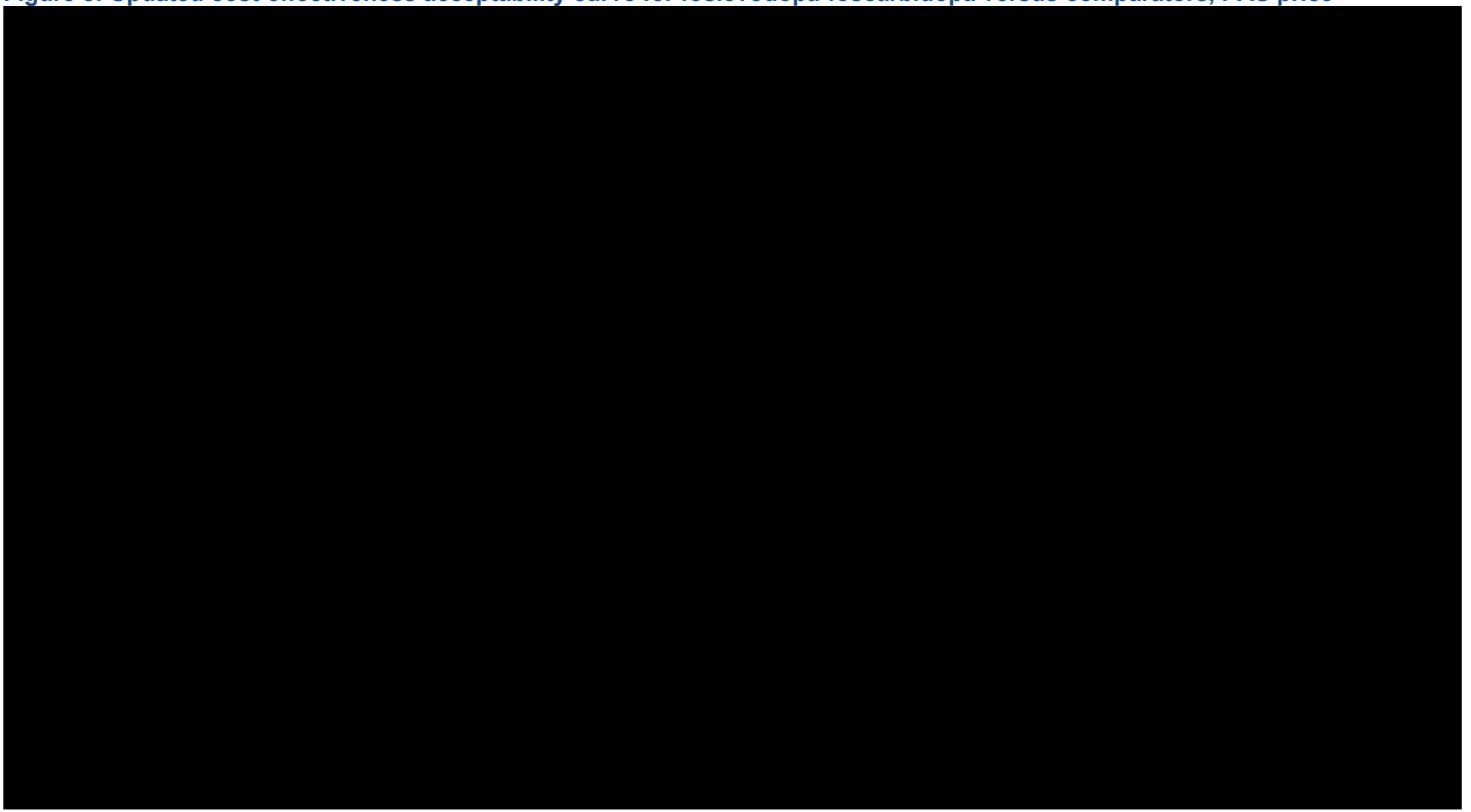
[a]SW quadrant ICER: costs saved per QALY forgone.
Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Figure 7: Updated cost-effectiveness plane for foslevodopa-foscarbidopa versus comparators, PAS price



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

Figure 8: Updated cost-effectiveness acceptability curve for foslevodopa-foscarbidopa versus comparators, PAS price



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

Figure 9: Updated tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus LCIG, PAS price

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

Figure 10: Updated tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus BMT, PAS price

Abbreviations: BMT: best medical therapy; NHB: net health benefit; PAS: patient access scheme.

Table 57: Updated probabilistic scenario analyses cost-effectiveness results, PAS price

#	Description	Foslevodopa-foscarbidopa		LCIG				BMT			
		Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHB[a] (QALY)	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHB[a] (QALY)
Base case (probabilistic)		[redacted]	5.22	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
Model time horizon											

#	Description	Foslevodopa-foscarbidopa		LCIG				BMT			
		Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHB[a] (QALY)	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHB[a] (QALY)
1	10 years	[redacted]	4.28	[redacted]	−0.07	[redacted]	[redacted]	[redacted]	0.60	Dominant	[redacted]
2	15 years	[redacted]	4.97	[redacted]	−0.08	[redacted]	[redacted]	[redacted]	0.68	Dominant	[redacted]
3	30 years	[redacted]	5.28	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
Wastage											
4	5% standard wastage for LCIG	[redacted]	5.23	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
5	10% standard wastage for LCIG	[redacted]	5.23	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
Foslevodopa-foscarbidopa and LCIG efficacy estimates											
6	Months 3-24: LOCF Months 24+: Natural history	[redacted]	5.15	[redacted]	−0.06	[redacted]	[redacted]	[redacted]	0.63	Dominant	[redacted]
Foslevodopa-foscarbidopa discontinuation rates											
7	Months 0-3: M15-736 Months 3-24: M15-741 and M15-737 (Full cohort) Months 24+: "standard rate"	[redacted]	5.14	[redacted]	−0.17	[redacted]	[redacted]	[redacted]	0.61	Dominant	[redacted]
8	Months 0-12: M15-741 (sample 1) Months 12-24: M15-737 Months 24+: "standard rate"	[redacted]	5.14	[redacted]	−0.17	[redacted]	[redacted]	[redacted]	0.62	Dominant	[redacted]
9	Months 0-12: M15—741 (full cohort) Months 12-24: M15-737 Months 24+: "standard rate"	[redacted]	5.18	[redacted]	−0.14	[redacted]	[redacted]	[redacted]	0.64	Dominant	[redacted]

#	Description	Foslevodopa-foscarbidopa		LCIG				BMT			
		Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHB[a] (QALY)	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHB[a] (QALY)
Mortality rate											
10	Standard mortality rate	[redacted]	6.46	[redacted]	−0.11	[redacted]	[redacted]	[redacted]	0.84	Dominant	[redacted]
Baseline characteristics											
11	Baseline age 61.4 years (−5 from baseline)	[redacted]	5.88	[redacted]	−0.10	[redacted]	[redacted]	[redacted]	0.77	Dominant	[redacted]
12	Baseline age 71.4 years (+5 from baseline)	[redacted]	4.18	[redacted]	−0.07	[redacted]	[redacted]	[redacted]	0.57	Dominant	[redacted]
Carer disutilities											
13	Include carer disutilities	[redacted]	4.83	[redacted]	−0.11	[redacted]	[redacted]	[redacted]	0.93	Dominant	[redacted]
EAG clarification questions scenarios											
B6	6-month transition probabilities for foslevodopa-foscarbidopa and LCIG during LOCF period	[redacted]	5.22	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.69	Dominant	[redacted]
B7a	Equal efficacy between foslevodopa-foscarbidopa and LCIG	[redacted]	5.23	[redacted]	−0.11	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
B19	Ara and Brazier source for utility adjustment for age and gender	[redacted]	5.15	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.69	Dominant	[redacted]
B25	No patients receiving NG tube insertion	[redacted]	5.22	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
B32	17% of patients receiving respite care	[redacted]	5.23	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]

[a]NHB at a WTP threshold of £30,000
[b]SW quadrant ICER; costs saved per QALY forgone
Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; LCIG: levodopa-carbidopa intestinal gel; LOCF: last observation carried forward; NG: nasogastric; NHB: net health benefit; NMA: network meta-analysis; QALY: quality-adjusted life year; SW: south-west.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

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

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

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

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

Information on completing this submission

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable

We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.

Your response should not be longer than 10 pages

About you

1.Your name	[redacted]
2. Name of organisation	Parkinson's UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Parkinson's UK has around 35,000 members. We provide support and advice to people with Parkinson's and their families and friends through our network of local advisers and over 350 local support groups. We want everyone to get the best health and social care, so we bring professionals together to drive improvements that enable people to live life to the full. We also inspire and support the international research community to develop life-changing treatments, faster. We are funded by donations.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	In 2021 Parkinson's UK received £10,393.75 from AbbVie for: ● Speaker fees for AbbVie events - £393.75 ● Sponsorship for supporting leaflets that helped groups to transition back to face-to-face activities post lockdown - £10,000
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	I met with a clinician who has run a trial of the therapy. And ran a workshop with 3 people with Parkinson's and 2 carers who have experience of the therapy.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	We estimate there are 145,000 people living in the UK (around 121,000 in England) with Parkinson's. By 2025 we expect the number of people with Parkinson's will rise by nearly a fifth to 168,582 and by 2065 it is expected to have doubled, due to an ageing population. While the majority of people develop Parkinson's symptoms after the age of 65, thousands of working age people are also affected (Parkinson's UK, 2018 - https://www.parkinsons.org.uk/news/parkinsons-diagnoses-set-increase-fifth-2025 accessed 16 May 2019). Parkinson's is a progressive, fluctuating neurological condition that affects all aspects of daily living including talking, swallowing and writing. Every person's symptoms are different. People with Parkinson's often find it hard to move freely. There are also other issues such as pain, depression, anxiety, dementia, freezing, hallucinations, continence problems, orthostatic hypotension and constipation which stops oral medication from working properly. The severity of symptoms can fluctuate from day to day and people often experience rapid changes in functionality over the course of the day. There is no cure for the condition, but medication can help people manage their symptoms. However, these regimes can be complex and over time oral medication can become less effective at controlling symptoms. This can also be referred to as 'wearing off'. There's a growing amount of evidence of other medications being added to an individual's regime to help manage their 'off' periods, however they are limited in their effectiveness, where possibly Foslevodopa has been more successful, based on personal experience of the therapy. Care partners of people with Parkinson's often report these elements of the condition are particularly troubling: ● the unpredictability of the fluctuating nature of Parkinson's, especially as the condition advances. As a care partner you become unable to leave the house for shopping or leisure activities without having systems in place to take care of their partner. Also the care partner must advocate for the person with Parkinson's across a range of appointments and interventions including those with therapists and benefit assessors, as people with Parkinson's may not be able to hold a lucid telephone call. ● the stress of supporting and enabling their partner, as a major issue. Research indicates that the quality of life and wellbeing of care partners of people with Parkinson's decreases as the condition progresses and the longer they have been caring for them (Hand et al, 2013 - https://onlinelibrary.wiley.com/doi/abs/10.1111/ggi.12204). Therefore, greater formal care input including Foslevodop could enable people to live at home longer and also may reduce care home admissions and avoid some unplanned hospital admissions. ● sleep deprivation, especially as the condition of the person they care for advances. Some people with Parkinson's experience REM sleep disorder which includes them having vocal outbursts throughout the night, thrashing around violently and also falling out of bed. Also sleep can be disturbed by medication 'wearing off' overnight which results in the care partner having to wake to help their partner move or go to the toilet.

	Also, care partners and families of people with Parkinson's face accentuated financial distress, in addition to the physical and psychological changes of the condition. Research reveals that a household where someone has Parkinson's in the UK is on average £16,582 per year worse off (Parkinson's UK, 2017 - https://www.parkinsons.org.uk/news/whats-cost-living-parkinsons). Not every care partner or person with Parkinson's is able to access state support to help them manage the extra costs of living with the condition.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Research conducted by Lancaster University in 2020 and 2021 found that both motor and non-motor symptoms were heavily impacted. ● Overall, 8 in 10 people with fatigue (86%), stiffness (83%) and slowness of movement (88%) reported a decline in these symptoms. ● Anxiety and depression also increased considerably with 7 in 10 people reporting that their anxiety had worsened in 2021, more than doubling the percentage from the previous year. And almost 4 times as many people with the condition said their depression got worse (rising from 13% to 48%). ● Slowness of movement, fatigue and sleeping issues all doubled year-on-year, while muscle cramps increased threefold. We believe these significant declines could be in part because of government restrictions that limited people's access to physical activity. Also, people with Parkinson's have experienced reduced access to healthcare appointments and therapeutic interventions, as services struggled to meet the needs placed on them. ● In the 3 months before our 2021 survey, over half (54.3%) of people with Parkinson's had an appointment with their care provider cancelled, with consultants cancelling slightly more frequently than nurses (31% compared to 28%). ● Other appointments that had been cancelled include physiotherapist (18%), speech/language therapist (18%), occupational therapist (14%) and psychologist (6%). ● Almost 3 in 5 people with Parkinson's (58%) had a phone or online appointment with their Parkinson's nurse and over a third (35%) had had one with their consultant. While aspects of these were seen positively, only 4 in 10 (40%) said they were pleased with the outcome of their consultant appointment. ● Just under half (46%) of people with Parkinson's surveyed felt their doctor could understand them well, and fewer than a quarter (23%) felt the connection with their doctor was comparable to that of a face-to-face appointment. ● Only 1 in 10 (12%) would recommend online or phone appointments to another person with Parkinson's. (Parkinson's UK, 2022 - https://www.parkinsons.org.uk/news/research-reveals-impact-pandemic-parkinsons-community) We are currently conducting the latest Audit of Parkinson's services, which includes a patient reported experience measure that will outline the views of people with Parkinson's on their access to health and care services. We would be happy to share it with NICE when it is published in early 2023.

8. Is there an unmet need for patients with this condition?	Yes, as there are limited treatment options for people living with advanced Parkinson's, where oral medications are not controlling their symptoms. Research suggests there are roughly 48% people with Parkinson's in complex and palliative stages of the condition (MacMahon DG, Thomas S (1998) 'Practical approach to quality of life in Parkinson's Disease' Journal of Neurology; 245 (suppl 1) S19-22 and MacMahon DG, Thomas S, Campbell S (1999) 'Validation of pathways paradigm for the Management of PD' Parkinsonism Rel. Disord; 5:S53). Data from the 2019 UK Parkinson's Audit of Elderly Care and Neurology services shows over 40% of patients are in the same stages of the condition. We believe the discrepancy could be explained by this data being based on consultants' caseloads, with a possible higher percentage of people in the more advanced stages in the population, for instance those who live in care homes and therefore not on consultants caseloads. Also when fluctuations are acute current advanced therapies aren't always appropriate for these individuals and apomorphine can also exacerbate impulsive and compulsive behaviours. Current treatment options, which are commissioned nationally for these individuals includes: ● deep brain stimulation (DBS) - NHS England commissions around 300 implants per year, data from 2018 shows that 230 implants were completed. ● Levodopa-carbidopa intestinal gel (LCIG) - NHS England commissions this therapy for around 75 people per year. It is worth noting that referrals for these therapies can be variable depending on where you live.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	***People with Parkinson's*** ● *"My symptoms are usually really well controlled. I do still get some off parts of the day. If it's really bad I can use a boost, but I tend not to. The therapy gives me the right 'flow' of medication so throughout the day and night I am significantly more balanced in terms of being 'on' and suffer far less with movement and joint ache compared to pre-trial."* ● *"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."* **Care partners experience of the therapy** ● *"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."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	● *"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."* (Person with Parkinson's) ● *"You do get used to it, but it isn't easy at first. We do the medication together as a team, you could do it on your own if needed, but we find it's better for us if we do it together."* (Care partner of someone with Parkinson's) ● *"Also you need access to a fridge to store the medication. This could be an issue for travelling or holidays. We've bought a fridge we travel with in the car. However, not all will be able to do that."* (Care partner of someone with Parkinson's) ● "We've recently had an issue with the chilled supply chain, where it broke down. My husband couldn't get his Foslevodopa, and as he's still on the trial protocol other medication couldn't be substituted. This meant he was 'off' most of the day. He was freezing, shuffling and couldn't think clearly. The delivery drivers will undergo retraining, but it is important to ensure robust supply procedures are put in place to ensure people get the therapy when they need it." (Care partner of someone with Parkinson's) ● The pump is generally easy to use once you have practised. However it would be useful to involve patients in the design of future devices to ensure they are as easy to use as possible. ○ *"I would imagine there would be some who might struggle if they have poor or very limited dexterity as the pump does require a degree of managing and some of the elements used in administering the drug can be fiddly but this could be overcome with the right support."* (Person with Parkinson's) ○ *"It's a steep learning curve to get to grips with the pump."* (Person with Parkinson's) ○ *"If you have poor cognition it might be tricky to use. If you're based in a nursing home you'd need to depend on staff who are trained to administer the therapy and that might be tough."* (Care partner of someone with Parkinson's)

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	● Older people who may not be deemed suitable for DBS or LCIG. Or for whom it is not accessible, for instance those living in rural populations and not close to a specialist centre. ● Those people who have apomorphine contraindicated, they either exhibit psychosis or orthostatic hypotension. ● Someone with visual impairment may have difficulties with the connectors and managing the pump.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Age**: The condition predominantly impacts people over 65 years old, but thousands of working age people are also living with the condition. **Physical disabilities**: Parkinson's is a movement related disorder. The most common movement symptoms of Parkinson's are slowness of movement, rigidity and stiffness.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

14a. How often do patients experience "off" time and for how long ("off" time is when Parkinson's symptoms, motor and/or non-motor, happen between medication doses)? **14b. How do patients and/or carers manage "off" time?**	A) Most people with Parkinson's will experience 'off' periods, however they can be associated with how long someone has lived with the condition, as this paper states. (Port et al, 2021 https://pubmed.ncbi.nlm.nih.gov/33459664/). And it can be debilitating as someone may not be able to do anything, until their medication kicks in. The oral forms of levodopa are affected by both bowel transit time and meals containing protein, which is essential for maintaining muscle mass. Constipation increases off time and mood problems. Having a non oral, non gut absorption route is far superior. Also oral forms of levodopa can, as the condition progresses, cause dyskinesia at peak dose which along with fatigue, weak voice and social anxiety restrict the social interactions or care partners and people with Parkinson's alike. People with Parkinson's shared how being 'off' impacted them: ● *"In my case 'off' means my right leg becomes heavy and weak, and from a sitting or lying position I struggle to raise it. Sometimes, but not always. I drag my right leg when walking. It also means my right arm becomes weak and my fingers stiffen and are difficult to move. If I am sat in a deep armchair it means I struggle to stand up. If I am in bed I struggle to turn over or get in/out of bed."* ● *"Apart from walking everything is in slow motion and my tremor gets much worse. Non-motor symptoms, like constipation, tend to be "off" almost the whole time."* ● *"Immoblie, stuck in a chair, but shaking uncontrollably,or not being able to get up from a chair, for hours. Being stuck in the bedroom not able to get dressed in the morning or walk downstairs, and the same at night. Being so frozen that everything has to be done for me."* ● *"As my Foslevodopa starts to wear off I experience pain, however if I boost my dose the pain disappears."* ● *"The uncertainty of my fluctuations means that I can't risk go day fishing, as I used to."* B) Some people with Parkinson's have shared they manage their medication using alarms on their phone, this reminds them to take their medicines on time. Some tweak their medicines based on the activities they're planning on the day, so their meds will give them the maximum time to be 'on' when they're undertaking activities. One care partner shared that before their partner with Parkinson's used Foslevodopa they used to take up to 3 dispersible madopar and up to 5 doses of apomorphine to manage their 'off' times. They stated the most effective way to manage it is simply taking the medication at the right time, but this doesn't always work - as oral medication loses its efficacy over time. However, the same person with Parkinson's now manages their 'off' time by boosting their Foslevodopa dose. The care partners stated that it's easier to spot when the 'off' is approaching and it can be managed quickly by the therapy. The care partner also shared that as Parkinson's progresses the flow rate of the Fosloevodopa pump can be adjusted. However this does mean physical appointments. They commented that if the dose could be changed remotely with the necessary safeguards in place, it could save clinician time as well as time for the patient and their care partner.

15. How often do patients experience sleep symptoms such as insomnia, tiredness because of lack of sleep etc.?	This article summarises some of the more common sleep problems experienced by people with Parkinson's (Open Access, 2017, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5311042/) People with Parkinson's frequently experience sleep issues and it was one of the most commonly reported non motor symptoms in this survey (Port et al, 2021 https://pubmed.ncbi.nlm.nih.gov/33459664/). During lockdown sleep was specifically mentioned as one of the symptoms that worsened, with reports of issues doubling between 2020 and 2021 (Parkinson's UK, 2022 https://www.parkinsons.org.uk/news/how-have-coronavirus-covid-19-restrictions-impacted-people-affected-parkinsons and 2021, Open Access, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8461662) One care partner shared the impact of sleep disturbance on the person they care for and them: *"My husband has REM sleep disorder which means he shouts at the top of his voice and thrashes around in bed. Sometimes he even falls out. This impacts my sleep and means we don't sleep in the same bed, in fact if we ever go away we have to make sure we get twin beds, as it's not safe for me to sleep with him. I also have to sometimes turn him at night and help him get out of bed to go to the toilet."*

Key messages

16. In up to 5 bullet points, please summarise the key messages of your submission.	• Foslevodopa could be a life changing therapy for people with Parkinson's. • While oral medication can control symptoms it becomes less effective over time and 'off' periods can be debilitating. • There are limited treatment options for people with advanced Parkinson's and these do not currently meet the needs of the people with Parkinson's who live with the advanced stage of the condition. • The experience of a small number of people with Parkinson's who have used Foslevodopa demonstrate that the advantages of using the therapy significantly outweigh the disadvantages. Also care partners of people with Parkinson's report positive outcomes from the use of the therapy, including greater wellbeing and independence. • Healthcare services have been severely impacted by COVID-19 and people with Parkinson's conditions have also deteriorated during this time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Professional organisation submission

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

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

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

Information on completing this submission

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

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists Movement Disorders Advisory Group
3. Job title or position	Consultant Neurologist and Movement Disorder specialist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	Non-profit Association.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim is to improve symptom control of motor symptoms
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would involve meaningful increase in mobility without excessive dyskinetic movements It could be measured by UPDRS scale motor subsection (around 0.9 points is considered potentially significant) It could be measured by reduction in on off motor fluctuations and freezing/dyskinesias Increased ON time without dyskinesias Reduced OFF time It could perhaps be measured by the impact on patient function as a measure of Quality of life (QoL) eg by UPDRS II or PDQ 39). Measure of reduced carer burden might also be helpful.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a great need for more effective and well tolerated treatments for advanced Parkinson's disease

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Parkinson's disease which has not responded to optimal doses of oral medications can be managed in several ways, which include consideration of Deep brain stimulation (eg subthalamic nucleus stimulation), subcutaneous apomorphine infusion or levodopa/carbidopa intestinal gel formulation
9a. Are any clinical guidelines used in the	NG71 Parkinson's disease in adults (NG71)www.nice.org.uk/guidance/ng71

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is reasonably well defined There are variations in practice across the NHS for several reasons. Access to device-aided therapies is variable. There are geographical variations in access to some specialist services, support and resource provision between services. Specialist neuroscience centres and/or access to specialists with experience of managing patients on device aided therapies may account for some variation in practice across NHS. In many cases there is no evidence that one form of treatment is superior to another; they all have their place in certain clinical scenarios.
9c. What impact would the technology have on the current pathway of care?	At the point where patients are not tolerating or not well controlled on oral medications, patients face a difficult choice ahead. The current alternatives involve potential surgery with attendant risks of stroke or infection, or a levodopa/carbidopa intestinal gel which requires a PEJ tube to be inserted before it can be administered. Neither of these are without risks. Deep brain stimulation is not considered in patients with dementia and is not considered helpful in cases where there are axial symptoms such as freezing of gait. It is usually not given to those over 70, with some exceptions. Therefore there are situations where a subcutaneous infusion would be very useful. Apomorphine is given subcutaneously and represents one of the choices in this situation and is perhaps the most relevant comparator in terms of ease of use and method of administration. Apomorphine requires an “apomorphine challenge” test before it can be set up for a particular patient and this requires a PD nurse specialist team to assess. Apomorphine also requires monitoring after infusion set up. Apomorphine has several potential contraindications such as severe impulse control disorders which will not apply so much to the proposed treatment as it is levodopa based. Apomorphine also requires blood monitoring long term. Since the new technology is a better tolerated drug ie levodopa could potentially have greater accessibility.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The new technology will be used in the situation where oral medication does not optimally control the patients motor symptoms or the oral medication causes unacceptable side effects.
10a. How does healthcare resource use differ between the technology and current care?	Avoidance of a percutaneous jejunostomy tube for a levodopa/carbidopa intestinal gel would be safer and easier for patients. Avoidance of brain surgery would also be easier and safer for patients. The technology under current review is relatively easy to administer, set up and to discontinue if ineffective or not tolerated. The new technology appears to be 24 hour drug delivery which could also impact positively on sleep disturbance due to

	nocturnal underdosing which is common in Parkinson's disease. This would benefit both patient and carer if it led to improved sleep pattern for the patient. The new technology might potentially be able to be delivered outside of a specialist neuroscience centre ie in a Parkinsons service more local to patients. It does provide 24 hour drug delivery. This might impact positively on sleep disturbance which could also reduce carer burden.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It is best limited, certainly initially, to secondary care to set up and stabilise patients in specialist clinics for PD Thereafter community teams could help with the ongoing administration in the community. They may also require PD specialist nurse input. The clinical setting depends on the chosen model to set up and support the therapy. It will depend on whether it requires specialist PD nurses and looking at the logistics it is likely that without intensive nurse support, it will be challenging to set up in community. Training will be required to give it safely and to look after the skin care regimen.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment in staff with expertise in PD, who need to be trained and equipped with local facilities including clinical space within the hospital setting. Staff training will be required in particular the PD specialist nurse team who can then help train patients and carers as well as community staff. Sufficient community PD nurse specialists in community settings would be needed for ongoing monitoring and care
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes I am hopeful that the technology will provide at least similar benefit to some of the other advanced therapies mentioned above, with the added benefit that it is relatively straightforward to set up and administer.
11a. Do you expect the technology to increase length of life more than current care?	I do not expect this outcome
11b. Do you expect the technology to increase health-related quality of life more than current care?	I do think this is a potential outcome, given the treatment is easier to administer than other advanced therapies. There is insufficient evidence to be able to say with certainty at this stage

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with Parkinson's disease Patients without associated PD Dementia

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Potentially it may be a lot easier than some other advanced therapies. Apomorphine, a dopamine agonist which is administered subcutaneously, is a relevant comparator. It is likely that fewer pre treatment tests eg ECG and blood tests may be required and pre treatment with antiemetics may also not be required. The technology will still involve the use of a pump device so support would be needed for that. As with any new therapy, it will need to be monitored closely for side effects. These may include skin reactions or nodules.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The general principles are that unacceptable side effects or lack of efficacy at therapeutic doses is an indication to stop the treatment. Starting the treatment is at the point of lack of efficacy of standard oral PD medications.
15. Do you consider that the use of the technology will result in any	no

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This technology is innovative. Yes it may improve the way that the current need is met
16a. Is the technology a 'step-change' in the management of the condition?	Apomorphine is administered in a similar manner but the administration of levodopa in this way rather than a dopamine agonist is a step change.
16b. Does the use of the technology address any particular unmet need of the patient population?	It addresses the need for a therapy that is effective in the advanced phases of the disease without the need for surgery. Moreover the provision of dopamine replacement therapy overnight could positively impact on sleep and early morning off periods. Apomorphine given as nocturnal infusion can also potentially address this need. The new technology is therefore a meaningful alternative to apomorphine and the new technology is not limited over a 24 hour period, whereas it is optimal to limit apomorphine infusion so it is not given in both daytime and at night for long periods.
17. How do any side effects or adverse effects of the technology affect the management of the	Insufficient evidence to answer this question

condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Evidence not available
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Evidence not available
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Evidence not available
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

21. How do data on real-world experience compare with the trial data?	Evidence not available

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	the drug needs to be stored in a fridge and other accessory items that are needed also take space. This is an important issue. Apomorphine does not need to be stored in a fridge. People who don't have easy access to fridge or storage space in their home might struggle to utilise this therapy. The pump can be adjusted by patients but this presupposes sufficient visual function so those with visual impairment might find it more difficult to adjust. Finally it may be that wearing the pump might be felt to be stigmatising.
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

23a. How often do patients experience "off" time and for how long ("off" time is when Parkinson's symptoms, motor and/or non-motor, happen between medication doses)? **23b. How is "off" time managed?**	In PD the amount of off and on time is extremely variable between patients Its severity also varies greatly Off time is managed by increasing unit dose or frequency of oral medication, adding oral medication such as COMT inhibitors or MAOI inhibitors. Dopamine agonists are considered
24a. How often do patients experience and report sleep symptoms such as insomnia, tiredness because of lack of sleep etc.? **24b. How are sleep symptoms managed?**	Patients often report insomnia with Parkinsons disease This is due to many factors and these include: Urinary frequency Nocturnal bradykinesia Restless legs syndrome REM sleep disorder Depression and anxiety Each of these is managed in different ways.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• The new technology appears to be a novel one. • Easy to set up, administer and discontinue • Avoids potential surgery for other available advanced therapies in PD • Appears to be a soluble, stable prodrug • potential benefits for overnight motor symptoms and sleep

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

STA Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; validation of the company's analyses; carried out clinical analyses and drafted the critique of the decision problem and the clinical evidence
Alex Allen	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the background, the clinical literature review, and critique of the clinical trials
Isaac Mackenzie	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; and drafted the utility and cost sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
BK50	Median bradykinesia score
BL	Baseline
BMI	Body mass index
BMT	Best medical therapy
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CEM	Cost-effectiveness model
CI	Confidence interval
COMT	Catechol-o-methyl-transferase
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSAI	Continuous subcutaneous apomorphine infusion
CSCI	Continuous subcutaneous infusion
CSR	Clinical study report
DBS	Deep brain stimulation
DIC	Deviance information criterion
DK50	Median dyskinesia score
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
EAG	External assessment group
FAS	Full analysis set
FE	Fixed effect
fMRI	Functional magnetic resonance imaging
GP	General practitioner
HCRU	Healthcare resource use
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IR	Immediate release
IRT	Interactive response technology
ITT	Intention-to-treat
J2R	Jump-to-reference
LCIG	Levodopa-carbidopa intestinal gel
LED	Levodopa equivalent dose
LOCF	Last observation carried forward
LS	Least squares
LYG	Life years gained

MAO	Monoamine oxidase
MCMC	Monte Carlo Markov Chain
MDS-UPDRS	Movement Disorders Society-Unified PD Rating Scale
MHRA	Medicine and Healthcare Products Regulatory Agency
MMRM	Mixed model for repeated measured
MRI	Magnetic resonance imaging
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
ONS	Office for National Statistics
PAS	Patient access scheme
PD	Parkinson's disease
PDQ-39	39-item PD Questionnaire
PDSS-2	Parkinson's Disease Sleep Scale-2
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PICOS	Population, Intervention, Comparison, Outcomes and Study
PKG	Personal KinetiGraph™
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RE	Random effects
RR	Relative risk
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SPECT	Single Photon Emission Computed Tomography
SUCRA	Surface under the cumulative ranking curve
SW	South-west
TEAE	Treatment emergent adverse event
TLR	Targeted literature review
VAS	Visual Analogue Scale
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

Issue	Summary of issue	Report sections
1	Potential overestimation of treatment benefit for foslevodopa-foscarbidopa	2.3.1, 3.2, and 3.3
2	Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG	3.4 and 4.2.6.4
3	OFF states 0-16 is inadequate at capturing the range of health effects of advanced Parkinson's, given the data available	4.2.4.3, 4.2.6.4 and 4.2.10.1
4	Patients are assumed to retain a lasting benefit from treatment following discontinuation	4.2.4.3
5	The LOCF assumption does not align with the trial data	4.2.6.4
6	Problems with the use of Palmer *et al.* 2002 in informing BMT	4.2.6.4
7	The company did not use the trial M15-736 trial data on the comparator arm	4.2.6.4
8	The company uses efficacy data and discontinuation data from different sources	4.2.7.1
9	Troublesome dyskinesia appears to be a source of unaccounted for patient burden	4.2.8.1
10	The regressions used for health state cost by OFF time appear inappropriate	4.2.4.3
11	The utility values used in the company's base case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making	4.2.4.3

Abbreviations: BMT, best medical therapy; LCIG, Levodopa-carbidopa intestinal gel; LOCF, last observation carried forward

1.2 Overview of key model outcomes

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

Overall, the technology is modelled to affect QALYs by:

- Reducing the number of OFF hours per day experienced by patients compared to best medical therapy (BMT) (LCIG is better at reducing OFF hours relative to BMT due to a lower discontinuation rate);
- Causing adverse events.

Overall, the technology is modelled to affect costs by:

- Reducing the number of OFF hours per day which reduces the number of healthcare costs compared to BMT and raising compared to LCIG;
- Its higher unit price compared to BMT, [redacted];
- Higher discontinuations compared to LCIG, meaning less time spent on foslevodopa-foscarbidopa;
- Lower initiation and administration costs compared to LCIG as no surgery is required, higher costs than BMT as foslevodopa-foscarbidopa is a subcutaneous injection;
- No adjunctive treatment costs compared to LCIG;
- No surgery related recurring AE costs compared to LCIG.

The modelling assumptions that have the greatest effect on the ICER are:

- Source of discontinuation rates used;
- Patients discontinue into the same OFF state they were in while on treatment meaning they maintain superior outcomes with foslevodopa-foscarbidopa compared to patients in the BMT arm;
- The trial transition probabilities observed between month 0 and month 3 of the M15-736 trial continue for 3 years for both foslevodopa-foscarbidopa and LCIG (with an NMA multiplier applied to LCIG);
- OFF time per day encompasses all health-related quality-of-life issues with Parkinson's (aside from first cycle AEs);

- Healthcare costs from the real-world Adelphi data, modelled with a linear regression, better represents the real world than using the direct data;
- QoL data from the trials, modelled with a linear regression, better represents the real world than using the direct data;
- The M15-736 comparator trial data showing a benefit for BMT is not clinically plausible and should not be used, BMT can only be represented by a gradual increase in OFF time sourced from Palmer *et al*, 2002.[1]

1.3 Summary of the EAG's key issues

The EAG acknowledges there are a large number of key issues identified. This is because the model is heavily driven by a number of assumptions due to the lack of available data for this disease area.

Table 2. Issue 1. Potential overestimation of treatment benefit for foslevodopa-foscarbidopa

Report section	2.3.1, 3.2, 3.3
Description of issue and why the EAG has identified it as important	The company has focused their submission on a subpopulation of the population in the NICE final scope; adults with PD that is responsive to levodopa, but with symptoms not adequately controlled by their current medical therapy and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control. Overall, the EAG considers this population to be reasonable given this represents a subset of patients covered in the conditional marketing authorisation with a particularly high unmet need in terms of treatment options. It is unclear to what extent the effectiveness of foslevodopa-foscarbidopa differs between the population specified in the scope, the patient population in the main trial (M15-736), and the narrower population the company is focusing on. In M15-736 prior DBS was not allowed, and it is unclear how many patients had prior apomorphine and if patients who hadn't received these treatments prior to the trial were unsuitable for them. M15-736 is a well conducted double blind RCT, which provides the best available evidence of the relative clinical effectiveness of foslevodopa-foscarbidopa compared with oral CD/LD. However, a large proportion of trial participants are likely to have correctly deduced which treatment they had been randomised to, mainly due to the large difference in morning akinesia between foslevodopa-foscarbidopa and oral CD/LD. The key efficacy outcome, OFF time, was captured in patient reported PD diaries which are subjective and at higher risk of bias. Although the magnitude of this bias is unknown it is likely that patients on foslevodopa-foscarbidopa may overestimate the efficacy of their treatment and that patients on BMT may underestimate the efficacy of treatment. In addition, treatment discontinuations were highly imbalanced between the foslevodopa-foscarbidopa and oral CD/LD arms in M15-736. Missing data were captured appropriately in the primary analysis (MMRM) to inform the outcomes of patients on treatment in the economic model. However, as an estimate of the efficacy of foslevodopa-foscarbidopa treatment in the full trial population, the J2R sensitivity analysis gives more plausible results.
What alternative approach has the EAG suggested?	Additional clinical input could provide some insight into the likely biases introduced by the narrower population and the potential failure of blinding in the trial.
What is the expected effect on the cost-effectiveness estimates?	If the treatment effect of foslevodopa-foscarbidopa is overestimated, then the estimated ICERs are likely to be underestimated. However, the EAG is unsure of the magnitude of the overestimated treatment effect.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence or analyses are unlikely to be available or possible. To resolve the uncertainty additional clinical input should be sought.

Abbreviations: BMT, Best medical therapy; CD/LD; DBS, Deep brain stimulation; EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; J2R, Jump-to-reference; MMRM, Mixed model for repeated measured; NICE, National Institute for Health and Care Excellence; PD, Parkinson's disease; RCT, Randomised controlled trial

Table 3. Issue 2. Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG

Report section	3.4 and 4.2.6.4
Description of issue and why the EAG has identified it as important	The company conducted indirect treatment comparisons (ITC) to compare the efficacy of foslevodopa-foscarbidopa and LCIG. The data from the trials included in the NMAs in the company's analyses were inconsistent, comparing estimates of LS means and observed means. The methods used for accounting for missing data also differed between the included trials. The EAG considers least square (LS) mean to be more appropriate than the observed mean and provides results based on LS mean data, where available. These should be considered illustrative as not all relevant trials are included. In addition, data based on consistent methods for accounting for missing data were not available. The NMAs of ON time without troublesome dyskinesia and OFF time suffer from the same uncertainty and high risk of bias as the underlying M15-736 data. There is also likely to be some heterogeneity between the trials due to the difference in BMT and the variation in patients' PD. The results of the NMAs, both the company's and the EAG's, were not statistically significant.
What alternative approach has the EAG suggested?	The EAG recommends assuming equal efficacy between foslevodopa-foscarbidopa and LCIG in the economic model
What is the expected effect on the cost-effectiveness estimates?	Assuming equal efficacy improves the cost-effectiveness of foslevodopa-foscarbidopa versus LCIG compared to using the results of the EAG's updated analysis, but it decreases the cost-effectiveness compared to using the company's original NMA results
What additional evidence or analyses might help to resolve this key issue?	The company should update the NMAs of OFF time and ON time without troublesome dyskinesia to include LS mean data and using MMRM to account for missing data for all three included trials; M15-736, Olanow 2014 and DYSCOVER.

Abbreviations: ICER, incremental cost effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel; NMA, network meta-analysis

Table 4. Issue 3. OFF states 0-16 is inadequate at capturing the range of health effects of advanced Parkinson's, given the data available

Report section	4.2.4.3, 4.2.6.4 and 4.2.10.1
Description of issue and why the EAG has identified it as important	Evidence of utility by H&Y and OFF time was found by the company as part of their systematic literature review. This demonstrated significant variation between H&Y state outside of OFF state, with H&Y seeming to contextualise what OFF time means to a patient. In addition, the only other model identified that used OFF state alone, was one submitted to CADTH and was heavily criticised for not accurately capturing the heterogeneity associated with the condition. The linear regressions used to match OFF state to utility data and healthcare resource use data appear to show OFF state alone as an insufficient predictor. Using the direct data by OFF state, instead of a regression, results in a vastly different set of values, in addition to many of the health states having little or no data informing it. This is also an issue for the efficacy data, as there are only data for 47 patients in the foslevodopa-foscarbidopa arm of the M15-736 trial being used to inform transitions for 17 health states, resulting in 8 of the states having no data to inform transitions and two health states' transitions being informed by single patients.
What alternative approach has the EAG suggested?	These issues would be alleviated by using the same or a similar model structure to: Kalabina *et al.* 2019, Walter and Odin 2015, Chaundhuri *et al.* 2022, Lowin *et al.* 2011 and Lowin *et al.* 2017. This involved health states driven by OFF time and H&Y state. OFF states were set into 4 or 5 categories: 0-25%, 26-50%, 51-75% and 76-100% of the day spent in OFF time, with some of the models electing to use 0 hours of off time as a separate health state.
What is the expected effect on the cost-effectiveness estimates?	Given the MDS-UPDRS appears to be more favourable for foslevodopa-foscarbidopa in the M15-736 trial versus the comparator it would improve the cost-effectiveness versus LCIG and BMT
What additional evidence or analyses might help to resolve this key issue?	Since the trial data does not contain H&Y scores, some analysis will need to be undertaken to either convert the MDS-UPDRS scores taken in the trial to H&Y or use these scores in their place. Most aspects of the model would need a significant overhaul to accommodate the structural changes.

Abbreviations: CADTH, Canadian ; ICER, incremental cost effectiveness ratio; H&Y, Hoehn and Yahr scale; LCIG, levodopa-carbidopa intestinal gel; MDS-UPDRS, movement disorder society-unified Parkinson's disease rating scale;

Table 5. Issue 4. Patients are assumed to retain a lasting benefit from treatment following discontinuation

Report section	4.2.4.3
Description of issue and why the EAG has identified it as important	Patients who discontinue treatment do so into the OFF state they were in while on treatment and then follow the BMT transition matrix, meaning they effectively have a lifetime advantage over patients who are just provided BMT. The result of this assumption is that following the LOCF period, patients who discontinue will have the same outcomes for OFF time as those who remain on foslevodopa-foscarbidopa or LCIG; a clinically implausible situation. This assumption is a significant source of both incremental cost and incremental QALY benefit for LCIG and foslevodopa-foscarbidopa over the BMT arm in the model
What alternative approach has the EAG suggested?	The EAG's clinical experts have suggested declines in OFF time would be seen immediately and it would be reasonable to assume these patients would have similar outcomes to those on BMT, unless they were discontinued onto another advanced therapy. Unless the company can provide data on patients who have discontinued retaining this benefit, patients should be assumed to have equal outcomes to the BMT arm.
What is the expected effect on the cost-effectiveness estimates?	Substantial decreases in the cost-effectiveness for foslevodopa-foscarbidopa versus BMT and LCIG due to the higher rate of discontinuation in the foslevodopa-foscarbidopa arm.
What additional evidence or analyses might help to resolve this key issue?	Evidence to substantiate that patients who discontinue either foslevodopa-foscarbidopa or LCIG have superior outcomes in OFF time while not on treatment compared to patients treated with BMT.

Abbreviations: ICER, incremental cost effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel; LOCF, last observation carried forward;

Table 6. Issue 5. The LOCF assumption does not align with the trial data

Report section	4.2.6.4
Description of issue and why the EAG has identified it as important	The LOCF assumption carries forward the transition rates for the first 3 months of treatment for the following three years. Trial data from both M15-736 and M15-741 suggests the benefit to OFF time from treatment occurs almost entirely within the first month, following this period patients in M15-741 saw only a minor decrease in OFF time and patients in M15-736 saw a slight increase. Given this it seems inappropriate to carry forward the transition probabilities that occur in the first 3 months of the M15-736 trial.
What alternative approach has the EAG suggested?	Assume patients remain in their health states for the LOCF period.
What is the expected effect on the cost-effectiveness estimates?	Decrease in the cost-effectiveness for foslevodopa-foscarbidopa versus BMT and mildly increase the cost-effectiveness versus LCIG, as greater discontinuations in the foslevodopa-foscarbidopa arm mean deteriorations in on treatment efficacy have a bigger impact on LCIG.
What additional evidence or analyses might help to resolve this key issue?	Data from the M15-736 trial extension, M20-098 would be preferred to informing the LOCF period transitions if/when it is available.

Abbreviations: ICER, incremental cost effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel; LOCF, last observation carried forward;

Table 7. Issue 6. problems with the use of Palmer *et al.* 2002 in informing BMT

Report section	4.2.6.4
Description of issue and why the EAG has identified it as important	The data from Palmer et al, 2002[1] used is based on two data points, these represent the average time on levodopa for patients with >25% and <25% OFF time. The data in this paper comes from a survey, published in 2000, of 60 patients in the US. This is used to inform the transitions for the full time horizon of the BMT arm and the transitions of all patients who discontinue. This is very limited data to base such a significant part of the model on but there does not appear to be a viable alternative. In addition, the current method of extraction assumes everyone in an OFF state has the same level of time on levodopa, despite using this assumption to then graph a curve that relates levodopa exposure to incremental changes in OFF time.
What alternative approach has the EAG suggested?	If using Palmer et al 2002 the midpoints (or if available average OFF time) for the <25% and >25% categories should be graphed as opposed to the current assumption that they are flat lines, effectively saying everyone in an OFF category has the same level of levodopa exposure. Furthermore, Palmer et al, 2000 should be analysed for the five levels of OFF that were referenced in the abstract, as this could provide a more robust data set.
What is the expected effect on the cost-effectiveness estimates?	The effect of more data would be unknown. The impact of using the midpoints would likely be a steeper curve and because duration of levodopa therapy is in the Y axis and OFF time in the X axis this would effectively mean the predicted time for OFF transitions would go up. This would mean foslevodopa-foscarbidopa would become less cost effective versus BMT and more cost effective versus LCIG.
What additional evidence or analyses might help to resolve this key issue?	A newer source of information with more data to extract than two points would be preferable but as no other relevant papers appear to be available, examining Palmer *et al*, 2000 may provide additional data points.

Abbreviations: ICER, incremental cost effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel;

Table 8. Issue 7. The company did not use the trial M15-736 trial data on the comparator arm

Report section	4.2.6.4
Description of issue and why the EAG has identified it as important	The company has opted to use the Palmer et al data to represent BMT over the trial data from M15-736, arguing the observed benefit to patients from BMT was a result of exposure to the healthcare system. This is an issue firstly because the alternative data source is particularly weak as discussed in Table 7 and secondly because any non-clinically realistic benefit from exposure to the healthcare system would also apply to the foslevodopa-foscarbidopa arm. The major problem here is the company excluding their own comparator arm trial data makes it ambiguous how much of the benefit from foslevodopa-foscarbidopa is real or a placebo.
What alternative approach has the EAG suggested?	Use the M15-736 trial data and assume the LOCF for two cycles (i.e. the benefit lasts 1 year).
What is the expected effect on the cost-effectiveness estimates?	This will make foslevodopa-foscarbidopa more cost effective versus LCIG and less cost effective versus BMT.
What additional evidence or analyses might help to resolve this key issue?	Trial data identifying how long this trial effect for the comparator arm continues. 1 year is likely a conservative estimate made in absence of better information.

Abbreviations: ICER, incremental cost effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel;

Table 9. Issue 8. The company uses efficacy data and discontinuation data from different sources

Report section	4.2.7.1
Description of issue and why the EAG has identified it as important	The company uses discontinuations from cohort 2 of the M15-741 to maintain a consistent source for discontinuation for the foslevodopa-foscarbidopa arm. The problem with this is the best predictor for discontinuations for patients with the efficacy and baseline characteristics of M15-736 trial would be the discontinuations from that trial. Having a consistent source of discontinuations does not improve the model's predictive validity, having the best available source for each period does. The company claims M15-741 cohort 2 used a superior administration method to cohort 1 that led to fewer discontinuations, but this method was also used by all patients in the M15-736 trial.
What alternative approach has the EAG suggested?	The EAG suggests using the best available data for each period. This involves using M15-736 trial data for the trial period, M15-741 cohort 2 for the following year and the M15-737 full cohort (or just cohort 2 if the data are available) from year 1 to year 2. Following this, discontinuations should be assumed to be equal to LCIG given the lack of data.
What is the expected effect on the cost-effectiveness estimates?	This will increase the discontinuation rate for foslevodopa-foscarbidopa making it less cost effective versus both BMT and LCIG.
What additional evidence or analyses might help to resolve this key issue?	M20-098 discontinuations would be preferable to use during the first year and cohort 2 of M15-737 would be the best available data for discontinuations in year 2.

Abbreviations: ICER, incremental cost effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel;

Table 10. Issue 9. Troublesome dyskinesia appears to be a source of unaccounted for patient burden

Report section	4.2.8.1
Description of issue and why the EAG has identified it as important	A significant health effect experienced by people with Parkinson's disease (PD) is troublesome dyskinesia. This is usually the result of overmedication and will generally get worse with time. While not as significant a decrement to patient quality of life as OFF-time, troublesome dyskinesia represents a common health related impact from PD that is unaccounted for in the model.
What alternative approach has the EAG suggested?	The CSRs for foslevodopa-foscarbidopa and LCIG trials contain data on the ON time with troublesome dyskinesia experienced by treatment line, these could be used in the short to medium term to explore comparative rates of troublesome dyskinesia.
What is the expected effect on the cost-effectiveness estimates?	Unclear, in theory, given how the treatment operates, foslevodopa-foscarbidopa and LCIG would be expected to result in the greatest improvement in troublesome dyskinesia but the M15-736 trial showed patients average daily normalized ON time with troublesome dyskinesia increased more in the foslevodopa-foscarbidopa arm than in the comparator arm.
What additional evidence or analyses might help to resolve this key issue?	The addition of short and long term estimates of troublesome dyskinesia by arm and its impact on utility and cost.

Abbreviations: ICER, incremental cost effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel;

Table 11. Issue 10. The regressions used for health state cost by OFF time appear inappropriate

Report section	4.2.4.3
Description of issue and why the EAG has identified it as important	The company's approach to estimating health state costs in the model is flawed and leads to an overestimation of costs. The results of 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. Crucially, the EAG disagrees with the company's assessment that a regression analysis was needed due to a lack of available data for several OFF states in the model and notes that the lack of data for each hour of OFF time is more likely to be a problem arising from the company's choice of modelling approach. The EAG also disagrees with the company's decision to include patients with early and intermediate PD in the analysis and notes that there is a reasonably robust sample size of patients with advanced PD in the Adelphi study. Furthermore, including patients with early and intermediate PD misrepresents the population in the foslevodopa-foscarbidopa SmPC, which restricts the use of the drug to the advanced PD population. Finally, the EAG notes that the key drivers of the health state costs are the professional care cost, followed by hospital costs and by respite care. During its investigation of these cost data, the EAG found several discrepancies between the observed data provided by the company and the results reported in the Adelphi study (as detailed in Section 4.2.11.6).
What alternative approach has the EAG suggested?	1.Explain the differences identified by the EAG in the sample size of patients reported for hospitalisation and professional care costs in the company's reply to clarification questions and the respective number of patients reported in the Adelphi study; 2.Use the observed data from the Adelphi study, instead of the fitted data; 3.Use the UK population with advanced PD only; 4.Investigates the possibility of analysing resource use by categories of OFF hours - for example, the Adelphi data suggests that it would be more robust to assume the same resource use for 10+ OFF hours.
What is the expected effect on the cost-effectiveness estimates?	Reduces the cost effectiveness of foslevodopa-foscarbidopa versus BMT and improves it versus LCIG as correction to an overestimate of higher OFF state costs will advantage the treatments that have lower efficacy.
What additional evidence or analyses might help to resolve this key issue?	The additional analysis requested in the alternative approach.

Abbreviations: ICER, incremental cost effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel;

Table 12. Issue 11. The utility values used in the company's base case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making

Report section	4.2.4.3
Description of issue and why the EAG has identified it as important	The EAG does not consider the company's approach of combining the utility data in studies M15-736; M15-741; M20-098; and M15-737 to be appropriate. The EAG notes that baseline utility values across these studies (Table 53 of the EAG report) show a paramount lack of comparability across mean utility values for the same OFF states at baseline in the two main studies (M15-736; M15-74). For example, for the OFF state 5, the mean utility value at baseline in M15-736 and M15-741 was 0.83 and 0.63,

	respectively. This suggests that patients' quality of life was considerably lower in M15-741 than in M15-736 at baseline, and/or that trying to capture the granular impact of hourly OFF changes in patients' quality of life is not appropriate, as discussed in Issue 3. The EAG also has several concerns with the regression models used to estimate utility values in the model. The EAG is unclear why age, sex, baseline OFF hours and treatment duration at baseline were not tested as variables in the regression models. The EAG is also concerned with the uncertainty around the utility values used for the OFF state 10 or above, as several utility estimates seem to be based on only 2 or 1 patients The EAG notes that the underlying rationale to the company's approach that quality of life only depends on total hours of OFF time (by hourly increments) seems at odds with the data used to run the utility analysis. If treatment arm was found to not be statistically significant in predicting patients' quality of life, then the company should have used utility data from both treatment arms in every study where this was available, therefore increasing the sample size and robustness of the analysis.
What alternative approach has the EAG suggested?	1. Attempt to convert the MDS-UPDRS data to an estimate for H&Y states of patients or use the MDS-UPDRS as a health state directly if plausible. 2. The company should investigate the impact of variables such as age; OFF hours at baseline; and treatment duration on patients' quality of life. The company should also include the utility data available in comparator arms of the relevant studies. The company should investigate the possibility of analysing changes in mean utility by categories of OFF hours - for example, Table 51 and Table 52 show that aggregating changes in OFF hours by 0% to 25%; 31% to 50% and 50% to 100% categories could provide more robust sample sizes and therefore, potentially more robust utility estimates. 3. If step 1 and 2 do not lead to more consistent mean utility values within the same OFF states across studies, the company could investigate the possibility of using an individual study, instead of aggregating studies to estimate utility values in the model. 4. The company should use the data from the UK population with severe PD from the real- word Adelphi study to estimate utility values for the same OFF categories as those chosen in step 2, in order to validate the estimates used in the updated analysis.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict.
What additional evidence or analyses might help to resolve this key issue?	The additional analysis requested in the alternative approach.
Abbreviations: ICER, incremental cost effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel;	

1.4 Other key issues: summary of the EAG's view

Item	Section
The data source for discontinuations for LCIG appears to go on for 16 years but only 2 years of data was used.	4.2.7.1
The source for the rate of dyskinesia in LCIG patients appears to relate to oral levodopa.	4.2.8.1
Applying AEs only in the first cycle is inappropriate when most of these AEs would be expected to progress over time.	4.2.8.1
LCIG recurring AEs continue occurring at the same rate regardless of the percentage of patients on treatment	4.2.8.1
The Dirichlet distribution applied to the health state transition probabilities for the PSA appears to have been calculated erroneously	6.1
LCIG administration and treatment management costs appear to be overestimated	4.2.11.44.2.11.6

1.5 Summary of EAG's preferred assumptions and resulting ICER

Table 13 summarises the EAG's preferred assumptions for the model and the cumulative impact these have on the ICER.

Table 13. EAG's preferred model assumptions, probabilistic and deterministic results

Preferred assumption	Section in EAG report	Cumulative ICER vs LCIG probabilistic (£/QALY)	Cumulative ICER vs LCIG deterministic (£/QALY)	Cumulative ICER vs BMT probabilistic (£/QALY)	Cumulative ICER vs BMT deterministic (£/QALY)
Company base case	5.1.2	[redacted]	[redacted]	Dominant	Dominant
EAG corrections					
Corrected NMA results	6.1 and 3.4.4	[redacted]	[redacted]	Dominant	Dominant
Corrected PSA Dirichlet distribution	6.1	[redacted]	[redacted]	Dominant	Dominant
Company provided scenarios					
Change utility source to Ara and Brazier	4.2.10	[redacted]	[redacted]	Dominant	Dominant
Efficacy between foslevodopa-foscarbidopa and LCIG assumed equal	4.2.6.2	[redacted]	[redacted]	Dominant	Dominant
Adjust TP to match cycle length change from 3 months to 6	4.2.6.1	[redacted]	[redacted]	Dominant	Dominant
Exclusion of NG tube insertion cost	4.2.11.4	[redacted]	[redacted]	Dominant	Dominant
EAG additional preferred scenarios					

No change in efficacy during the LOCF period	4.2.6.4	[redacted]	[redacted]	Dominant	Dominant
Use 736 discontinuations, 741 cohort 2 and 737	4.2.7.1	[redacted]	[redacted]	Dominant	Dominant
Turn off injection related AEs for BMT	4.2.8.1	[redacted]	[redacted]	Dominant	Dominant
Injection related AEs continue for life/time horizon for foslevodopa-foscarbidopa	4.2.8.1	[redacted]	[redacted]	Dominant	Dominant
Adjust LCIG recurring AEs by the percentage of cohort on treatment	4.2.8.1	[redacted]	[redacted]	Dominant	Dominant
Foslevodopa-foscarbidopa dose as per trial	4.2.11.1	[redacted]	[redacted]	Dominant	Dominant
LCIG administration cost	4.2.11.4	[redacted]	[redacted]	Dominant	Dominant
LCIG tx management costs	4.2.11.4	[redacted]	[redacted]	Dominant	Dominant
Health state costs	4.2.11.6	[redacted]	[redacted]	[redacted]	[redacted]
Patients who discontinue have equivalent outcomes to natural disease progression arm	4.2.4.3	[redacted]	[redacted]	[redacted]	[redacted]

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

Abbreviations: EAG, evidence review group; ICER, incremental cost-effectiveness ratio; NG, nasogastric; QALY, quality adjusted life year; TP, transition probability;

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are, no efficacy difference between foslevodopa-foscarbidopa and LCIG, no improvement during the LOCF period, utilisation of direct health state cost data and patients who discontinue treatments have equivalent outcomes to patients who were treated with BMT from the beginning.

Modelling errors identified and corrected by the EAG are described in 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see 6.3.

2 Introduction and background

2.1 Background

Within Section B.1 of the company submission (CS), the company provides an overview of Parkinson's disease (PD), detailing symptoms and disease progression. Overall, based on advice from its clinical experts, the External Assessment Group (EAG) considers the CS to present an accurate overview of PD as a multifaceted neurodegenerative disease with both motor and non-motor aspects. The clinical experts advising the EAG agreed that the gravity and complexity of symptoms vary between people and from day-to-day. The progression of symptoms is inexorable but varies in speed between patients and may not be smooth. The EAG's clinical experts stated that one assessment of a person's PD may be through the Hoehn and Yahr scale, which assesses the severity of PD using 5 stages. However, these are broad stages, too coarse to reflect change between clinic visits, and do not necessarily dictate the treatment someone may receive.

It is understood that symptoms are linked to fluctuations in a person's dopamine level. When dopaminergic stimulation is too low, people with PD experience periods where they may not be able to talk, walk or eat, described as "OFF time". When dopamine stimulation is normal or too high a person is able to move freely (described as "ON time"). However, a consequence of having too much dopamine stimulation can lead to dyskinesia – atypical, uncontrollable, involuntary movements. These can be troublesome and can adversely affect a person's quality of life.

Parkinson's disease cannot be cured but medications can help control the symptoms and this is done by attempting to keep a person's dopamine levels within the 'therapeutic window', neither too low nor too high. These medications can act in a number of ways:

- Increase the amount of dopamine in the brain;
- Act as a dopamine substitute by stimulating dopamine receptors in the brain ;
- Block the action of other factors (enzymes) that break down dopamine.

The EAG's clinical experts indicated initial treatment of PD most often begins with either oral levodopa or dopamine agonists. Levodopa acts to increase the amount of dopamine in the brain while dopamine agonists act to stimulate dopamine receptors.

Regular reviews of treatment are required as the condition progresses. This involves changes to the dose and timing of their initial treatment followed by the addition of further oral treatments to the regime. It is broadly termed "best medical therapy" (BMT) and could be utilised for years before advanced therapy is required. For a majority of older patients, advanced therapy is never

considered, for a number of reasons. These include clinician unfamiliarity, increasing cognitive fragility (making the most accessible advanced therapy of apomorphine less suitable, and DBS contraindicated), reluctance to travel to tertiary centres for DBS or LCIG, and increasing burden of co-morbidities taking priority or making interventions more challenging.

Treatment is initiated and optimised through conversations between the treating clinician and the person with PD. A person's specific symptoms, experiences of various therapies, and treatment goals will inform the prescribed therapy. For example, an individual may prefer longer periods of ON time with troublesome dyskinesia to even short periods of OFF time. For others the amount of OFF time per day may be less important than how predictable the patterns of OFF hours are, and when they happen in the day.

As a person's PD progresses, they may find they experience increasing OFF time and the timing of these periods becomes less predictable or more frequent and prolonged. In addition, they may have an increase in the severity of their dyskinesia. These motor fluctuations are linked to a person's dopamine 'therapeutic window' narrowing and so becoming more difficult to consistently maintain within. The CS calls this "advanced Parkinson's disease"; the term complex Parkinson's with motor fluctuations would be used clinically. These motor fluctuations are an indication that advanced therapy should be considered.

The advanced therapies that currently have marketing authorisation for PD are apomorphine (+/- BMT), deep brain stimulation (DBS), or levodopa-carbidopa intestinal gel (LCIG). The CS describes a treatment pathway that moves from BMT to either apomorphine or DBS. If apomorphine and DBS are unsuitable for a person, or for whom these treatments have failed, then the next treatment offered is LCIG. However, the EAG's clinical experts indicated that while apomorphine is the most commonly used advanced treatment, as it is less invasive and more easily reversible than either DBS or LCIG, any of the three advanced treatments may be utilised after BMT. Guidance suggests apomorphine would be considered first, with consideration of either DBS or LCIG if side effects from (or prior contraindications to) apomorphine prevented its use.

People may decide to discontinue advanced treatment and either change to another advanced treatment or move back to "optimised" BMT. People might choose BMT if they do not wish to have the adverse events associated with their advanced therapy and prefer to manage with some more OFF time, or a person could reach a point where the benefits of advanced therapy are similar to the benefits they could expect from BMT and so prefer a less invasive therapy. However, the EAG's clinical experts indicated that discontinuation of advanced therapies is generally rare, once established successfully.

2.2 Positioning of foslevodopa-foscarbidopa in the UK treatment pathway

The company proposes that foslevodopa-foscarbidopa be used as an alternative to LCIG, after apomorphine and DBS have been found to be either ineffective or are unsuitable for the person with PD. This is in line with the criteria for use of LCIG in NHS England, which states a person should be unable to tolerate or unsuitable for apomorphine, and is unsuitable for DBS, has refused to consent for DBS, or DBS has failed.[2]

The EAG's clinical experts highlight the importance of an approach tailored to the individual patient and that while either of the three currently available advanced therapies can be utilised first, the majority of people begin with apomorphine as this is less invasive and more easily reversible. The experts also notes that foslevodopa-foscarbidopa would be a valuable alternative as a first line advanced therapy to apomorphine, which has more contraindications, needs monitoring and pre-loading with antiemetics.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE[3] together with their rationale for any deviation from the final scope (Table 14). The differences between the decision problem addressed in the CS and the scope are discussed in the sections that follow.

Table 14. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with PD that is responsive to levodopa, with motor symptoms uncontrolled by standard therapy.	Adults with PD that is responsive to levodopa, with symptoms not adequately controlled by their current medical therapy (i.e. BMT) and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control.	The population addressed in the submission is narrower than the full anticipated license population as it reflects the population in which foslevodopa-foscarbidopa offers best value for money.	The proposed population for foslevodopa-foscarbidopa is similar to the population eligible for LCIG, according to NHS England commissioning criteria. However, the clinical evidence presented in the CS is for a broader population as it is not limited to those for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control. It is unclear how this may affect the generalisability of the trial results to the population the company has focused on.
Intervention	Foslevodopa-foscarbidopa	Foslevodopa-foscarbidopa	N/A – in line with the NICE final scope	N/A
Comparator(s)	•BMT for treating PD, including: o Levodopa plus the following adjunctive treatments: ▪ Dopamine agonist ▪ MAO-B inhibitors	•LCIG •BMT	Throughout all stages of PD, treatment choice is highly individualised and based on patient and clinician preference. As an advancement of continuous levodopa-carbidopa based therapies, it is anticipated that foslevodopa-foscarbidopa would be used in a patient population similar to LCIG rather than other advanced therapies, providing patients with	As the proposed positioning of foslevodopa-foscarbidopa is for patients for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control, the EAG agrees that DBS and apomorphine are not relevant comparators. Although the company has focused on a population which largely overlaps with

	▪ COMT inhibitors o Amantadine •Apomorphine, with or without standard oral medication •DBS •LCIG		greater convenience and improved 24-hour dosing. As patients progress to advanced PD, some advanced treatment options may be unsuitable for some patients, or there can be a need to discontinue an advanced therapy. Patients unsuitable for or discontinued from advanced therapies will remain on BMT, despite the insufficient control of their symptoms. Additionally, some patients may not have access to advanced therapies or may choose not to take them for individual reasons and remain on BMT; apomorphine is not available locally in every clinical commissioning group and DBS and LCIG are only available to patients at tertiary centres. Introduction of foslevodopa-foscarbidopa would increase the available treatment choices for patients and clinicians. LCIG and BMT therefore represent the two relevant comparators for this evaluation.	patients eligible for LCIG, in clinical practice only a small proportion may receive LCIG due to capacity issues and the majority of patients instead receive BMT. The EAG, therefore, agrees that LCIG and BMT are the key comparators to foslevodopa-foscarbidopa.
Outcomes	The outcome measures to be considered include: •ON/OFF time •dyskinesia •motor complications •cognitive functioning •mortality •adverse effects of treatment HRQoL	The outcome measures used in this submission include: •ON/OFF time •dyskinesia •motor complications •cognitive functioning •mortality •adverse effects of treatment	N/A – in line with the NICE final scope. All outcome measures included in the scope are either captured in the pivotal trials and/or the economic analysis	Most outcomes listed in the scope have been captured and presented in the CS. The exception being cognitive functioning. The EAG notes that the aim of foslevodopa-foscarbidopa treatment is to primarily relieve motor symptoms of PD and it is not expected to impact on non-motor symptoms such as cognitive functioning.

		HRQoL		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: •Subgroups based on the proportion of time spent in the OFF state •People for whom apomorphine is not suitable •People for whom DBS is not suitable	N/A – no subgroups were considered as part of the cost-effectiveness evidence presented in this submission	A scarcity of available evidence for comparisons based on the proportion of time spent in the OFF state meant that such a comparison would lack robustness and be associated with a high level of uncertainty. Based on the anticipated positioning of foslevodopa-foscarbidopa (i.e. for patients with advanced PD who are unsuitable for apomorphine and DBS), subgroups of patients for whom apomorphine or DBS are not suitable are no longer of relevance for this evaluation. These patients are covered within the main population given this anticipated positioning.	Although the company has specified the population of interest to be the subgroup of patients for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control, data were not available for this subgroup. The EAG agrees that the data for subgroups based on the proportion of time spent in the OFF' state are sparse but notes that the baseline distribution of patients and transition probabilities in the economic model are based on patients' daily hours of OFF time from the M15-736 trial.

Abbreviations: BMT, Best medical therapy; CS, company submission; COMT, catechol-o-methyl-transferase; CSR, clinical study report; DBS, Deep brain stimulation; EAG, External Assessment Group; HRQoL, Health-related quality of life; LCIG, Levodopa-carbidopa intestinal gel; MAO-B, Monoamine oxidase type B; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, Parkinson's disease

2.3.1 Population

Clinical effectiveness data in the CS are derived from the randomised controlled trial (RCT) M15-736, comparing foslevodopa-foscarbidopa treatment with oral carbidopa/levodopa (CD/LD), and from the single arm foslevodopa-foscarbidopa trial M15-741. In the economic model, however, although the treatment effectiveness of foslevodopa-foscarbidopa is based on data from M15-736, the relative effectiveness of foslevodopa-foscarbidopa compared with carbidopa/levodopa (CD/LD) is not used. Instead, treatment effectiveness of oral CD/LD was modelled based on natural history of PD, but informed by an external data source, Palmer et al. 2002.[1]

The patient population in the two key trials, M15-736 and M15-741, are in line with the population specified in the NICE final scope;[3] adults with PD that are responsive to levodopa and with motor symptoms uncontrolled by standard therapy. However, the company specifies a population in the decision problem that is narrower than that in the NICE final scope[3] and the populations in the M15-736 and M15-741 trials, restricting it to patients for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control. Overall, the EAG considers this narrower population in the decision problem to be reasonable given this represents a subset of patients covered in the anticipated marketing authorisation with a particularly high unmet need in terms of treatment options. The EAG's clinical experts suggest that foslevodopa-foscarbidopa may be useful as an alternative to apomorphine and DBS rather than as an option when these options are unsuitable or no longer providing adequate symptom control. However, the experts stated that the company's positioning of foslevodopa-foscarbidopa is reasonable given that patients who fail on apomorphine and/or DBS have limited treatment options. This population is eligible to receive LCIG, according to NHS England commissioning criteria; however, the majority of patients will receive best medical therapy (BMT) rather than LCIG due to capacity issues or not wanting surgery.

Some differences were noted between the trial populations and patients with advanced PD in UK clinical practice, such as men being slightly overrepresented in the trials and distribution of race likely differing in UK clinical practice. However, the experts advising the EAG stated that there is no evidence for differences in the prognosis of PD between ethnic groups or sex. Overall, the EAG's clinical experts considered that the populations in the two trials are broadly representative of those seen in UK clinical practice with PD.

In summary, the EAG's clinical experts consider the company's proposed positioning and target population for foslevodopa-foscarbidopa to be reasonable given it is a subgroup with a particularly high unmet need and that the data from the key trials are likely to be relevant for UK patients. However, the EAG has some concerns about the generalisability of the full trial population to the population the company specifies in the decision problem.

2.3.2 Intervention

The intervention covered in the CS is foslevodopa-foscarbidopa, which matches the NICE final scope.[3] The marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) for foslevodopa-foscarbidopa is anticipated in [redacted], under the trade name [redacted]. The expected marketing authorisation is for the [redacted] Foslevodopa-foscarbidopa is administered as a continuous subcutaneous infusion, 24 hours/day, with patients able to self-administer the product following appropriate training. The dose of foslevodopa-foscarbidopa depends on the patient's levodopa intake and can be adjusted to maximise the ON time and minimises the number and duration of OFF episodes and ON episodes with troublesome dyskinesia.

2.3.3 Comparators

The comparators specified in the NICE final scope[3] include best medical therapy (BMT), apomorphine, DBS and LCIG. As the company has focused on the population for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control, apomorphine and DBS are not considered relevant comparators to foslevodopa-foscarbidopa.

LCIG was granted a marketing authorisation by the EMA in 2005. It has not been appraised by NICE (in July 2022 the NICE Topic Selection Oversight Panel [TSOP] concluded it would not be appraised) but is used to a limited extent in the NHS. According to the clinical commissioning policy for LCIG produced by NHS England,[2] the criteria for commissioning of LCIG are patients that:

- have advanced levodopa-responsive PD with severe motor fluctuations, including significantly disabling OFF periods and/or dyskinesia that have not responded satisfactorily to available combinations of PD medications;
- have at least 50% OFF periods;

- should not be disabled by symptoms unlikely to respond to levodopa;
- have a disease course of at least 5-years;
- are contraindicated to further reasonable drug therapeutic options due to co-morbidities or late-PD disease complications;
- are unable to tolerate or unsuitable for apomorphine;
- are unsuitable for DBS, has refused to consent for DBS or DBS has failed.

The population eligible for LCIG in NHS England is largely the population the company focuses on for foslevodopa-foscarbidopa. However, the EAG highlights that the commissioning of LCIG is limited to patients who have at least 50% OFF periods; a restriction not expected for foslevodopa-foscarbidopa. That is, the company has put forward foslevodopa-foscarbidopa as an alternative to patients who would otherwise be considered for LCIG, but only a minority of patients of those eligible for LCIG actually receives it, and the main comparator within this population is BMT.

The EAG's clinical experts confirmed that BMT for the treatment of PD varies substantially and is based on patient's symptoms, experiences of various therapies, and specific treatment goals. As specified in the NICE final scope,[3] BMT may include levodopa plus adjunctive treatments such as dopamine agonists, MAO-B inhibitors, COMT inhibitors or amantadine. The comparator in the key clinical trial, M15-736, was oral CD/LD, which forms the main component ofBMT.

2.3.4 Outcomes

Most outcomes relevant to the NICE final scope[3] are provided in the CS for the M15-736 and M15-741 trials including ON and OFF time, dyskinesia, adverse events, mortality, and HRQoL. Motor complications were captured within OFF time and dyskinesia.

The aim of foslevodopa-foscarbidopa treatment is to relieve motor symptoms of PD and it is not expected to impact on non-motor symptoms such as cognitive functioning. The EAG therefore considers it reasonable that no outcome data have been presented for this outcome.

However, the EAG notes that outcome data on ON time without troublesome dyskinesia, which was the primary outcome of M15-736, did not inform the company's economic model, which focused on changes in OFF time. As described in the CS and in Section 2.2 of this report, dyskinesia can be a significant burden for patients with PD, affecting their quality of life, whereas ON time is an important measure of symptom control. Instead, the effect of foslevodopa-foscarbidopa was

captured as changes in OFF time in the economic model and dyskinesia was only captured when it qualified as an adverse event (AE) associated with a product complaint.

Issues around the treatment effectiveness and AE data informing the model are discussed in Sections 4.2.6 and 4.2.8.

2.3.5 Subgroups

The NICE final scope[3] specified subgroups to be considered based on the proportion of time spent in the OFF state, people for whom apomorphine is not suitable, and people for whom DBS is not suitable. Based on the company's positioning of foslevodopa-foscarbidopa (i.e. for patients with advanced PD who are unsuitable for apomorphine and DBS), the subgroup of patients for whom apomorphine and DBS are not suitable is the relevant patient population for this appraisal. The EAG requested baseline characteristics data for this subgroup at the clarification stage Prior continuous daily infusion apomorphine use was not captured in M15-736 as such patients were excluded. M15-736 excluded patients with prior DBS, whilst M15-741 allowed patients with prior DBS to participate in the trial. Therefore, the full trial populations were used to inform the clinical effectiveness. As mentioned previously (Section 2.3.1), this may have implications for the generalisability of the trial results to the population the company is focusing on.

Subgroup data based on the proportion of time spent in the OFF state were not presented in the clinical section of the CS due to scarcity of data, associated with a high level of uncertainty. In response to a clarification request the company provided the observed number of patients by time in the OFF state at different timepoints. These data, on patients' daily hours of OFF time from the M15-736 trial, informed the baseline distribution of patients and transition probabilities, at least for patients on foslevodopa-foscarbidopa, in the company's economic model. However, there are a substantial number of "OFF hour categories" where there were no patients at baseline. This is discussed in Section 4.2.4.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify all relevant literature reporting on efficacy, quality-of-life (QoL) and safety outcomes for advanced therapy in people with Parkinson's Disease (PD). The SLR was conducted in accordance with the requirements set out by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement 2020 and NICE requirements for reporting identification of clinical evidence.[4] The company presented the methods and results of the SLR in Appendix D of the company submission (CS), and the External Assessment Group's (EAG's) critique is presented in Table 15 below.

The inclusion criteria for the SLR were very broad and led to many studies being formally included but not utilised for the analysis in the submission. In total 190 publications were included in the review. The company presented separate inclusion criteria for the indirect treatment comparison (ITC) in Table 26 of the CS. Based on these seven studies (out of the 190 publications) met the inclusion criteria and were considered for inclusion in the ITC.

In addition to the trials included in the ITC, data from three single arm studies, two of which were ongoing, were utilised in the analysis.

Table 15. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the advanced therapies for Parkinson's disease

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1	**The EAG considers the sources and dates searched to be comprehensive.** Databases searched: ● Embase; MEDLINE; Cochrane Central Register of Controlled Trials, Cochrane Database for Systematic Reviews Registries: Conference proceedings: ● American Academy of Neurology (AAN) ● European Academy of Neurology (EAN) ● International Congress of Parkinson's Disease and Movement Disorders (MDS) The original database search was conducted in June 2021, which were updated in January 2022 and then again in June 2022. Conferences were searched between 2019 and 2022.

Search strategies	Appendix D.1.1	**The EAG is satisfied that the company's searches have identified all evidence relevant to the decision problem.** The search strategies for the literature review used free-text keywords, medical subject headings (MeSH) and EMTREE terms for the population and interventions of interest, along with study design filters The search terms for trials and observational studies were based on the filters provided by the Scottish Intercollegiate Guidelines Network (SIGN).
Inclusion criteria	Appendix D.1.2. (Table 5)	**The EAG considers it unlikely that relevant evidence was excluded based on the eligibility criteria used.** The eligibility criteria included the target population, intervention, comparators, outcomes defined by NICE in the final scope. However, the inclusion criteria were very broad and included both study designs and interventions that are irrelevant to the question.
Screening	Appendix D.1.2	**The EAG considers the reporting of methods for screening to be adequate.** Records were dual screened at both the abstract and full text review stage.
Data extraction	Appendix D.1.2	The EAG considers the methods of data extraction to be adequate. Data extraction was conducted on the seven studies included in the ITC and on the 3 single-arm studies included in the analysis. Data extraction was conducted by one researcher extracted the data and a second researcher independently reviewed its accuracy.
Tool for quality assessment of included study or studies	Appendix D.1.3 and CS B.2.3.3 for M15-736 and B.2.4.3 for M15-741	**The EAG agrees with the company's choice of quality assessment tool of RCTs.** The quality assessment for comparative clinical trials in the ITC, including M15-736, was conducted using the Revised Cochrane risk of bias tool for randomised trials.[5] The quality assessment for the single arm extension study, M15-741, utilised the Institute of Health Economics Quality Appraisal Checklist for Case Series Studies. The quality assessment for the M15-736 and M15-741 were presented as yes/no answers without explanatory text. The EAG's assessments of the included studies are presented in Section 3.2 below.

Abbreviations: CS, company submission; EAG, external assessment group; ITC, indirect treatment comparison

3.2 Critique of trials of the technology of interest

One RCT (M15-736) and one single arm (M15-741) study were included in the assessment of the efficacy and safety of foslevodopa-foscarbidopa as a treatment for advanced PD in the CS. However, the EAG highlights that in the economic model, data from M15-736 only informs the efficacy of foslevodopa-foscarbidopa. The relative efficacy of foslevodopa-foscarbidopa versus the comparator in the trial (oral CD/LD) did not inform the model. In addition, in the model, foslevodopa-foscarbidopa discontinuation data were based on data from three different sources: M15-736, M15-741, and the M15-741 open-label extension study, M15-737. Health-related quality of life (HRQoL)

data for foslevodopa-foscarbidopa were based on the same three studies as well as the M15-736 extension study, M20-098. All four studies are, therefore, described briefly in the following section followed by a summary and quality assessment of the M15-736 and M15-741 trials (Table 16), and a critique of the internal validity and a summary of the external validity of these two trials.

M15-736 is a Phase III, randomised, double-blind, double-dummy, parallel group, multicentre study comparing the efficacy, safety and tolerability of foslevodopa-foscarbidopa to oral carbidopa/levodopa (CD/LD) in patients with advanced PD. The trial consisted of a screening period (6 to 60 days), an open-label oral CD/LD stabilisation period (14 to 21 days) during which all levodopa-containing medications were converted to an equivalent amount of CD/LD IR and optimised to achieve the best possible control of each patient's motor symptoms, and a 12-week double-blind treatment period. The dosing of oral CD/LD attained during the stabilisation period was converted to a levodopa equivalent dose (LED) of foslevodopa-foscarbidopa for those patients in the intervention arm during the double-blind treatment period.

The primary objective of M15-741, a Phase III open-label, single-arm study, was to assess the safety and tolerability of foslevodopa-foscarbidopa. The 52-week study period consisted of a 4-week optimisation period, followed by a 48-week maintenance period. Similar to M15-736, during the optimisation period of M15-741, patients' foslevodopa-foscarbidopa dose was adjusted to achieve optimal symptom control, as determined by study investigator. Patients were then continued on this optimal dose during the maintenance period.

M20-098 is an open-label extension study of M15-736 and M20-339. M20-339 is a randomised, open-label comparative study of levodopa and carbidopa bioavailability when foslevodopa-foscarbidopa is administered at different subcutaneous sites in patients with PD. Patients who completed the randomised treatment period in either M15-736 (12 weeks) or M20-339 (12 days) could enter M20-098 for up to 96 weeks of foslevodopa-foscarbidopa treatment. In response to a clarification request the company confirmed that a total of 103 patients who completed M15-736 have been enrolled in M20-098. However, HRQoL data at baseline and at three months of follow-up only seems to be available for [redacted] patients. It is unclear how many patients entered M20-098 from M20-339. Of note is also that patients from M15-736 would have had 12 weeks of foslevodopa-foscarbidopa treatment before entering the follow-up study, whereas patients from M20-339 would only have had 12 days of foslevodopa-foscarbidopa treatment. As mentioned above, HRQoL data from M20-098 was used together with HRQoL data from three other foslevodopa-foscarbidopa

studies to inform the economic model. The last Primary Study Visit for M20-098 is currently projected for [redacted].

Upon completion of the 52-week treatment period in M15-741 patients could enter a separate ongoing extension study, M15-737, for 96 weeks of additional foslevodopa-foscarbidopa treatment. M15-737 is an open-label extension study, evaluating the long-term safety, tolerability, and efficacy of foslevodopa-foscarbidopa in patients with advanced PD. As mentioned above, M15-737 informed both HRQoL and foslevodopa-foscarbidopa discontinuation rates in the economic model. Approximately 130 patients who completed M15-741 are expected to enrol in this study. The last Primary Study Visit for study M15-737 is projected for [redacted] However, the baseline HRQoL data is based on [redacted] patients, and 24-month follow-up data on [redacted] patients.

The company's quality assessment of M15-736 and M15-741 are provided in Table 8 and Table 21 of the CS, respectively. The EAG agrees with the company's assessments of M15-736, which was assessed as of good quality and generally of low risk of bias. Although the company acknowledges that there was an unexpected imbalance in the number of discontinuations between the treatment and control arm of the trial. The EAG considers that the open label, single arm M15-741, will suffer from the same high risks of bias as other single arm, prospective studies. The EAG expects the risk of bias associated with M20-098 and M15-737 to be similar to that of M15-741 as they are all single arm, open label, prospective studies.

Table 16. A summary and critique of the design, conduct and analysis of M15-736 and M15-741

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique of M15-736	EAG's critique of M15-741
Randomisation	B.2.3.1.1	**Appropriate** Interactive Response Technology (IRT) system utilised for randomisation	**NA** **Single arm trial**
Concealment of treatment allocation	B.2.3.1.1	**Appropriate** Concealment via the IRT. This system manages the assignment of a person to a treatment arm.	**NA** **Single arm trial**
Eligibility criteria	B.2.3.1.1 and B.2.4.1.1	**Appropriate, but not completely aligned with the company's proposed positioning of foslevodopa-foscarbidopa** The population in the trials is appropriate for the use of advanced PD treatment. The validity of the population in light of the company's positioning of foslevodopa-foscarbidopa in the treatment pathway is discussed in Section 2.3	
Blinding	B.2.3.1.1	**Some concerns** The participants, people delivering the interventions, and outcome assessors were blinded to treatment throughout the study. However, the EAG has concerns linked to unintentional unblinding due to the treatment effect of foslevodopa-foscarbidopa. This is discussed on Section 3.2.2	**NA** **Single arm trial**
Baseline characteristics	B.2.3.1.2 and B.2.4.1.2	**Well-balanced between groups** Baseline characteristics for the full analysis set (FAS) population were well-balanced between foslevodopa-foscarbidopa and oral carbidopa/levodopa (CD/LD) groups.	A comparison of the patients enrolled in M15-736 and M15-741 is provided in Section 3.2.1.
Dropouts	B.2.8.1.1 and B.2.8.2.1	**Not balanced between groups** There was a disparity between treatment groups in dropouts, [redacted] patients in the foslevodopa-foscarbidopa arm discontinued the study drug compared to [redacted] in the oral CD/LD arm. This is discussed on Section 3.2.2	**Unexpectedly high** This is discussed on Section 3.2.2
Statistical analysis			

Sample size and power	B.2.3.2 and B.2.4.2	**Appropriate** Sample size calculations were undertaken to provide 90% power to detect a statistically significant difference for normalised ON time without troublesome dyskinesia. Underlying this calculation was an assumption of a difference in change from Baseline to Week 12 of 1.86 hours per day and a common standard deviation of 2.9. The estimated required sample size was 52 patients per treatment arm. An estimate of 20% discontinuation rate was utilised.	**Appropriate** Approximately 240 patients were planned to be enrolled in order to obtain exposure data from at least 100 patients treated with foslevodopa-foscarbidopa for at least 12 months. With 240 patients receiving foslevodopa-foscarbidopa, the probability of observing an AE with an annual incidence rate of 0.005, 0.01, and 0.02 was 70%, 91%, and 99%, respectively.
Handling of missing data	B.2.3.2 and B.2.4.2	**Some concerns** The primary analysis for key efficacy outcomes was based on the mixed model repeated measures (MMRM) method and no imputation was utilised for missing data. Two sensitivity analyses were undertaken: • Analysis of covariance (ANCOVA) • Jump-to-reference (J2R) analytical approach. The merits of the different analyses are discussed in Section 3.2.4	**Some concerns** If no valid PD diary day was available for a visit, the average daily normalised OFF or ON times were imputed as missing for that visit. Management of missing data discussed in Section 3.2.4
Outcome assessment	B.2.3.1.1 and B.2.4.1.1	**Some concerns** The primary outcome was patient PD diary. The EAG's clinical experts indicated that daily PD diary is the standard method of assessment in PD trials. A patient's assessment of whether they are experiencing OFF or ON time and whether their dyskinesia is troublesome or not, may be subjective but is improved by training in diary use. This is discussed in Section 3.2.5.	

Abbreviations: ANCOVA, analysis of covariance; CD/LD, carbidopa/levodopa; EAG, external assessment group; IRT, Interactive response technology; J2R, Jump-to-reference; MMRM, Mixed model for repeated measured; NA, not applicable; PD, Parkinson's disease

3.2.1 Trial populations

The company states that the baseline characteristics were generally well-matched across M15-736 and M15-741. The majority of patients in both studies were male, and the mean age of patients were [redacted] and [redacted] years in M15-736 and M15-741, respectively. The mean duration since PD diagnosis was lower in M15-736 than in M15-741 ([redacted] versus [redacted] years, respectively). The baseline normalised OFF time was relatively well matched between the two populations, with patients experiencing a mean of [redacted] hours in M15-736 and [redacted] hours in M15-741. However, HRQoL at baseline differed more between the two studies; baseline EQ-5D-5L summary index was [redacted] and [redacted] in the foslevodopa-foscarbidopa and oral CD/LD arms of M15-736, respectively, and in M15-741 the baseline EQ-5D-5L was [redacted]. This suggests that patients' QoL was considerably [redacted] in M15-736 than in M15-741 at baseline.

Patients who received prior DBS were excluded from the M15-736 trial. However, patients recruited into M15-741 were eligible to receive foslevodopa-foscarbidopa after DBS; of the 244 patients in the M15-741 safety analysis set, [redacted] received a DBS procedure. It is unclear if prior apomorphine therapy was allowed in M15-736, although patients could receive intermittent apomorphine injections as rescue medication during the screening period ([redacted]). Patients who received previous continuous subcutaneous infusion (CSCI) of apomorphine were eligible for recruitment into M15-741, although they must have discontinued within 30 days of commencing foslevodopa-foscarbidopa. A total of [redacted] patients out of 244 in the safety analysis set [redacted], received prior CSCI apomorphine.

The company considers the trial populations to be generalisable to the narrower population the company has focused on, of patients for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control.

The clinical experts advising the EAG consider both trial populations to be broadly generalisable to patients with PD eligible for advanced therapy in UK clinical practice. The proportion of men was higher in both trials than would be expected in the UK PD population which has a more even split between the sexes. However, men may have a more rapid disease progression and the high proportion of males as well as the mean age in the studies are likely to be representative of a population that may be considered for advanced therapy in current practice.

3.2.2 Blinding

In M15-736, patients and outcome assessors were blinded to treatment allocation throughout the trial. CD/LD immediate release (IR) tablets were over-encapsulated and identical in appearance to the placebo capsules, and these were packaged identically. The foslevodopa-foscarbidopa solution and the placebo solution for infusion were also packaged identically. That is, appropriate measures were taken during the trial to ensure blinding of study participants and investigators throughout the entire trial period.

The EAG generally considers double-blind studies to be at a significantly reduced risk of bias, which is especially important when assessing subjective outcomes such as PD diary. However, the EAG has concerns linked to unintentional unblinding of patients in M15-736 primarily due to the treatment effect but potentially also due to the safety profile of foslevodopa-foscarbidopa.

Foslevodopa-foscarbidopa is administered as a continuous subcutaneous infusion, 24 hours/day whereas oral CD/LD was taken during the daily waking hours. As could be expected, this led to a substantial difference between the treatment arms in morning akinesia (Section 3.3.1.4). Foslevodopa-foscarbidopa treatment was also associated with substantially higher rates of AEs, especially AEs related to infusion site reactions or infections (Section 3.3.3.2). It is, therefore, highly likely that a large proportion of patients in the trial will have correctly deduced which treatment they had been randomised to while on treatment.

The primary outcome for M15-736 is ON time without troublesome dyskinesia and the efficacy outcome utilised in the cost-effectiveness model is OFF time; both are patient reported outcomes assessed by a patient's PD diary. The EAG is concerned a patient's subjective assessment of their ON and OFF time may be affected by the patient's knowledge or educated guess of which treatment they are on. Although the magnitude of this bias is unknown it is likely that patients on foslevodopa-foscarbidopa may overestimate the efficacy of their treatment and that patients on BMT may underestimate the efficacy of treatment. It is also possible that having less morning OFF time would make later OFF times more subjectively noticeable, as OFF time is usually identified by comparison with pre-morning dose OFF time. As that state is reduced, the subjective threshold for identifying and recording the OFF state may reduce also.

3.2.3 Discontinuations

During M15-741, a higher than anticipated number of premature discontinuations was noted, which was attributed to difficulties using the drug delivery system and to infusion site skin AEs. Changes were made to the trial methodology including an update to the study protocol: study sites and patients underwent retraining, with a specific focus on the correct use and application of the infusion set cannula, and the infusion set was changed from Cleo 90™ to Neria™ guard. The Neria™ guard is the only intended commercial infusion set for delivery of foslevodopa-foscarbidopa, and it was the infusion set used in M15-736. Fewer patients enrolled after the protocol change (cohort 2) which specified the use of the Neria™ guard, discontinued treatment due to adverse events compared with patients enrolled prior to the change (cohort 1).

In M15-736 there was a disparity between treatment groups in treatment discontinuations; [redacted] patients in the foslevodopa-foscarbidopa arm discontinued the study drug compared to [redacted] in the oral CD/LD arm. The majority of discontinuations were linked to the infusion, whether it was AEs such as infusion site related infections and non-infection reactions, or "difficulty with the drug delivery system."

3.2.4 Handling missing data

In M15-736, the primary analysis of key efficacy outcomes, ON time without troublesome dyskinesia and OFF time, was based on the mixed model for repeated measurement (MMRM) method. The MMRM approach is to use all available data, including subjects with partial data, in order to arrive at an estimate of the mean treatment effect. It follows the "missing at random" (MAR) assumption and assumes there are no systematic differences between the missing and observed outcomes.

Two sensitivity analyses were undertaken for the ON and OFF time outcomes: an analysis of covariance (ANCOVA) and a jump-to-reference (J2R) analytical approach. The ANCOVA analysis utilised the last available value to impute the missing Week 12 data, i.e. last observation carried forward (LOCF). This method depends on the assumption that the missing value, in this case the efficacy at Week 12 for someone who has discontinued foslevodopa-foscarbidopa treatment, is identical to the last observed value on treatment.

The J2R sensitivity analysis assumes MAR for the oral CD/LD arm and missing not at random (MNAR) for the foslevodopa-foscarbidopa arm. It is expected that people who drop-out of the foslevodopa-foscarbidopa arm would jump to that of the oral CD/LD arm immediately after discontinuation.

Under this assumption, after a person stops taking treatment from the intervention arm, their mean response distribution is then considered to be the same as of the control group.

The vast majority of missing data at the end of the 12-week treatment period in M15-736 were missing due to treatment discontinuation (Table 17). The EAG notes that patients who discontinue foslevodopa-foscarbidopa treatment cannot reasonably be assumed to be missing at random but can be expected to have an efficacy similar to the control arm. The EAG, therefore, considers the J2R analysis to provide the most appropriate estimate of the efficacy of foslevodopa-foscarbidopa treatment in the full trial population, as patients who discontinue foslevodopa-foscarbidopa are unlikely to retain the benefit of treatment but likely to go on to be treated with BMT, with an efficacy similar to the oral CD/LD arm. However, missing data were captured appropriately in the primary analysis (MMRM) to inform the outcomes of patients on treatment in the economic model.

Table 17. Summary of Patients Not Included in the Analysis of Parkinson's Disease Diary by Visit in the M15-736 Trial (FAS) (clarification response A12, Table 5)

	Treatment	N	Patients Not Included Due To…		
			Treatment Discontinuation	No Valid PD Diary Day	Any Other Reason
Baseline	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]
Day 29	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]
Day 57	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]
Day 85	FosL-FosC	[redacted]	[redacted]	[redacted]	[redacted]
	Oral CD/LD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CD/ LD: Carbidopa/ Levodopa; FAS: Full Analysis Set; FosL-FosC: Foslevidopa-Foscarbidopa; PD: Parkinson's Disease.

Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

In M15-741, the method used for handling missing data for outcomes linked to a patient's PD diary (ON time without troublesome dyskinesia and OFF time), was to impute the data for that visit. No

further details were provided in the CS, but the EAG assumes that this means that the LOCF was used for the imputation.

3.2.5 Outcome assessment

The primary outcome, ON time without troublesome dyskinesia, and the OFF time efficacy outcome used in the cost-effectiveness model, were assessed via a patient's PD diary. People were required to provide "valid" diary day entries for use in the analysis and this was defined as one that does not have more than 2 hours of missing data (4 or less missing 30-minute entries) for the entire 24-hours. Each valid PD diary day was normalised to a 16-hour waking day and averaged over three consecutive diary days to obtain the average daily normalised ON time without troublesome dyskinesia and average daily normalised OFF time. The EAG's clinical experts indicated that daily diaries are not often utilised in clinical practice but are the standard method of assessment in PD trials. A person's assessment of whether they are experiencing OFF or ON time and whether their dyskinesia during ON time is troublesome is subjective, but consistency can be improved by explanation and training. Also, whether a person finds their dyskinesia troublesome may be informed by their personal circumstances, lifestyle, and their PD symptom history. There are limited objective methods of assigning ON and OFF time. Parkinson's KinetiGraph (PKG™) is a small motion-tracking device worn on the wrist that can assess slowness of movement (bradykinesia), tremor and abnormal involuntary movements (dyskinesia). This device was used for this purpose in M15-736 but there are limitations to what it can assess, for example, it cannot decide whether dyskinesia is "troublesome".

3.2.6 Summary of critique of foslevodopa-foscarbidopa trials

In summary, the EAG considers M15-736 to be an RCT of good quality, and the best available evidence of the relative clinical effectiveness of foslevodopa-foscarbidopa compared with oral CD/LD. However, there is a potential risk of bias associated with the trial results as the majority of patients are likely to be aware of which treatment they were randomised to and the key outcomes of ON time without troublesome dyskinesia and OFF time, are both subjective outcomes based on patient reported PD diaries. Depending on the method used for handling missing data, the trial results are likely overestimating the efficacy of foslevodopa-foscarbidopa in the primary analysis, but the results for the full trial population are likely to be more appropriate with the J2R approach.

M15-741 provides longer follow up than M15-736, but no comparative data and treatment discontinuations were high and not accounted for appropriately in the analysis meaning the efficacy of foslevodopa-foscarbidopa is likely overestimated.

The EAG's clinical experts consider both trial populations to be broadly generalisable to UK patients but note that M15-741 is somewhat more generalisable, with slightly lower levodopa-equivalent dose at baseline, lower QoL, a more representative male to female ratio, and a longer mean duration since diagnosis.

3.3 Critique of the company's analysis and interpretation

3.3.1 M15-736

3.3.1.1 Primary outcome - ON time without troublesome dyskinesia

Treatment with foslevodopa-foscarbidopa resulted in a clinically meaningful and statistically significant increase in ON time without troublesome dyskinesia from baseline when compared with oral CD/LD (LS mean 1.75, SD 0.65, p-value 0.0083). At the end of the trial (12 weeks), patients in the foslevodopa-foscarbidopa arm experienced a LS mean improvement from baseline of 2.72 hours on the average ON time without troublesome dyskinesia compared with 0.97 hours for patients in the oral CD/LD group (Table 18).

Improvements in ON time without troublesome dyskinesia were observed in both trial arms at the first visit at Day 8, reaching a plateau around one month which persisted until the end of the 12-week trial period (

Figure 1).

The results of the two sensitivity analyses, which the company conducted to account for missing data are broadly consistent with the results of the primary analysis, although the difference in ON time without troublesome dyskinesia between foslevodopa-foscarbidopa an oral CD/LD was [redacted] than in the primary analysis (Table 18). The ANCOVA analysis, imputing missing values based on the LOCF, resulted in an increase in from baseline in ON time without troublesome dyskinesia of [redacted] hours (p-value [redacted]) for foslevodopa-foscarbidopa compared with oral CD/LD. With the jump-to-reference (J2R) analysis, which is the EAG's preferred analysis that assumes patients in the foslevodopa-foscarbidopa arm with missing data had similar outcomes to those in the comparator arm, treatment with foslevodopa-foscarbidopa resulted in a [redacted] increase in ON time without troublesome dyskinesia from baseline when compared with oral CD/LD of [redacted] hours (p-value [redacted]).

Table 18. Change from baseline to Week 12 in hours of average daily normalised ON time without troublesome dyskinesia (FAS) (adapted from CS Table 9 and Appendix M.4.1. Tables 42 and 43)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	73	67
Mean, hours (SD)	[redacted]	[redacted]
Week 12		
Primary analysis - MMRM		
N	[redacted]	[redacted]
Mean change, hours (SD)	[redacted]	[redacted]
LS mean change, hours (SD)	2.72 (0.52)	0.97 (0.50)
LS mean difference, hours (SD)	1.75 (0.65)	
p-value	0.0083	
Sensitivity analysis - ANCOVA		
N	[redacted]	[redacted]
Mean change, hours (SD)	[redacted]	[redacted]
LS mean change, hours (SD)	[redacted]	[redacted]
LS mean difference, hours (SD)	[redacted]	
p-value	[redacted]	
Sensitivity analysis – J2R		
LS mean difference, hours (SD)	[redacted]	

p-value	[redacted]

ON time without troublesome dyskinesia is the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia.

This endpoint was analysed with an MMRM.

Abbreviations: CD/LD: carbidopa/levodopa**;** FAS: Full Analysis Set; J2R: jump to reference; LS: least square; MMRM: mixed-effect model for repeat measures; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

Figure 1. Plot of mean change over time (from baseline to Week 12) of average daily normalised ON time without troublesome dyskinesia (FAS) (reproduced from CS Figure 4)

These data were analysed with an MMRM.

Day 22 was an optional visit at the investigator's discretion and based on the patient's PD symptoms.

Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; MMRM: mixed-effect model for repeat measures; PD: Parkinson's disease.

Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

3.3.1.2 Key secondary outcome - OFF time

Treatment with foslevodopa-foscarbidopa resulted in a statistically significant and clinically meaningful reduction in OFF time from baseline when compared with oral CD/LD (LS mean −1.79, SD 0.63, p-value 0.0054).[7] At the end of the trial (12 weeks), patients in the foslevodopa-foscarbidopa arm experienced a LS mean reduction from baseline of 2.75 hours in OFF time compared with a reduction of 0.96 hours for patients in the oral CD/LD arm (Table 19).

Reductions in OFF time were observed in both trial arms at the first visit at Day 8, with a maximum reduction after ********** of treatment in the foslevodopa-foscarbidopa arm and ********** in the oral CD/LD arm (

Figure 2).

As for ON time without troublesome dyskinesia, the EAG's preferred analysis is the J2R sensitivity analysis assuming patients with missing data in the foslevodopa-foscarbidopa arm had similar outcomes to those in the comparator arm. This analysis shows that treatment with foslevodopa-foscarbidopa result in a [redacted] reduction in OFF time from baseline when compared with oral CD/LD of [redacted] hours (p-value [redacted]).

Table 19. Change from baseline to Week 12 in hours of average daily normalised OFF time (FAS) (adapted from CS Table 10 and Appendix M.4.2. Tables 44 and 45)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	73	67
Mean, hours (SD)	[redacted]	[redacted]
Week 12		
Primary analysis - MMRM		
N	[redacted]	[redacted]
Mean change, hours (SD)	[redacted]	[redacted]
LS mean change, hours (SD)	−2.75 (0.50)	−0.96 (0.49)
LS mean difference, hours (SD)	−1.79 (0.63)	
p-value	0.0054	
Sensitivity analysis - ANCOVA		
N	[redacted]	[redacted]
Mean change, hours (SD)	[redacted]	[redacted]
LS mean change, hours (SD)	[redacted]	[redacted]
LS mean difference, hours (SD)	[redacted]	
p-value	[redacted]	
Sensitivity analysis – J2R		
LS mean difference, hours (SD)	[redacted]	
p-value	[redacted]	

This outcome was analysed with an MMRM.

Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; MMRM: mixed-effect model for repeat measures; PD: Parkinson's disease SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

Figure 2. Plot of mean change over time (from Baseline to Week 12) of average daily normalised OFF time as assessed by the PD diary (FAS) (reproduced from CS Figure 5)

These data were analysed with an MMRM.

Day 22 was an optional visit at the investigator's discretion and based on the patient's PD symptoms.

Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; MMRM: mixed-effect model for repeat measures; PD: Parkinson's disease.

Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

None of the aggregate data analyses presented above were used to inform changes in OFF time in the economic model. Instead, OFF time data in the model are based on individual patient data (IPD) for the foslevodopa-foscarbidopa arm of M15-736 on daily OFF hours at baseline and on the change in OFF hours from baseline to Week 12. However, data for the oral CD/LD arm of M15-736 were not used in the model. As the population modelled are patients who are inadequately controlled by standard therapy, treatment effectiveness of oral CD/LD was modelled based on natural history of PD, informed by an external data source.

The EAG notes that in clinical practice it would be unexpected to see a decrease in OFF time in patient receiving oral CD/LD (as is the case in the trial) whose PD is not well controlled on oral CD/LD. However, the EAG considers any trial-based factors (e.g. enhanced care compared to clinical practice) leading to a decrease in OFF time with CD/LD would similarly affect the foslevodopa-foscarbidopa arm. The EAG, therefore, stresses the inappropriateness of using two disconnected data sources for the efficacy of foslevodopa-foscarbidopa and BMT, especially when data from a direct comparison in a good quality RCT is available.

3.3.1.3 *Health-related quality of life*

In M15-736 the change in EQ-5D-5L summary index scores show a greater improvement in the foslevodopa-foscarbidopa arm compared with the oral CD/LD arm (Table 20), [redacted].

PDQ-39 summary index data, which assesses the impact of PD on daily living, functioning and wellbeing, similarly show HRQoL benefits with foslevodopa-foscarbidopa over oral CD/LD (CS Section B.2.3.4.3).

However, the EAG highlights that in the economic model the EQ-5D-5L data are based on data combined from M15-736, M15-098, M15-741, and M15-737, despite the clear difference in QoL at baseline between these studies. This is discussed in detail in Section 4.2.10.

Table 20. Change from baseline to final visit in EQ-5D-5L summary index (FAS) (reproduced from CS Table 16)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

This outcome was analysed with an ANCOVA model; the sample is balanced across baseline and Week 12.

Abbreviations: ANCOVA: analysis of covariance; CD/LD: carbidopa/levodopa; EQ-5D-5L: EuroQol 5-Dimensions 5-Levels Questionnaire; FAS: Full Analysis Set; LS: least square; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

3.3.1.4 *Additional outcomes not captured in the economic model*

3.3.1.4.1 Movement Disorders Society-Unified PD Rating Scale (MDS-UPDRS) Part II score

The MDS-UPDRS Part II score, which was a key secondary outcome of the trial, specifically measures the impact of motor symptoms on patients' daily living. The score goes from 0-2 points, no disability; 3-16, mild; 17-31, moderate; and 32 points or more, severe, which a decreased score signifying an

improvement in motor symptoms.[8] The MDS-UPDRS Part II score could potentially be considered a useful "surrogate" measure of disease severity which is more commonly captured through the Hoehn and Yahr scale.

Reductions in motor symptoms were observed in the MDS-UPDRS Part II score for both treatment arms but only in the foslevodopa-foscarbidopa arm was the reduction likely to be clinically significant.[7] However, the difference in MDS-UPDRS Part II score for foslevodopa-foscarbidopa compared with the oral CD/LD arm [redacted] (Table 21).

Table 21. Change from Baseline to Week 12 in MDS-UPDRS Part II Score (FAS) (reproduced from CS Table 11)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; PD: Parkinson's disease SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

3.3.1.4.2 Morning akinesia – early morning OFF status

PD is often associated with early morning OFF time, or akinesia. The continuous administration of foslevodopa-foscarbidopa has the potential to reduce morning akinesia compared with oral treatments associated with delayed ON time in the morning.

There was a [redacted] reduction the number of patients who experienced morning akinesia in the foslevodopa-foscarbidopa arm compared with the oral CD/LD arm from baseline to Week 12 (Table 22).

Table 22. Presence of morning akinesia at Week 12 (FAS) (reproduced from CS Table 12)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
LS mean of OR (SE)	[redacted]	
p-value	[redacted]	

Although the nominal p-value is ≤0.05, statistical significance cannot be claimed because the second key secondary efficacy endpoint was not met.

Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; OR: odds ratio; PD: Parkinson's disease SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

3.3.1.4.3 Dyskinesia and bradykinesia measured by the Parkinson's KinetiGraph™/Personal KinetiGraph™

The Parkinson's KinetiGraph™/Personal KinetiGraph™ (PKG) is a device worn by patients on the wrist which provides continuous data on motor fluctuations and tremor during routine daily activity. These data can then be translated to a dyskinesia or a bradykinesia score, with reduced scores indicating reduced dyskinesia or bradykinesia.[9] Bradykinesia means slowness of movement, the opposite of dyskinesia and the motor problem associated with PD and OFF time.

Table 23 shows the change in median dyskinesia score (DK50), and Table 24 shows the change in median bradykinesia score (BK50), as measured by the PKG from baseline to Week 12. The results for bradykinesia were not presented in the CS but were provided by the company in response to a clarification request.

The results show a numerical, [redacted], reduction in DK50 scores in the foslevodopa-foscarbidopa arm compared with the oral CD/LD arm, indicating better control of dyskinesia with foslevodopa-foscarbidopa.

For bradykinesia, the results show a numerical, [redacted], increase in BK50 scores in the foslevodopa-foscarbidopa arm compared with the oral CD/LD arm. The company

states that it is likely a result of the analysis being conducted at a group level rather than stratifying patients according to their baseline bradykinesia and dyskinesia scores. The EAG notes that the difference in baseline bradykinesia score was small.

Table 23. Change from baseline to Week 12 in median dyskinesia score (DK50) as assessed by the PKG wearable device (FAS) (reproduced from CS Table 14)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

This outcome was analysed with an MMRM.

Abbreviations: CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; MMRM: mixed-effect model for repeat measures; PKG: personal kinetograph; SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

Table 24. Change from Baseline to Week 12 in median bradykinesia (BK50) as assessed by the PKG wearable device (FAS) (adapted from clarification response A16, Table 11)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

Abbreviations: CD/LD: carbidopa/levodopa; FAS: full analysis set; LS: least squares; PKG: Parkinson's KinetiGraph; SD: standard deviation; SE: standard error

Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

3.3.1.4.4 Sleep symptoms - PDSS-2

PD is often associated with severe sleep disorders[10] and the continuous administration of foslevodopa-foscarbidopa has the potential to improves patients' quality of sleep.

In M15-736 changes in patient's sleep symptoms were measured by the PDSS-2 score, a validated tool for measuring sleep disorders in PD.[11] Patients in the foslevodopa-foscarbidopa arm reported a [redacted] reduction in PDSS-2 scores (indicating fewer symptoms during sleep) from baseline to Week 12 compared with patients receiving oral CD/LD (Table 25).

Table 25. Change from baseline to Week 12 in sleep symptoms as assessed by the PDSS-2 total score (FAS) (reproduced from CS Table 13)

Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Baseline		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 12		
N	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
LS mean change (SD)	[redacted]	[redacted]
LS mean difference (SD)	[redacted]	
p-value	[redacted]	

This outcome was analysed with an ANCOVA model; the sample is balanced across baseline and Week 12.

Although the nominal p-value is ≤0.05, statistical significance cannot be claimed because the second key secondary efficacy endpoint was not met

Abbreviations: ANCOVA: analysis of covariance; CD/LD: carbidopa/levodopa; FAS: Full Analysis Set; LS: least square; PD: Parkinson's disease SD: standard deviation.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

3.3.2 M15-741

This section focuses on the efficacy data from M15-741 that informs or could inform the treatment effectiveness of foslevodopa-foscarbidopa in the economic model. That is, OFF time and ON time without troublesome dyskinesia, and HRQoL captured as EQ-5D. Safety data and data on treatment discontinuations in M15-741 and the other foslevodopa-foscarbidopa trials are presented and discussed in Section 3.3.3. Results for other outcomes from M15-741, such as motor symptoms and early morning non-sleep symptoms as assessed by PDSS-2, HRQoL assessed by PDQ-39 summary

index, and PD symptoms assessed by MDS-UPDRS Part I–III, are presented in the CS Sections B.2.4.4.2 – B.2.4.4.4.

3.3.2.1 ON time without troublesome dyskinesia and OFF time

Treatment with foslevodopa-foscarbidopa resulted in a [redacted] reduction in OFF time and a [redacted] improvement in ON time without troublesome dyskinesia, from baseline to all time points measured, up to 12 months. At the end of the study period (Week 52), the mean ON time without troublesome dyskinesia increased [redacted] hours and the decrease in OFF time was [redacted] hours (Table 26). Improvements were observed in both outcomes from the first assessment at Week 1, increased throughout to Week 26, and then remained stable to the end of the treatment period at Week 52 (Figure 3).

The mean change from baseline to Week 13 was an increase of [redacted] and a decrease of [redacted] hours in ON time without troublesome dyskinesia and OFF time, respectively. The equivalent data from M15-736 at Week 12 was an increase of [redacted] and a decrease of [redacted] hours in ON time without troublesome dyskinesia and OFF time, respectively. That is, the results of M15-741 support those seen in M15-736; however, the improvement from baseline in ON time without troublesome dyskinesia and OFF time in M15-741 at 12 months are more similar than the 12-week data to the results at Week 12 in M15-736. The differences in results highlight the likely effect of the differences in the populations, design and setting between the trials. As discussed earlier, the EAG considers M15-736 to be a well conducted RCT, which provides the best available evidence of the relative clinical effectiveness of foslevodopa-foscarbidopa compared with oral CD/LD. However, the EAG's clinical experts consider the trial population of M15-741 to be the most generalisable to PD patients eligible for advanced therapy in UK clinical practice, and thus the best available evidence of the absolute clinical efficacy of foslevodopa-foscarbidopa in a more generalisable population.

Table 26. Average daily normalised ON time without troublesome dyskinesia (adapted from the CS, Table 22 and Table 23)

Characteristic	Baseline	Week 13	Week 26	Week 52
Average daily normalised ON time without troublesome dyskinesia				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
Average daily normalised OFF time (FAS)				

N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

A PD diary recording day with no more than 2 hours of missing data (4 or less missing entries) or at least 12 awake hours (i.e., at least 24 OFF or ON time entries) for the entire 24-hour diary is considered as a valid PD diary day

Abbreviations: PD: Parkinson's disease; SD: standard deviation; FAS: full analysis set.

Source: AbbVie Data on File. M15-741 Clinical Study Report.[12]

Figure 3. Mean average daily normalised ON time without troublesome ON time with troublesome dyskinesia, and OFF time based on the PD diary (FAS) (reproduced from CS Figure 11)

Abbreviations: BL: baseline; PD: Parkinson's disease; FAS: full analysis set; W: Week.

Source: AbbVie Data on File. M15-741 Clinical Study Report.[12]

As with M15-736, there was a substantial amount of missing data in M15-741, which were not accounted for in the analysis presented above. The primary reason for missing data was treatment discontinuations (Table 27). As described in Section 3.2.3, the majority of discontinuations were in cohort 1 due to problems with the infusion device. In cohort 2, there were fewer but still substantial discontinuations. Discontinuations are discussed in more detail in Section 3.3.3.1.

No sensitivity analysis accounting for missing data were performed for M15-741 and, as in M15-736, the EAG considers it likely that patients who discontinued treatment in M15-741 will have an efficacy similar to BMT and that the study results are likely to overestimate the efficacy of foslevodopa-foscarbidopa.

Table 27. Summary of Patients Not Included in the Analysis of Parkinson's Disease Diary by Visit in the M15-741 Trial (FAS) (adapted from clarification response A12 Table 6)

	N	Patients Not Included Due To…		
		Treatment Discontinuation	No Valid PD Diary Day	Any Other Reason
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS: Full Analysis Set.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

3.3.2.2 Health-related quality of life

In M15-741, the EQ-5D-5L summary index scores show a [redacted] improvement that was maintained across the trial period (Table 28). The EAG notes that the baseline EQ-5D-5L value in M15-741 ([redacted]) differed from the baseline value in the foslevodopa-foscarbidopa arm of M15-736, which was [redacted]. The mean change from baseline to Week 13 was an increase of [redacted] in M15-741, compared with an increase of [redacted] in M15-736 at Week 12. As mentioned previously, in the economic model the company combined the EQ-5D-5L data from M15-736, M15-098, M15-741, and M15-737 despite clear differences in QoL at baseline. This is discussed in Section 4.2.10.

Table 28. Change from baseline in the EQ-5D-5L summary index score (reproduced from CS Table 25)

Characteristic	Baseline	Week 13	Week 26	Week 52
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PD: Parkinson's disease; SD: standard deviation.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[12]

3.3.3 Safety

3.3.3.1 Drug exposure, interruptions and discontinuations

A total of [redacted] patients in the foslevodopa-foscarbidopa arm and [redacted] patients in the oral CD/LD arm completed 12 weeks of treatment in M15-736. Overall, [redacted] of patients had infusion interruptions ([redacted] in the foslevodopa-foscarbidopa arm and [redacted] in the oral CD/LD arm). The mean number of days of study drug interruption was [redacted] in the foslevodopa-foscarbidopa arm and [redacted] in the oral CD/LD arm. Among the [redacted] of patients in the foslevodopa-foscarbidopa arm who discontinued treatment during the trial, the most common reasons for discontinuation were infusion site related non infection reactions ([redacted]), withdrawal of consent [redacted]), lack of efficacy ([redacted] and difficulty with the drug delivery system [redacted].

In M15-741 a total of [redacted] patients had completed the 52-week treatment period at the time of the data cut-off, for [redacted] patients treatment was still ongoing and [redacted] had discontinued treatment. The most common reasons for treatment discontinuation were withdrawal of consent ([redacted], infusion site related non-infection reactions ([redacted]), infusion site related infection ([redacted]), and lack of efficacy ([redacted]).

As highlighted in Section3.2.3, there was a change in protocol in M15-741 to address problems with the infusion device initially used in the trial. Treatment discontinuation rates in the first 12 weeks of treatment in cohort 1 (patients enrolled prior to the protocol change 8th July 2020) were higher ([redacted]) than for cohort 2 (patients enrolled on or after the 8th July 2020, [redacted]). The company did not report the discontinuation rates of cohort 1 and cohort 2 at the end of the study period (52 weeks). The mean number of days of study drug interruption was [redacted] days for [redacted] patients. However, the majority ([redacted]) of patients reported an infusion interruption of less than 2 days.

Discontinuation data used in different scenarios in the economic model were based on M15-736, M15-741 and M15-737, the extension study of M15-741. Therefore, discontinuation data from M15-737 are summarised here for completeness.

Of the 105 patients who completed M15-741 and were enrolled in the extension study M15-737, [redacted] had discontinued treatment. The EAG notes that it is unclear at what timepoint/data cut off these data are from. The company report that at the data cut off for an interim report dated 2nd March 2022, 116 patients were enrolled in the study.

Table 29: Patient disposition (all screened patients)

		Characteristic	Foslevodopa-foscarbidopa	Oral CD/LD
Trial	Follow up	Patient flow		
M15-736	12 weeks	Initiated treatment, n (%)	[redacted]	[redacted]
		Completed treatment, n (%)	[redacted]	[redacted]
		Discontinued, n (%)	[redacted]	[redacted]
M15-741	52 weeks	Initiated treatment, n (%)	[redacted]	[redacted]
		Completed treatment, n (%)	[redacted]	[redacted]
		Discontinued, n (%)	[redacted]	[redacted]
		Ongoing treatment, n (%)	[redacted]	[redacted]
M15-737	24 months*	Total patients enrolled, n (%)	[redacted]	[redacted]
		Treatment ongoing, n (%)	[redacted]	[redacted]
		Discontinued, n (%)	[redacted]	[redacted]

Abbreviations: CD/LD carbidopa/levodopa

*Follow up from the start of treatment in M15-741

3.3.3.2 Adverse events

3.3.3.2.1 M15-736

Adverse events (AEs) in both treatment arms of M15-736 were mostly mild or moderate in severity. There were slightly more AEs and SAEs in the foslevodopa-foscarbidopa arm compared with the oral CD/LD arm and [redacted] AE leading to death in the oral CD/LD arm and [redacted] in the foslevodopa-foscarbidopa arm (Table 30). However, the incidence of AEs considered treatment related and AEs leading to treatment discontinuation were both markedly higher in the foslevodopa-foscarbidopa arm compared with the oral CD/LD arm. The most common AEs leading to discontinuation of foslevodopa-foscarbidopa were infusion site AEs: infusion site cellulitis ([redacted]), infusion site pain ([redacted]), infusion site oedema ([redacted]), infusion site bruising ([redacted]), and infusion site haemorrhage ([redacted]). .

Table 30. Overview of AEs (SAS) (adapted from CS Table 33)

AE category	Foslevodopa-foscarbidopa	Oral CD/LD
	N = [redacted]	N = [redacted]
Any TEAE, n (%)	[redacted]	[redacted]
Any serious TEAE, n (%)	[redacted]	[redacted]

Any TEAE leading to study drug discontinuation, n (%)	[redacted]	[redacted]
Any severe TEAE, n (%)	[redacted]	[redacted]
Any TEAE considered related to study drug, n (%)	[redacted]	[redacted]

Abbreviations: AE: adverse event; CD/LD: carbidopa/levodopa; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

Adverse events of special interest for foslevodopa-foscarbidopa include infusion site infections and reactions, falls and associated injuries, hallucinations/psychosis. The majority of these events were mild or moderate in severity and resolved without treatment discontinuation. Infusion site infections and reactions were more common in the foslevodopa-foscarbidopa arm than in the oral CD/LD arm, as was the incidence of hallucinations/psychosis (Table 31). The incidence of falls and associated injuries was higher in the oral CD/LD arm than in the foslevodopa-foscarbidopa arm.

Table 31. Adverse events of special interests (AESIs) (SAS)

AE category	Foslevodopa-foscarbidopa	Oral CD/LD
	N = [redacted]	N = [redacted]
Infusion site infection, Any TEAE, n (%)	[redacted]	[redacted]
Non-infection reactions, Any TEAE, n (%)	[redacted]	[redacted]
Falls and associated injuries, Any TEAE, n (%)	[redacted]	[redacted]
hallucinations and psychosis, Any TEAE, n (%)	[redacted]	[redacted]

Abbreviations: CD/LD: carbidopa/levodopa; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-736 Clinical Study Report.[6]

The EAG notes that dyskinesia was included in the economic model based on events classed as AEs associated with product complaints rather than all dyskinesia AEs or based on troublesome dyskinesia captured in the primary outcome of the trial. Dyskinesia as an AE was defined by the trial investigator and not the patient PD diary. The EAG does not consider dyskinesia as an AE to adequately capture the nature and impact of dyskinesia and also notes that if it is incorporated as AEs in the model, it should include all events and not be limited to those associated with a product complaint, as done in the CS. This is discussed in more detail in Section 4.2.8.

3.3.3.2.2 M15-741

As in M15-736, TEAEs in M15-741 were mostly mild or moderate in severity. However, during the 12-month trial period [redacted] of patients had a serious TEAE, compared with [redacted] at three months in M15-736 (Table 32). [redacted] patients died due to AEs, which were not considered by the investigators

to be related to foslevodopa-foscarbidopa. In the full study population [redacted] of patients had AEs that led to treatment discontinuation during the 12-months of the trial. In M15-736 the equivalent number after three months was [redacted]. In M15-741, the most common AEs leading to discontinuation were hallucination in [redacted] patients, infusion site cellulitis in [redacted] patients, infusion site erythema in [redacted] patients, and dyskinesia in [redacted] patients.

Table 32. Overview of AEs (SAS) (adapted from CS Table 41)

AE category	Foslevodopa-foscarbidopa
	N = [redacted]
Any TEAE, n (%)	[redacted]
Any serious TEAE, n (%)	[redacted]
Any TEAE leading to study drug discontinuation, n (%)	[redacted]
Any severe TEAE, n (%)	[redacted]
Any TEAE considered related to study drug, n (%)	[redacted]

Abbreviations: AE: adverse event; TEAE: treatment emergent adverse event.
Source: AbbVie Data on File. M15-741 Clinical Study Report.[62]

In terms of adverse events of special interest for foslevodopa-foscarbidopa, most cases were infusion site non-infection reactions, infusion site infections, and falls and associated injuries, occurring in [redacted], [redacted] and [redacted] of patients, respectively. The majority of these were mild or moderate in severity. However, serious infusion site reactions were reported for [redacted] patients, serious infusion site infections were reported for [redacted] patients (most of which resulted in hospitalisation), [redacted] experienced a SAE of fall, and serious hallucinations/psychosis events were reported for [redacted] patients.

3.4 Critique of indirect treatment comparison

3.4.1 Trials identified and included in the indirect treatment comparison

Given the lack of head-to-head trials comparing foslevodopa-foscarbidopa and levodopa-carbidopa intestinal gel (LCIG), the company performed network meta-analyses (NMAs) to obtain comparative evidence. The clinical systematic literature review (SLR), as critiqued in Section 3.1, was used to identify studies relevant for inclusion in the NMAs. Seven randomised controlled trials (RCTs), including M15-736, met the inclusion criteria and were included in the NMAs. However, only four of the trials were required to appropriately connect the interventions of relevance to the decision problem; foslevodopa-foscarbidopa, best medical therapy (BMT) and LCIG. Of the remaining three trials, two compared BMT with deep brain stimulation (DBS) and one compared BMT with apomorphine. Although the company included all seven trials in the analyses, results were reported only for the comparisons of interest. At the clarification stage the EAG requested the company re-run the NMAs excluding the three trials that didn't contribute to the comparison of foslevodopa-foscarbidopa and LCIG. This was in order to reduce the potential heterogeneity added by the inclusion of heterogenous studies that should not directly influence the results of the comparisons of interest but might introduce addition uncertainty due to the common heterogeneity assumption used in an RE model.

NMAs were performed for three outcomes: ON time without troublesome dyskinesia, OFF time and PDSS-2. However, only the results of the OFF time NMA were used in the economic model. The sections below provide a summary and critique of the three trials (M15-736, DYSCOVER, Olanow 2014) contributing to the company's updated NMAs for OFF time and ON time without troublesome dyskinesia (Figure 4). The network of trials was the same for both outcomes and is presented in Figure 4. Results for the company's original NMAs, which included RCTs with comparators that are not of interest and results for PDSS-2, can be found in the CS Section B.2.7.4.3.

Figure 4. Network of studies included in the ON and OFF time analysis

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel.

A comparison of baseline characteristics and results across the included trials is provided in the CS, appendix D.3, Table 8. Table 9 in the same document provides a summary of trial characteristics and eligibility criteria, and the company's quality assessment of the trials is presented in Table 11.

Olanow 2014 and DYSCOVER are both 12-week, multicentre, RCTs evaluating LCIG versus treatments that can be considered BMT. The comparator in DYSCOVER was oral optimised medical treatment (OMT), that is, patients remained on their current optimised and stable anti-PD medication throughout the trial. Olanow 2014, similar to M15-736, specifically utilised CD/LD IR and patients were moved to this treatment if they were not already using it and concurrent PD drugs (except apomorphine) were permitted. The LCIG treatment was consistent between the two trials, with LCIG delivered to the upper intestine by percutaneous endoscopic gastrostomy with J tube extension (PEG-J).

The Olanow 2014 and DYSCOVER trials both recruited similar populations to that in M15-736; patients who were responsive to levodopa but had persistent motor fluctuations with dyskinesia despite treatment with BMT. All three trials excluded patients who had received DBS.

DYSCOVER was an open label trial, whereas Olanow 2014 was a double-blind trial similar to M15-736. In all three trials, PD diaries were used to capture ON and OFF time and change from baseline in the outcomes were assessed at 12 weeks.

3.4.2 Indirect treatment comparison methods

A Bayesian framework using Monte Carlo Markov Chain (MCMC) was used to fit NMA models. Fixed effects (FE) and random effects (RE) models were evaluated and model selection was determined based on the deviance information criterion (DIC) model fit statistic; when the difference between the DICs of two models was small (less than three to five units), the least complex model was selected. The EAG is concerned about basing the decision solely on the least complex model if there is a difference of less than three units between models. An *a priori* expectation might be that a RE model would be more appropriate, given the likely heterogeneity introduced by dissimilar treatments considered BMT and the heterogeneous nature of PD. However, the EAG acknowledge that in simple networks with a paucity of trials it is likely there will be insufficient data to accurately estimate between study heterogeneity.

Other than issues that are discussed in the following section (Section 3.4.3), the EAG consider that, overall, the methods used are appropriate. Full details of methods used are provided in Section B.2.7.3 of the CS.

3.4.3 EAG critique of trial selection and ITC methods

3.4.3.1 Inclusion of comparators not of interest

The EAG notes that due to the star shape (without closed loops) of the company's original network, it is not possible to borrow strength from the included DBS and apomorphine trials for the comparison of foslevodopa-foscarbidopa and LCIG. The inclusion of these trials may instead have contributed to the company's reported convergence issue for the RE model. The EAG's preference is, therefore, to exclude these trials. The company re-ran the NMAs excluding these trials and these results are presented in Appendix 8.2.

3.4.3.2 Inconsistency in data used

The EAG notes that the data underpinning the company's NMAs are based on the observed mean change from baseline for M15-736 rather than the least square (LS) mean. The DYSCOVER data used were based on LS mean, whereas for Olanow 2014 it wasn't specified in the publication and so the EAG assumes that it is the observed mean that has been reported. To retain internal consistency within the dataset, the results presented in Section 3.4.4 are based on LS mean data from M15-736 and DYSCOVER, analysed by the EAG. The results of the company's updated NMAs of M15-736, DYSCOVER and Olanow 2014, based on the mix of observed and LS means, are presented for reference in Appendix 8.2.

As all three trials were funded by the company, the EAG considers that the company has access to the individual patient data (IPD), as such the EAG encourages the company to provide updated analysis at the technical engagement (TE) stage including all three trials using LS mean analysis for all treatments considered in the NMA.

3.4.3.3 Blinding and subjectivity of PD diary

The EAG generally considers double-blind studies, such as Olanow 2014 and M15-736, to be at significantly reduced risk of bias for subjective outcomes such as PD diary. However, as mentioned in Section 3.2.2, a substantial proportion of patients in M15-736 is likely to be aware of the treatment allocation, despite robust methods to ensure blinding, due to the clear differences in safety profile

and the decrease in morning akinesia with foslevodopa-foscarbidopa compared with oral LD/CD. In contrast to M15-736, there isn't such a stark contrast in the safety profile between LCIG and BMT. LCIG is administered as a morning bolus followed by continuous infusion at a constant rate for the remainder of each patient's waking day (approximately 16 hours, with the infusion being stopped overnight). Consequently, the likelihood of patients in either arm of Olanow 2014 correctly assuming which treatment they had been randomised to would be significantly reduced. However, the DYSCOVER trial was open label and therefore at an increased risk of bias, similar to M15-736.

3.4.3.4 Methods accounting for missing data

Olanow 2014 imputed missing data using last observation carried forward (LOCF). A mixed model repeated measures (MMRM) analysis was performed as a sensitivity analysis. The MMRM analysis was reported to give similar results to the LOCF but was not used in the NMA. M15-736 and DYSCOVER also analysed the data using an MMRM approach. As pointed out in the critique of M15-736 (Section3.2.4), the EAG does not consider the assumption that data are missing at random (MAR) to hold in these trials, especially not in M15-736 and the open label DYSCOVER trial, and consider the jump-to-reference (J2R) sensitivity analysis in M15-736 to be more appropriate. Sensitive analyses similar to the J2R analysis in M15-736 were not presented for the comparator trials. However, as both LCIG trials were funded by the company, the ERG considers it likely that they have access to the IPD from both studies. As such, the EAG suggests the company explore J2R sensitivity analysis for both LCIG trials at technical engagement (TE).

3.4.3.5 BMT variability

The EAG highlights the markedly different in absolute treatment effects in the BMT arm across the three trials in the NMA as a potentially important issue. The change from baseline in OFF time in the BMT arms ranged from a decrease of 2.14 hours in Olanow 2014 to an increase of 0.18 hours in DYSCOVER, and similarly for ON time without troublesome dyskinesia change from baseline varied from an increase of 2.24 hours in Olanow 2014 and a decrease of 0.12 hours in DYSCOVER. The EAG notes that differing ON and OFF time results may not be unexpected as BMT will be defined differently in the trials and that outcomes captured with a patient reported PD diary are subjective and likely associated with large variability. The clinical experts advising the EAG stated that as long as treatment is optimised it is unlikely to matter what the BMT is comprised of and the BMT in the three trials may be considered equivalent. However, although the absolute results from the trials are very different, the relative treatment effect of LCIG compared with BMT is consistent across the two

trials. If BMT is equivalent across the studies, then whatever factors that may be influencing the absolute results in the BMT arm of these trials is likely to affect both arms within each of the trials equally, which may be the reason why the relative treatment effect is comparable when the absolute treatment effects are different. Similarly, the absolute results of the BMT arm of M15-736 differ from the results of the BMT arm in the LCIG trials but the relative effectiveness of foslevodopa-foscarbidopa vs BMT is likely to be robust.

3.4.4 Results of the indirect treatment comparison

The results presented here are for the indirect comparison of foslevodopa-foscarbidopa and LCIG based on the EAG's analysis of LS mean change from baseline in ON time without troublesome dyskinesia and OFF time. As highlighted in Section 3.4.3.2, these analyses only include M15-736 and DYSCOVER and should be considered illustrative. A coherent analysis including a consistent dataset for all three relevant trials should be able to be provided by the company at technical engagement (TE).

The DICs for the FE and RE models were similar in terms of goodness of model fit (similar DIC) (Table 33 and Table 34) for both outcomes. For the original NMAs presented in the CS, the company mentioned that the RE models did not converge. In addition, the company considered the datasets for both outcomes of OFF time and ON time without troublesome dyskinesia to be too sparse to appropriately inform the RE model. For these reasons, the company selected the FE model for both outcomes. For the updated analysis, provided by the EAG below, both the RE and FE models converged. The EAG agrees with the company's preference of the FE model due to the limited data available to inform the between trial heterogeneity.

3.4.4.1 ON time without troublesome dyskinesia

The results of the NMA demonstrate a statistically significant improvement in ON time without troublesome dyskinesia for foslevodopa-foscarbidopa and LCIG versus BMT using the FE model (Table 33). The difference versus BMT was not statistically significant for foslevodopa-foscarbidopa or LCIG in the RE model. The difference in ON time without troublesome dyskinesia between foslevodopa-foscarbidopa and LCIG was [redacted] in favour of LCIG, but it did not reach statistical significance for either the FE or the RE models (Table 33).

Table 33. Difference in LS mean ON time without troublesome dyskinesia change from baseline (95% CrI)

Treatment	RE (DIC =2.5)	FE (DIC=2.5)
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]
EAG analysis including M15-736 and DYSCOVER Abbreviations: BMT: best medical therapy; CrI: credible interval; DIC: deviance information criteria; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.		

3.4.4.2 OFF time

The results of the NMA demonstrate a [redacted] decrease in OFF time for foslevodopa-foscarbidopa and LCIG versus BMT using the FE model (Table 34). The difference versus BMT was [redacted] for foslevodopa-foscarbidopa or LCIG for the RE model. The difference in OFF time between foslevodopa-foscarbidopa and LCIG was [redacted] but did [redacted] the FE or the RE models (Table 76).

Table 34. Difference in LS mean OFF time change from baseline (95% CrI)

Treatment	RE (DIC = 1.3)	FE (DIC= 1.3)
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]
EAG analysis including M15-736 and DYSCOVER Abbreviations: BMT: best medical therapy; CrI: credible interval; DIC: deviance information criteria; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.		

3.5 Conclusions of the clinical effectiveness section

The evidence submitted by the company in support of the clinical efficacy and safety of foslevodopa-foscarbidopa in the treatment Parkinson's disease (PD) is primarily derived from the double-blind randomised controlled trial (RCT) M15-736, but also from the single arm trial M15-741. However, the relative efficacy of foslevodopa-foscarbidopa versus the comparator in M15-736 (oral CD/LD) did not inform the model. Instead, data on the efficacy of foslevodopa-foscarbidopa was based on M15-736 and the treatment effectiveness of oral CD/LD was modelled based on natural history of PD, informed by an external data source. In addition, in the model, foslevodopa-foscarbidopa discontinuation data were based on data from three different sources (M15-736, M15-741, and M15-737) and health-related quality of life (HRQoL) data for foslevodopa-foscarbidopa were based on the combined results of four studies (M15-736, M15-741, M15-737 and M20-098), despite substantial differences in HRQoL at baseline between these studies.

The EAG considers M15-736 to be a good quality randomised controlled trial (RCT) that provides the best available evidence of the relative clinical effectiveness of foslevodopa-foscarbidopa compared with oral carbidopa/levodopa (CD/LD). The M15-736 trial shows that foslevodopa-foscarbidopa treatment leads to a [redacted] clinically meaningful decrease in OFF time and a [redacted] increase in ON time without troublesome dyskinesia compared with oral CD/LD at 12 weeks of treatment.

Although M15-736 is a double-blind trial, a large proportion of trial participants are likely to have correctly deduced which treatment they had been randomised to, mainly due to the large difference in morning akinesia between foslevodopa-foscarbidopa and oral CD/LD. There is, therefore, an increased risk of bias of the results of the subjective outcome of changes in ON and OFF time, which were captured through patient reported diaries. Although the magnitude of this bias is unknown it is likely that patients on foslevodopa-foscarbidopa may overestimate the efficacy of their treatment and that patients on BMT may underestimate the efficacy of treatment.

Treatment discontinuations were substantially higher in the foslevodopa-foscarbidopa arm than in the oral CD/LD arm. The most common reasons for discontinuation in the foslevodopa-foscarbidopa arm were infusion site related non-infection reactions, withdrawal of consent, lack of efficacy and difficulty with the drug delivery system. A sensitivity analysis based on the jump to reference (J2R) approach provides the most robust results in terms of the efficacy of the full trial population.

However, the primary analysis, based on the MMRM approach, is more representative of the results expected for patients who remain on treatment. This is what has informed the indirect treatment comparison (ITC) with LCIG, informing the economic model.

The foslevodopa-foscarbidopa trial M15-741 provides longer follow up than M15-736, but it does not provide comparative data. Treatment discontinuations were high and not accounted for appropriately in the analysis meaning the efficacy of foslevodopa-foscarbidopa is likely overestimated in M15-741.

The EAG's clinical experts consider both the M15-736 and M15-741 trial populations to be broadly generalisable to UK patients but note that M15-741 is somewhat more generalisable.

The company has focused their submission on a subpopulation of the population in the NICE final scope; adults with PD that is responsive to levodopa, but with symptoms not adequately controlled by their current medical therapy and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control. Overall, the EAG considers this population to be reasonable given this represents a subset of patients covered in the conditional marketing authorisation with a particularly high unmet need in terms of treatment options. However, the EAG's clinical experts notes that foslevodopa-foscarbidopa would be a valuable alternative as a first line advanced therapy to apomorphine, rather than limited to patients for whom apomorphine is unsuitable.

It is unclear to what extent the effectiveness of foslevodopa-foscarbidopa differs between the population specified in the scope, the patient population in the M15-736, and the narrower population the company is focusing on. In M15-736 prior DBS was not allowed, and it is unclear how many patients had prior apomorphine and if patients who hadn't received these treatments prior to the trial were unsuitable for them.

The company did not identify any head-to-head trials comparing foslevodopa-foscarbidopa and levodopa-carbidopa intestinal gel (LCIG), and therefore performed network meta-analyses (NMAs) to obtain comparative evidence. The data from each of the trials included in the NMAs of ON time without troublesome dyskinesia and OFF time in the company's analyses were inconsistent, combining estimates of least square (LS) means and observed means. The methods used for accounting for missing data also differed between the included trials. The EAG considers least square (LS) mean to be more appropriate than the observed mean and provides illustrative results based on analyses of LS means where available. The EAG analyses showed a difference in OFF time between

foslevodopa-foscarbidopa and LCIG [redacted] but this was not [redacted]. A coherent analysis including a consistent dataset for all three relevant trials should be able to be provided by the company at technical engagement (TE). The NMA results suffer from the same uncertainty and high risk of bias as the underlying M15-736 data. There is also likely to be some heterogeneity between the trials due to the difference in BMT and the variation in patients' PD.

4 Cost effectiveness

The company's probabilistic base case results are given in Table 35 and deterministic in Table 36. The probabilistic results have experienced minor changes as a result of CQs and a deterministic base case was requested to more easily check results; this also helped the EAG to find errors in the model, like the one found in the Dirichlet distribution. This was found due to the consistent bias recognised in PSA results compared to deterministic.

In the company's probabilistic and deterministic base case, foslevodopa-foscarbidopa is associated with lower costs and lower quality-adjusted life years (QALYs) compared to levodopa-carbidopa intestinal gel (LCIG), resulting in a south-west quadrant incremental cost-effectiveness ratio (ICER) of [redacted] and [redacted] costs saved per QALY forgone, respectively. In the company's analyses, foslevodopa-foscarbidopa is dominant versus Best Medical Therapy (BMT). The discrepancy between the probabilistic and deterministic results was the result of an error in how the Dirichlet distribution was applied to health state transition probabilities. Correcting this error results in a probabilistic base case ICER of [redacted] as is recorded in section 6.1.

Table 35. Company's revised probabilistic base case results PAS price

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	NA	5.22	-	NA	-	-
LCIG	[redacted]	NA	5.31	[redacted]	NA	−0.09	[redacted][a]
BMT	[redacted]	NA	4.53	[redacted]	NA	0.70	Foslevodopa-foscarbidopa dominant

[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 36. Company's deterministic base case results PAS price

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	9.072	5.327	-	-	-	-
LCIG	[redacted]	9.072	5.430	[redacted]	0	−0.10	[redacted][a]
BMT	[redacted]	9.072	4.527	[redacted]	0	0.80	Foslevodopa-foscarbidopa dominant

[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.

4.1 EAG comment on the company's review of cost effectiveness evidence

The company carried out a systematic literature review (SLR), using a single search strategy, to identify existing:

- Economic evaluations for the treatment of advanced Parkinson's disease.
- Health-related quality of life (HRQoL) evidence (health-state utility values [HSUVs]) in the treatment of advanced Parkinson's disease (PD); and,
- Cost and resource use evidence for the treatment of advanced PD conducted.

Searches were run in August 2021, January 2022 and were last updated in June 2022. A summary of the EAG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 37. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 37. EAG's critique of company's systematic literature review

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Data sources	Section 2 of Appendix G	Section 2 of Appendix G	Section 2 of Appendix G	Appropriate. MEDLINE, EMBASE, EconLit and the American Psychiatric Association (APA) PSYCinfo. The company manually searched major HTA websites and health economic conference proceedings not indexed in EMBASE. These searches were done in: NHS EED/HTA, NICE, SMC, NCPE, ScHARR, ISPOR, AAN, EAN, MDS and PBAC.
Search terms	Table 12 Section 2 of Appendix G	Table 18 Section 2 of Appendix H	Table 18 Section 2 of Appendix H	Appropriate. Entacapone misspelt entacapoine in the TI,AB search but this will likely not have a significant impact since the EMB.EXACT search was spelt correctly (assuming this error was carried

				over into the SLR and not just a recording error in the report). Search for cost evidence using USA spelling for cost minimisation.
Inclusion criteria	Table 14 in Section 3 of Appendix G	Table 19 in Section 3 of Appendix H	Table 19 in Section 3 of Appendix H	Appropriate.
Screening	Section 4.1 of Appendix G	Section 4.1 of Appendix G	Section 4.1 of Appendix G	Appropriate PRISMA diagram is low resolution, difficult to read.
Data extraction	Table 15 +16 in Section 4.2 of Appendix G	Table 20 in Section 4 of Appendix H	Table 21 + 22 in Section 4.2 of Appendix I	Appropriate. Unit for costs is not clearly presented.
QA of included studies	Table 17 in Section 4.2 of Appendix G using the Drummond checklist	No QA checklist completed, but uncertainty (limitations) around the utility values is provided.	No QA checklist completed, but uncertainty (limitations) around the analysis provided.	Appropriate

Abbreviations: AAN, American academy of neurology; CS, company submission; EAG, evidence review group; EAN, European academy of neurology; EED, economic evaluation database; HRQoL, health related quality of life; HTA, health technology assessment; ISPOR, international society of pharmacoeconomics; MDS, international Parkinson's and movement disorders society; NCPE, national centre for pharmacoeconomics; NHS, national health service; NICE, National Institute for Health and Care Excellence; PBAC, the pharmaceutical benefits advisory committee; ScHARR, school of health and related research; SMC, Scottish medical consortium; TI,AB, limit to title or abstract.

The SLR identified a total of 2,459 with 2,350 retrieved from electronic databases and 109 identified through supplementary searches. In total, 28 publications of the 44 found reported on economic evaluations and were extracted as part of the SLR. This included 28 publications reporting economic evaluation results, 15 healthcare costs and resource use and two on utilities (one of these is counted both in utilities and healthcare costs as it included both).

Of the four cost-effectiveness studies conducted from the UK perspective, three indicate that LCIG is not cost effective versus SOC/BMT. Only one of the eight available cost-effectiveness studies for LCIG reported a cost saving vs SOC/BMT. Significant variation in incremental QALY benefit vs SOC/BMT appears to have occurred across LCIG papers, with the lowest being 0.06 from a Swedish study, Kristansen *et al*. 2009,[13] and the highest being 1.39 coming from Chaudhuri *et al.* 2022.[14]

The most commonly used time horizon across all studies was lifetime with most cycle lengths set to 6 months though this ranged from 3 months to 1 year. No model appeared to have the same structure as the company submission, though most models did use OFF time to help define health states. Only the two models for levodopa/carbidopa/entacapone (LCE) treatment modelled health states purely with OFF time/day with most models included a combination of OFF time and H&Y. Despite this, the company suggested no clear consensus on approach was available since none of the relevant PD models had been through the NICE submission process.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 38 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 38. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	No, the model does not account for on time with troublesome dyskinesia. Furthermore, evidence presented by the company from Norlin *et al.* 2021[15] suggests using OFF time alone does not accurately represent the heterogeneity of Parkinson's disease. This is discussed in more detail in section 4.2.4.3 and 4.2.8.1.
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes (20 years).
Synthesis of evidence on health effects	Based on systematic review	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D	Yes, EQ-5D-5L data from M15-736, M20-098, M15-741, and M15-

	is the preferred measure of health-related quality of life in adults.	737 was mapped to EQ-5D-3L based on algorithm. AEs and carer disutility's are all in EQ-5D form from various sources.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, M15-736 comes from 57 sites in the USA and Australia, M15-741 comes from study sites across Australia, Belgium, Canada, Denmark, Germany, Italy, Japan, Netherlands, USA and UK. The trial included three study sites in the UK, which enrolled a total of [redacted] patients. This was considered generalisable to the UK population
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Abbreviations: EAG, evidence review group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population considered in the NICE final scope consists of adult patients with advanced PD responsive to levodopa, with symptoms not adequately controlled by their current medical therapy.[16] The company's proposed target population is narrower than the NICE final scope and marketing authorisation because of its relevance to NHS clinical practice.

The company's additional restriction to the final scope from NICE is that apomorphine or DBS are unsuitable or no longer providing adequate symptom control. The justification for the narrower population is that this is the group that foslevodopa-foscarbidopa would offer the best value for money.

To inform the economic analysis the company used clinical effectiveness data from the randomised control trial, M15-736,[6] for foslevodopa-foscarbidopa alongside a network meta-analysis to inform the relative treatment effectiveness of LCIG arm and an external source, Palmer *et al*. 2002,[1] to inform BMT/natural disease progression. M15-736 informed the baseline patient characteristics including OFF time, age and % female as well as response to treatment in the foslevodopa-foscarbidopa arm. The baseline percent female used in the model is [redacted]% and the mean age is [redacted]. Baseline OFF time distribution can be observed in Table 39.

Table 39. Baseline distribution of patients entering model (recreation of table 53 in the CS)

Health state	Base case (M15-736 ITT population)
OFF 0	[redacted]
OFF 1	[redacted]
OFF 2	[redacted]
OFF 3	[redacted]
OFF 4	[redacted]
OFF 5	[redacted]
OFF 6	[redacted]
OFF 7	[redacted]
OFF 8	[redacted]
OFF 9	[redacted]
OFF 10	[redacted]
OFF 11	[redacted]
OFF 12	[redacted]
OFF 13	[redacted]
OFF 14	[redacted]
OFF 15	[redacted]
OFF 16	[redacted]
Death	[redacted]
Total	[redacted]

Abbreviations: ITT: intention-to-treat.

Due to the high number of health states and trial population restrictions/low trial population the EAG notes 7 of the 17 alive health states contain no patients. As a result, the EAG requested the company to run a scenario with fitted distributions for baseline OFF time based on the trial data. The company did produce several distributions: zero-inflated Poisson (ZIP) model, a negative binomial model, and a zero-inflated negative binomial model (ZINB) However, the scenario was not provided

as the company suggested implementing this would have limited impact and result in bias that could impact future transitions. This is likely accurate as the small quantity of data relative to the large number of health states have made the model insufficiently powered for predicting outcomes of populations other than the exact trial.

Discontinuation came from cohort 2 of the two-year long M15-741[12] (one year extension M15-737[17]) safety trial, with cohort 1 being excluded as it used a less effective method of administration that will not be available for use in the future. Utility data came from a combination of all available trial data for patients treated with foslevodopa-foscarbidopa. This included M15-736 and M15-741 along with their ongoing open label extensions; M20-098 and M15-737, respectively.

4.2.2.1 EAG comment

The EAG agrees that the population is appropriate given the NICE final scope and choice of comparators. The company has somewhat contradicted itself in response to CQs, stating that the requested scenario of utilising a modelled distribution for initial OFF time would have limited impact but also be significant enough to result in problematic bias. The EAG have requested the results of this analysis be provided at technical engagement. This analysis has been. The model in its current state appears to be inflexible to any deviations from the base case model population selected; likely due to the limited trial data available.

4.2.3 Interventions and comparators

4.2.3.1 Intervention

The economic analysis investigates the cost-effectiveness of foslevodopa-foscarbidopa (ABBV-951); a combination of levodopa monophosphate and carbidopa monophosphate administered subcutaneously. Doses are individual to the patient, but the maximum recommended daily dose is 25ml and the medication is sold in 10ml vials for infusion. Patients in the model are assumed to consume an average of one 10ml vial containing 1700mg of levodopa a day, which is slightly below the trial mean of 1723.9mg at the end of the M15-736 study period.

4.2.3.2 Comparators

The comparators listed in the NICE final scope are apomorphine, with or without standard oral medication, deep brain stimulation (DBS), levodopa-carbidopa intestinal gel (LCIG) and Best Medical Therapy (BMT) including levodopa with adjunctive treatments and amantadine. The advanced PD

treatments the company excluded were apomorphine as continuous subcutaneous infusion (CSCI) or as intermittent injection and DBS.

The treatments that made up BMT, proportions and doses are shown in Table 40. These were sourced from Adelphi 2017-2019 data on file[18]. This is a study, commissioned by the company, collecting a broad set of data from PD patient record forms (PRFs) and patient/caregiver self-completion questionnaires, across G7 countries (although only UK data was used to inform this model). This is discussed in more detail in section 4.2.10.

Table 40. Make up of BMT comparator

Drug	Dose (mg)	Proportion of patients
Amantadine	336.51	9.00%
Apomorphine rescue (i.e. injection)	66.64	1.29%
CR Levodopa + carbidopa (e.g. sinemet CR)	402.74	18.57%
Entacapone	761.90	6.00%
Numient (modified release Levodopa + carbidopa)	1306.25	0.29%
IR Levodopa + carbidopa (e.g. sinemet)	605.81	64.00%
Opicapone (Ogentys)	50.00	0.29%
Pramipexole (once daily)	1.94	4.29%
Pramipexole (standard form)	2.57	3.71%
Rasagiline	1.02	17.29%
Ropinirole (once daily)	11.61	12.71%
Ropinirole (standard form)	14.76	5.86%
Rotigotine	7.13	10.86%

Safinamide	75.00	0.29%
Selegiline	8.05	2.29%
Abbreviations: BMT: best medical therapy; CR: controlled release; CSAI: continuous subcutaneous apomorphine infusion; IR: immediate release; LCIG: levodopa-carbidopa intestinal gel		

4.2.3.3 EAG comment

The EAG's clinical experts agreed that the make-up and proportions for BMT was plausible, stating that it varies significantly across patients. The EAG agrees with the company that the choice of BMT and LCIG is appropriate for the comparators in the economic analysis.

4.2.4 Modelling approach and model structure

The company developed a *de novo* cost-effectiveness model in Microsoft Excel to evaluate the incremental cost-utility of foslevodopa-foscarbidopa versus LCIG and BMT, in adults with advanced PD who are levodopa responsive but inadequately controlled by current therapy. The model included a short-term (3 month) period, to capture the trial, followed by a last-observation-carried-forward (LOCF) period in which the transitions are assumed to continue as per the trial phase. Beyond this LOCF period, patients treated by foslevodopa-foscarbidopa and LCIG are assumed to have the same efficacy as those on BMT, which involves a gradual worsening of daily OFF time over subsequent cycles.

The impact of PD is captured by 17 health states and one absorbing death state. These 17 states were defined by daily OFF time normalised to a 16-hour day. Previous published models included health states based on: H&Y scale and 'ON' time without troublesome dyskinesia, responder 'OFF' time, responder 'OFF' time and H&Y scale, and unified PD rating scale (UPDRS). This is the first model to represent OFF time broken down by hour, with previous models opting for, at most, quartiles of OFF time[19]. The company justified the divergence from previous models at the clarifications stage, by stating that one hour was a clinically meaningful change, as validated by clinicians, and the granularity will better align to the assessment of advanced PD. Furthermore, since there has never been a PD submission to NICE, there is no consensus on the most appropriate model structure.

4.2.4.1 Assessment and LOCF period

At the start of the model, patients initiate treatment on foslevodopa-foscarbidopa, LCIG or BMT. Patients on BMT maintain the same efficacy throughout the model, as patients are assumed to

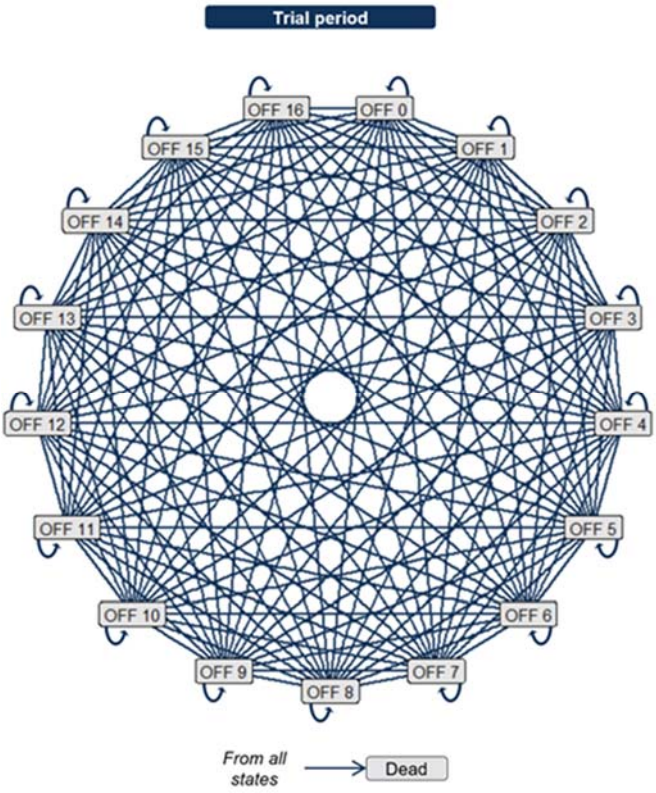
remain in either their present state or progress to the next OFF state as represented by Figure 7. The pivotal comparative trial comparing foslevodopa-foscarbidopa with BMT (M15-736) is not used as a source for treatment transitions for BMT, with the company instead opting to model this natural disease progression with an external source, Palmer *et al*. 2002[1]. This is discussed in further detail in section 4.2.6.

Patients in the foslevodopa-foscarbidopa and LCIG treatment arms can change from any OFF state to any other OFF state, as represented by Figure 6. Data for transitions is taken directly from the change in OFF time recorded in M15-736[6] trial data for the first 3 months in the foslevodopa-foscarbidopa arm. LCIG transitions have a fixed multiplier applied to the foslevodopa-foscarbidopa efficacy data based on the results of the NMA, this is covered in further detail in section 4.2.6.

After the 3-month trial period, all future cycles are assumed to have the same efficacy up to cycle 7 in the base case (month 36), although the model allows a user to limit this LOCF period to one cycle (month 6). Patients who discontinue immediately after the trial period or during the LOCF period will go onto BMT, starting in their current health state, but with the efficacy of BMT for all subsequent cycles. All patients after this 3-year point will converge towards the maximum possible OFF time (16 hours per day). This convergence occurs in the model past the current base case time horizon (20 years), at around cycle 50 (year 24-25), as can be observed in Figure 5.

Figure 5. Patient OFF time distribution across cycles by treatment

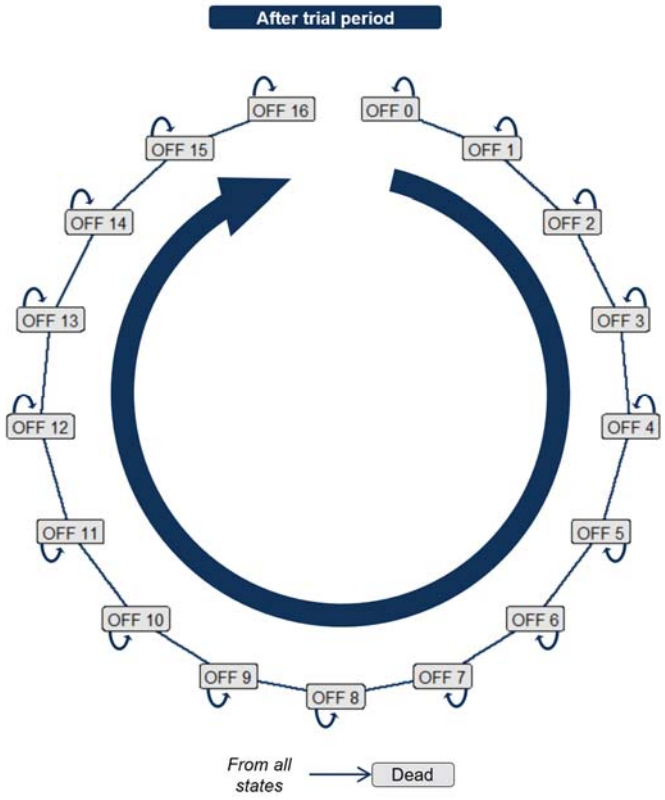
Figure 6. Overview of the model structure for the within trial and LOCF periods (reproduced from Figure 26 of the CS)



4.2.4.2 Post-assessment period

Following the LOCF period patients in the foslevodopa-foscarbidopa and LCIG arms have the same efficacy as BMT meaning patients can only transition to adjacent or worsening health states. This means patients who discontinue treatment in this period experience no difference in efficacy compared to those who continue treatment on LCIG or foslevodopa-foscarbidopa.

Figure 7. Overview of the model structure for the beyond LOCF period (reproduced from Figure 27 of the CS)



4.2.4.3 EAG comment

The company's model most closely resembles the one submitted to CADTH[19] in support of the evaluation of Movapo® (apomorphine) for the treatment of advanced PD. The CADTH review identified that the exclusion of H&Y does not accurately reflect the heterogeneity of condition. This is further demonstrated by the only relevant HRQoL paper found as part of the company's SLR (CS, appendix H). The results of Norlin 2021[15] are shown in Table 41, and shows that utility can vary significantly independent of reported OFF time. What makes this relevant to the model is that the increase in H&Y reduces the QoL benefit from reduced OFF hours. This means if we expect patients to increase H&Y from the recorded trial baseline over time then the model is currently overestimating the QoL benefit from a reduction in OFF time for later time periods.

Table 41. Predicted utility values (copy of table 20 from CS appendix H)

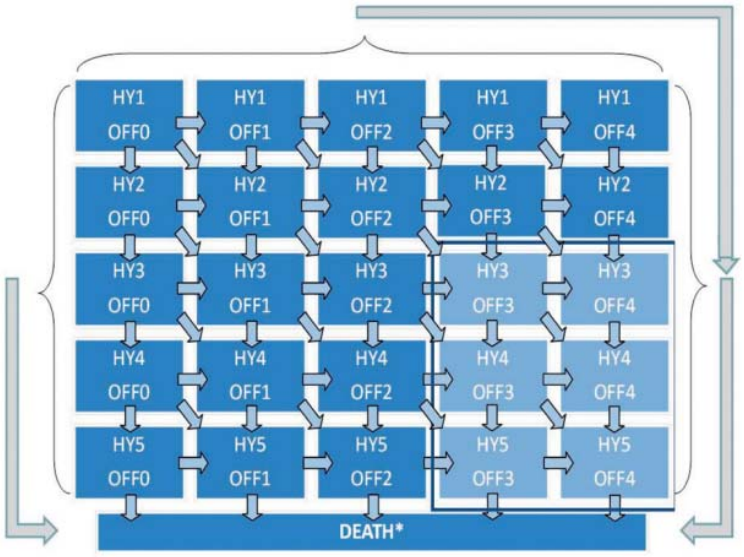
Off-category	H&Y I	H&Y II	H&Y III	H&Y IV	H&Y V
0%	0.733 (0.02)	0.649 (0.03)	0.521 (0.04)	0.333 (0.1)	− 0.081 (0.15)
0 to <25%	0.692 (0.02)	0.619 (0.02)	0.495 (0.02)	0.316 (0.04)	− 0.085 (0.05)
25 to <50%	0.659 (0.02)	0.595 (0.02)	0.475 (0.02)	0.303 (0.04)	− 0.089 (0.05)
50 to <75%	0.568 (0.03)	0.529 (0.03)	0.419 (0.03)	0.266 (0.06)	− 0.098 (0.09)

Off-category	H&Y I	H&Y II	H&Y III	H&Y IV	H&Y V
75-100%	0.486 (0.07)	0.469 (0.06)	0.368 (0.06)	0.233 (0.08)	− 0.106 (0.12)

Values presented as mean (SD).
Abbreviations: H&Y: Hoehn and Yahr scale; SD: standard deviation.
Source: Norlin 2021.13

Furthermore, the EAG believes the company does not have sufficient data to inform the number of OFF states they are using, which is an issue elaborated on in sections 4.2.6.4 and 4.2.10.1. All available models that include OFF time, including the CADTH submission, utilise OFF state categories rather than incrementally broken down by hour. As a consequence of these issues, the EAG would recommend that the company adopt the same structure as Kalabina *et al.* 2019[20], Walter and Odin 2015[21], Chaundhuri *et al.* 2022, Lowin *et al.* 2011[22] and Lowin *et al.* 2017[23] involving a combination of 5 OFF states and 5 H&Y states leading to 25 PD health states, as displayed in Figure 8. However, while the EAG appreciates the company did not collect H&Y data directly, the EAG considers that the MDS-UPDRS collected could be converted or used directly in place of H&Y.

Figure 8. model structure for Lowin *et al.* 2017[23]



*Death can be reached from any other state but that was not represented for simplicity.
In the frame is the base case.

Another issue with the current modelling approach appears to exist following the LOCF period, as patients who discontinue during this are assumed to experience the same efficacy as patients remaining on treatment. This seems intuitively implausible as, given the additional cost to the NHS and how much more burdensome a daily subcutaneous injection of foslevodopa-foscarbidopa or the

recurring LCIG AEs would be for a patient, they would be switched to BMT if it was just as effective. The EAG acknowledges that there is a lack of data available to inform the model by this time point but this assumption lacks face validity. The EAG experts have suggested that change in OFF time for patients who discontinue treatment to BMT would be seen within days and it would be a reasonable assumption that these patients would have similar outcomes to the BMT arm. As a result, unless the company can provide some evidence that patients who discontinue LCIG or foslevodopa-foscarbidopa retain some long term benefit from their treatment, these patients should be assumed to have the same outcomes as those in the BMT/natural disease progression arm.

Given the GLORIA trial[24] data demonstrating LCIG still is effective at 2 years the LOCF period duration of 3 years seems acceptable. Issues with efficacy data used will be addressed in section 4.2.6.4 and discontinuation issues in 4.2.7.1

4.2.5 Perspective, time horizon and discounting

The model was conducted from the perspective of the UK NHS and Personal Social Services (PSS), in line with the NICE reference case[25].

The time horizon of the model was 20 years. Based on a starting age of 66.4 years, patients would be 86.4 years old at the end of the time horizon. In scenario analysis, the company considered time horizons of 10, 15 and 30 years.

The cycle length in the model was 3 months for the first two cycles to match the follow up time of M15-736 and the pivotal RCTs for LCIG. Beyond these two cycles the cycle length is six months. A half-cycle correction is applied to all cycles throughout the model time horizon

Finally, an annual discount rate of 3.5% was applied to both costs and benefits, in line with the NICE reference case.

4.2.5.1 EAG comment

At the end of the 20-year time horizon 97.8% of patients will have died. For this reason, the EAG agrees with the company that extending the time horizon will have no meaningful impact on the results.

4.2.6 Treatment effectiveness

4.2.6.1 Foslevodopa-foscarbidopa

The treatment effectiveness in the trial and LOCF period is modelled, for foslevodopa-foscarbidopa, based on the patient-level observed change in daily OFF time recorded during the 3-month M15-736 trial period. These patient transitions can be observed in

Figure 9 and, where no data exists for a health state, patients are assumed to remain in that state. However, the EAG notes that the population at baseline is 73 patients and the population at the end of month 3 is 47, which can create issues due to how discontinuation is implemented uniformly, i.e. a patient was in OFF 14 at baseline but discontinued in the trial, meaning, due to model assumptions, patients will remain in OFF 14 throughout the trial/LOCF period with only uniform discontinuation rates applied.

The trial data, upon which the transitions are based on, can be seen in Figure 10. In the current base case these transition rates, observed over 3-months, continue in the same form regardless of cycle length, meaning when the cycle length changes to six months (from month 6 onwards) the rate of patients transferring between states per cycle remains the same until the end of the LOCF period. As part of CQs the company has provided a scenario in which this data is adjusted to match cycle length, the results of which can be found in Table 42.

Table 42. EAG requested scenario altering data to match change in cycle length (copy of table 14 from CQs)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	-	5.22	-	-	-	-
LCIG	[redacted]	-	5.31	[redacted]	-	−0.09	[redacted][a]
BMT	[redacted]	-	4.52	[redacted]	-	0.69	Foslevodopa-foscarbidopa dominant

[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.

Following the trial/LOCF period patients in the foslevodopa-foscarbidopa arm resort to the transitions of BMT patients.

Figure 9. Distribution of patients receiving foslevodopa-foscarbidopa at the start and end of the within M15-736 trial period (reproduced from Figure 28 of the CS)

Figure 10. Trial data used to inform transition matrices (taken from "Clinical Data Sheet" worksheet in the Excel model)

4.2.6.2 LCIG

Patients on LCIG have the same transition matrix as those on foslevodopa-foscarbidopa but with a relative risk multiplier applied based on the results of the NMA. This multiplier was calculated by dividing the foslevodopa-foscarbidopa change from baseline OFF time by the difference in change from baseline OFF time between foslevodopa-foscarbidopa and LCIG, found in the fixed effect NMA, subtracted from the foslevodopa-foscarbidopa change from baseline OFF time.

The NMA results presented in the original company submission contained an error which was fixed at CQs. The figure used in the NMA is [redacted] extracted from the results shown in Table 43 and the baseline mean change in OFF hours observed in the M15-736 trial is [redacted]. This means the multiplier used is calculated as being: [redacted]. This value was applied as a multiplier for any increase in OFF state and 1/1.096 was applied as a multiplier for any decrease in OFF state, with the transition to the unchanged OFF state being one minus the sum of patients transitioning to other OFF states.

Table 43. Difference in mean OFF time change from baseline relative to BMT (adapted from table 29 in the CS)

Treatment	FE (95% CrI)	FE SUCRA
BMT	-	[redacted]%
Foslevodopa-foscarbidopa	[redacted]([redacted] to [redacted])	[redacted]%
LCIG	[redacted]([redacted] to [redacted])	[redacted]%

Abbreviations: BMT: best medical treatment; CrI: credible interval; DIC: deviance information criterion; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects; SUCRA: surface under the cumulative ranking curve.

Due to the difference in treatment effectiveness between foslevodopa-foscarbidopa and LCIG not being statistically significant, the company was asked to provide a scenario which assumed equal efficacy between the two treatments. The results of this analysis can be found in Table 44. The company argued that it would be expected that foslevodopa-foscarbidopa would result in better patient outcomes due to the continuous infusion acting 24 hours a day leading to improvements in patient sleep and rates of morning akinesia.

Table 44. EAG requested scenario assume equal efficacy between foslevodopa-foscarbidopa and LCIG (copy of table 15 from CQs)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	-	5.22	-	-	-	-
LCIG	[redacted]	-	5.31	[redacted]	-	−0.09	[redacted]
BMT	[redacted]	-	4.52	[redacted]	-	0.69	Foslevodopa-foscarbidopa dominant

[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.

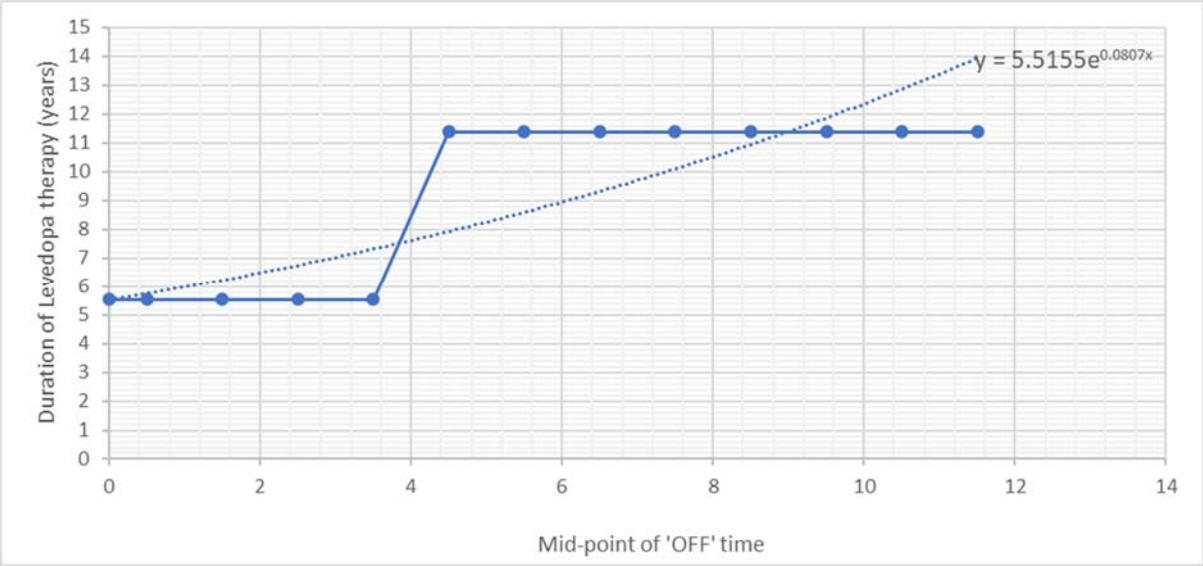
4.2.6.3 BMT/Natural disease progression

Due to the marketing authorisation for foslevodopa-foscarbidopa being based on the treatment of patients who are currently inadequately controlled by standard therapy, BMT was assumed to impart no benefit and result in natural disease progression. However, the pivotal RCT directly comparing BMT to foslevodopa-foscarbidopa (M15-736), did show a benefit but the company decided not to use the comparative data in the model. When asked about the exclusion of these data at CQs, the company stated that this benefit was likely due to the nature of the trial setting resulting in increased exposure to the healthcare system, leading to improved patient outcomes.

The company assumes patients on BMT and patients on LCIG or foslevodopa-foscarbidopa after the LOCF period can only have OFF time that is static or worsens by one each cycle. It was initially unclear how these transitions were derived from Palmer *et al.* 2002[1] but the company has elaborated in their response to CQs.

The Palmer *et al.* 2002 paper takes data from another study, Palmer *et al.* 2000[26]. According to the abstract, this study was attempting to derive OFF time related patient utility from a cohort of 60 patients. The relevant data for the company submission came from how long patients were treated with levodopa and patient OFF time per day, split into 5 categories. The OFF time was split into two categories within the Palmer *et al.* 2002 paper, with patients that experienced ≤25% OFF time having had on average 5.53 years of levodopa therapy and patients with >25% OFF time having had on average 11.38 years. These two data points were then graphed as shown in Figure 11, with the midpoint for every OFF time state set to 5.53 years or 11.38 depending if they were more or less than 25% of the patient day. An exponential curve fit to these data was then used to estimate the relationship between time on treatment and OFF time, with the assumption being that patients in lower OFF states are more likely to transition than those in higher OFF states.

Figure 11. Exponential model fitted to the two datapoints taken from Palmer *et al.* 2002 (copy of figure 6 from CQ response)



The relationship between OFF time and time on treatment of levodopa was represented by the formula:

Duration of Levodopa = $5.5155e^{0.0807*(\text{OFF time})}$

Using this formula, the estimated duration of levodopa treatment by OFF hour is calculated and then the rate of patients changing health state is derived by taking the reciprocal of the change in duration of levodopa treatment between OFF hours. This rate (r) is then converted to a 6-month (t=0.5) transition probability using the formula:

p(t) = 1 - e^-(rt)

The probability for remaining in the OFF state is one minus this calculated probability for increasing OFF time over 6 months. The results of these calculation steps are shown in Table 45.

Table 45. Calculated transition rates for BMT based on Palmer *et al.* (reproduced from tables 17/18 from CQ response)

No. of hours	Mid-point in OFF time	Duration of levodopa, years	Fitted duration of levodopa (exponential)	1/diff in mean	Transition probability for 6 months
OFF 0	0.005	5.53	5.518	4.446906439	0.8918
OFF 1	0.5	5.53	5.743	2.071935209	0.6451
OFF 2	1.5	5.53	6.225	1.911298883	0.6154
OFF 3	2.5	5.53	6.748	1.763116628	0.5859

OFF 4	3.5	5.53	7.316	1.626422885	0.5566
OFF 5	4.5	11.38	7.930	1.500326955	0.5277
OFF 6	5.5	11.38	8.597	1.384007193	0.4994
OFF 7	6.5	11.38	9.320	1.276705656	0.4718
OFF 8	7.5	11.38	10.103	1.177723166	0.4450
OFF 9	8.5	11.38	10.952	1.08641475	0.4191
OFF 10	9.5	11.38	11.872	1.002185439	0.3941
OFF 11	10.5	11.38	12.870	0.924486394	0.3701
OFF 12	11.5	11.38	13.952	0.852811325	0.3471
OFF 13	12.5	-	15.124	0.786693197	0.3252
OFF 14	13.5	-	16.396	0.725701181	0.3043
OFF 15	14.5	-	17.774	0.669437852	0.2845
OFF 16	15.5	-	19.267	-	-

[a]No patients with >75% OFF time were included in the original study by Palmer *et al*.[7] As such, model fitting was conducted with data up to OFF 12, and then extrapolated to OFF 16.

4.2.6.4 EAG comment

As can be observed in

Figure 12, the majority of the benefit from reduction in mean OFF hours is achieved by day 8 of the 3-month M15-736 trial, used for transitions in the LOCF period. Average OFF time even increases slightly between day 57 and day 85. In addition, the limited data available leads to implausible extrapolations when individual patient predictions are followed. An example of this is that there are [redacted] patients who started in OFF 6 and OFF 7 and their condition worsened to OFF 11 by month 3 of the M15-736 trial. However, because the [redacted] patient in OFF 11 improved to OFF 0 during the trial, by applying the LOCF assumption, these [redacted] patients are expected to do the same by month 6 and then remain in OFF 0 until the end of the LOCF period, since this state had [redacted] patients in at baseline resulting in no exit transition rate.

Figure 12. Plot of mean change in average daily normalised OFF time from M15-736 trial (reproduced from Figure 5 of the CS)

As a result, the LOCF assumption is unjustifiable and should be removed and replaced with a period where health states are fixed while on treatment. The company justified not running this as a scenario in the response to CQs by identifying that the M15-741 data showed a continuous decline in OFF time up to week 52; implying that the same can be assumed to occur with patients in the M15-736 trial. This is insufficient justification for extending the transition matrix throughout the LOCF period for several reasons:

- The M15-741 trial resulted in a smaller decline from baseline OFF time at 52 weeks than the M15-736 did at 3 months;
- The difference in OFF time from week 26 to later time points was not ;

As shown in

- Figure 13, the majority of the decline in OFF time still occurs in week 1 in the M15-741 trial, so extrapolating change from baseline to month 3 (W13 in the graph) would still be unjustified.

Figure 13. Plot of mean change in average daily normalised OFF time from M15-741 trial (reproduced from Figure 11 of the CS)

The difference between the change in OFF time from baseline for LCIG and foslevodopa-foscarbidopa taken from either the FE or RE is not statistically significant, as can be seen in Table 43. Furthermore, as discussed in section 3.4 the company has performed the NMA incorrectly and overestimated the advantage foslevodopa-foscarbidopa provides over LCIG, by alternating between using the least square mean and observed mean depending on the study/treatment.

The company has constructed its model to capture the important differences between treatments for the population under consideration. As such, the EAG was surprised to learn from the company that outcomes, considered by the company to be a benefit for foslevodopa-foscarbidopa, were not incorporated into their model. This included patient sleep and morning akinesia. The EAG acknowledges that PDSS-2 showed a statistically significant improvement but since this model is based entirely around the 16 hours of awake time this benefit could only be implemented with a change to the current model structure. Morning akinesia is also considered as improved but again, as this is not directly incorporated in the model. Only the difference in OFF time was considered relevant, which the EAG believes does not cover the heterogeneity of outcomes as stated in section 4.2.6.4. Given this it is recommended that equal efficacy be assumed between LCIG and foslevodopa-foscarbidopa.

The company's justification for their refusal to apply the comparative trial data for BMT in the model is insufficient. The argument that the benefit from BMT experienced in the trial was likely the result of increased exposure to the healthcare system seems plausible, given the population under

consideration. However, this would equally apply to the benefit experienced in the foslevodopa-foscarbidopa arm. If the company believes that there is an additional benefit derived from the M15-736 beyond the effect of treatment, then this "trial effect" needs to be removed from foslevodopa-foscarbidopa as well as BMT. The EAG considers this to be further justification for using the direct comparative evidence for foslevodopa-foscarbidopa and BMT from M15-736 ,as the impact of any "trial effect" would effectively "cancel" out in the comparison within the model. As a minimum, the EAG considers that the BMT trial data should be used for the first cycle of BMT and use the LOCF assumption for one cycle.

The Palmer data is based on very limited information, a single time point interview of 60 USA patients 22 years ago. However, the EAG acknowledges the lack of data available for this area. Any attempt to extrapolate the 3-month trial data consistently would result in BMT surpassing LCIG and foslevodopa-foscarbidopa in effectiveness. This would not produce a realistic projection of patients daily OFF-time trajectories over the long term, as it is established that the narrowing of the therapeutic window will lead to progressively more motor complications as the disease progresses.[27]

The abstract for Palmer *et al*. 2000 suggests the data was split into five levels of OFF time, instead of the two used from Palmer *et al*. 2002. If this is available, the company should use this to improve their fitted exponential model.

Furthermore, the fitted model is currently based on contradictory assumptions. As can be seen in Figure 11 the company effectively assumes all patients under 25% OFF and over 25% OFF time had the same time on treatment (i.e. no relationship) and then assumes there's an exponential relationship. The company should just plot the two midpoints of under 25% and over 25% OFF time or a weighted average OFF time for the categories if it is available.

Whilst Palmer *et al.* 2000 appears to be a relatively weak source of data, it is worth noting Kalabina *et al.* 2019[20], Walter and Odin 2015[21], Chaundhuri *et al.* 2022, Lowin *et al.* 2011[22] and Lowin *et al.* 2017[23] all used this to represent their "natural disease progression". Furthermore, the alternative presented in the CADTH model[19] was to assume patients remain at the baseline health states recorded in the relevant trial for 5 years, which would be an excessively simplified alternative.

4.2.7 Discontinuation

Patients could not discontinue from BMT as this remains the final option for treatment.

Discontinuation for foslevodopa-foscarbidopa was informed in the base-case by cohort 2 of the M15-741 trial.[12] The full sample from this trial was not used because this includes patients who experienced difficulties due to a less effective drug delivery system, that will now not be available for use in clinical practice. In CQ responses the company justified not using the same data source they used for transition rates as they stated, the one-year safety trial allows for a continuous source for discontinuation rates and reflects the infusion set intended for use. Although, the EAG notes that M15-736[6] did use the same updated infusion set.

Discontinuation from LCIG treatment in the model was informed by Nyholm *et al*. 2012.[28] This involved the company taking the data from the KM curve in Figure 14 and converting it to the probabilities, up to 24 months, found in Table 46, although the company did not elaborate on this process.

Figure 14. Discontinuations of LCIG as recorded in Nyholm *et al.* 2012

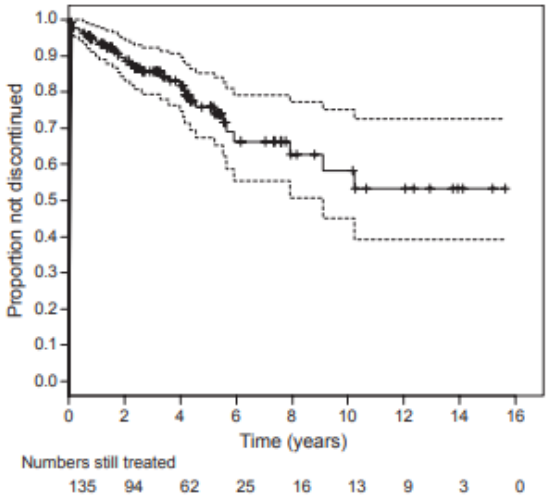


Table 46. Discontinuation rates used in model for LCIG (reproduced from table 59 in the CS)

Time	LCIG
0–3 months	2.0%
3–6 months	1.0%
6–12 months	2.1%
12–18 months	2.1%
18–24 months	4.3%

24+ months	3.5%

Abbreviations: LCIG: levodopa-carbidopa intestinal gel.

4.2.7.1 EAG comment

The discontinuation rates for the scenarios ran by the company can be found in Table 47 along with the EAG preferred case. It is the EAG's understanding that the new infusion set provided to cohort 2 in the M15-741 trial is also provided to all patients in the M15-736 trial. Given this was the trial the company used to inform efficacy and baseline OFF time, the company should use the discontinuation rate from this trial for the first period. Following this period, the company could use sample 2 of the M15-741 trial as the EAG agrees that including patients on the old infusion method would be inappropriate. Finally, the company should use the M15-737 data given this is the only direct evidence for foslevodopa-foscarbidopa discontinuations during the 12 to 24 month period.

Table 47. Discontinuation rates for foslevodopa-foscarbidopa from clinical trials

Time	M15-741 sample 2 (base case)a	M15-741 and M15-737 sample 1 (scenario)b	M15-736, M15-741 and M15-737 (scenario)c	M15-741 and M15-737 full cohort (scenario)d	EAG base case: M15-736, M15-741 cohort 2 and M15-737
0–3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3–6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6–12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12–18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18–24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 + months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]0–12 months: M15-741 sample 2; 12+ months: standard rate.
[b]0–12 months: M15-741 sample 1; 12–24 months: M15-737 sample 1; 24+ months: standard rate.
[c]0–3 months: M15-736; 3–12 months: M15-741; 12–24 months: M15-737; 24+ months: standard rate.
[d]0-12 months: M15-741; 12–24 months: M15-737; 24+ months: standard rate

4.2.8 Adverse events

Most AEs were applied as single event costs and utility decrements within the first cycle. Their incidence and expected duration are recorded in Table 48. If data were not available for duration it was assumed to be 28 days. During CQs the company was asked to justify applying these as a single cycle effect. They stated that though in practice these can occur throughout the duration of

treatment they indicated a lack of relevant data meant this approach was the simplest. The company did not add the requested scenario of continuous AEs.

As a result of CQs the company updated infusion site related AEs and falls duration to match the trial data, replacing the sourced or 28 day assumed length for these. In addition, the company corrected the rates of dyskinesia for foslevodopa-foscarbidopa and LCIG.

Table 48. Incidence of AEs (reproduced from Table 56 of the CS)

AE	Foslevodopa-foscarbidopa		BMT		LCIG		AE duration	
	Estimate	Source	Estimate	Source	Estimate	Source	Estimate (days)	Source
Infusion site erythema	[redacted]	CSR M15-736[6]	[redacted]	CSR M15-736[6]	13%	Fernandez *et al.* 2015[29]	14.5	NICE TA720
Infusion site nodule	[redacted]		[redacted]		0%	Assumption	14.5	Assumption
Infusion site cellulitis	[redacted]		[redacted]		0%	Assumption	22.5	Assumption
Infusion site pain	[redacted]		[redacted]		23%	Standaert *et al.* 2017[30]	14.5	Walter 2015
Infusion site reaction	[redacted]		[redacted]		29.7%	Olanow *et al.* 2014[31]	14.5	NICE TA720
Dizziness	[redacted]		[redacted]		[redacted]	Same as foslevodopa-foscarbidopa	28	Assumption
Hallucination	[redacted]		[redacted]		8.3%	Nyholm *et al.* (005[32]	28	Assumption
Depression	[redacted]		[redacted]		10.8%	Olanow *et al.* 2014[31]	28	Assumption
Anxiety	[redacted]		[redacted]		0.1%	Nyholm *et al.* 2005[32]	28	Assumption
Nausea	[redacted]		[redacted]		29.7%	Olanow *et al.* 2014[31]	28	Assumption
Falls (hospitalisation)	[redacted]		[redacted]		10.8%	Olanow *et al.* 2014[31]	5.7	Assumption based on an average of six weeks in a cast
Diarrhoea	[redacted]		[redacted]		[redacted]	Same as foslevodopa-foscarbidopa	15	NICE TA581
Dyskinesia	[redacted]		[redacted]		[redacted]	Walter and Odin 2015[21]	28	Assumption

Abbreviations: AE: adverse event: BMT: best medical therapy; CSR: clinical study report; LCIG: levodopa-carbidopa intestinal gel.

Recurring AEs were only applied to the LCIG arm and were the result of surgical issues. These rates can be observed in Table 49. The proportions in the table were applied as a percentage of the starting cohort and are not adjusted based on patients' discontinuations or deaths.

Table 49. Incidence of recurring AEs for LCIG (copy of table 57 in CS)

AE	Proportion Cycle 1	Proportion Cycle 2	Proportion Cycle 3	Proportion Cycle 4+	Source	Proportion Cycle 1
Replace/reposition tube with surgery	6.57%	6.57%	12.70%	11.89%	Fernandez *et al.* 2015, Fernandez *et al.* 2018	6.57%
Replace/reposition tube without surgery	7.47%	7.47%	14.39%	16.35%	Fernandez *et al.* 2015, Fernandez *et al.* 2018	7.47%

Abbreviations: AE: adverse event; LCIG: levodopa-carbidopa intestinal gel.

4.2.8.1 EAG comment

Applying most adverse events as single first cycle events does not seem justified. The company acknowledged that these AEs can occur throughout the duration of treatment and acknowledged that some of the AEs may progress. Despite this they maintained their current approach was appropriate and did not add this as a scenario.

The EAG's clinical experts identified infusion site nodule, infusion site erythema, infusion site pain, infusion site reaction, dizziness, falls and dyskinesia as AEs they expected to progress over time. The company claimed injection related AEs can be managed by education, hygiene, and rotating sites, but as the EAG clinical experts stated progression of these AEs would be expected in clinical practice. The company's assumption that these AEs stop occurring with better management techniques does not appear clinical plausible to the EAG's experts. As a result, the EAG recommends the infusion site related AEs be applied continuously throughout treatment.

With dizziness, falls and dyskinesia the company claimed that these may be features of disease progression. The EAG agrees with this, but the NICE reference case checklist requires the model to account for "all direct health effects, whether for patients or, when relevant, carers". Dizziness and falls could plausibly be accounted for by OFF time in the model, but, as the company claims in CQs, dyskinesia is likely a result of being overmedicated in ON time which is not a cost/utility decrement

currently accounted for. Troublesome dyskinesia appears to represent a potentially significant source of disutility not currently accounted for in the model. The EAG recommends that some attempt should be made to estimate and account for the effect of this over the course of the condition.

As a response to CQs, the company corrected the LCIG rate of dyskinesia, although it is now significantly higher than BMT and foslevodopa-foscarbidopa at a rate that appears clinically implausible, given the mechanism of action should result in a rate of dyskinesia between BMT and foslevodopa-foscarbidopa. This 7% value is sourced from the model described in Walter and Odin (2015) who cite the value as having come from Lowin *et al.* 2011. This paper states, "SC regimen AEs are not considered within the model" with the only relevant AEs appearing to be surgery related. However, this paper does cite a study relating to dyskinesia, Schrag and Quinn 2000. This cited paper appears to be where the 7% figure originated, with it representing the percentage of PD patients with motor fluctuations and dyskinesia, with a disease duration of less than or equal to 5 years and who are currently treated with levodopa. This value does not relate to patients treated with LCIG. If the EAG has appropriately located the company's source of the 7%, then it is an inappropriate value to use and should be replaced. Ideally if the company has access to the LCIG trial data this should be used as the source of dyskinesia.

The company's assumption that costs and QALYs for the recurring AEs contained within the model result in a fixed cost//decrement every cycle regardless of patient's deaths and discontinuations does not seem plausible. The AEs should be adjusted by the number of patients receiving treatment.

4.2.9 Mortality

The company obtained all-cause general population mortality from UK national life tables provided by the Office of National Statistics (ONS).[33] Data from Years 2018 to 2020 were used to inform the model. These probabilities were age and sex adjusted according to the baseline patient characteristics in the M15-736 study.

Disease specific mortality was accounted for in the model by applying a fixed ratio of 2.51, derived from Okunoye *et al*. 2021,[34] a UK based study comparing PD and non-PD patient mortality rates. This was applied to all patients regardless of health state or treatment.

4.2.10 Health-related quality of life

The company used EQ-5D-5L data collected in the M15-736, M20-098, M15-741, and M15-737 studies to estimate utility values in the model by combining the data from the foslevodopa-foscarbidopa arms and mapping it to EQ-5D-3L based on the algorithm and English value set developed by Hernandez *et al*.[35, 36]

The company then used a linear mixed model to estimate utility values for each of the 17 PD states (OFF 0 to OFF 16), as reported in Table 50. The same utility values were used for all treatment arms in the model. The company reported that, "*combining the EQ-5D data from all four studies allowed an increase in the sample size for more severe PD health states, which in turn improved the precision of the utility estimations for these health states*." The company also adjusted utilities for age, using population norms from Janssen *et al.*[37]

Table 50. Utility values based on a linear mixed model regression used in the model base case

Health state	Utility value (SE*)
OFF 0	[redacted]
OFF 1	[redacted]
OFF2	[redacted]
OFF 3	[redacted]
OFF 4	[redacted]
OFF 5	[redacted]
OFF 6	[redacted]
OFF 7	[redacted]
OFF 8	[redacted]
OFF 9	[redacted]
OFF 10	[redacted]
OFF 11	[redacted]
OFF 12	[redacted]
OFF 13	[redacted]
OFF 14	[redacted]
OFF 15	[redacted]
OFF 16	[redacted]
Dead	[redacted]

4.2.10.1 EAG comment

During clarification, the company provided the number of patients at baseline and at the end of follow-up for all the studies used in the utility estimations (Table 51 and Table 52, respectively). As reported in Table 51, combining the M15-736, M20-098, M15-741, and M15-737 studies did not provide additional data for the more severe states at baseline, compared to using the M15-736 study alone (with the exception of OFF state 10), despite the company's rationale for aggregating the studies. In fact, none of the M15-741 or M15-737 studies had baseline or end of study data for the 12; 14; 15 or 16 OFF states.

Overall, the EAG is concerned with the uncertainty around the company's utility estimations, particularly for the states including 10 or more hours of OFF time. Several utility estimates seem to be based on only 2 patients (for example, OFF states 12, 13 and 15); or 1 patient (OFF state 16), while OFF state 14 did not have any baseline or end of study observations (therefore, data based on potentially very few observations must have been collected at some point during M15-741 or 737).

As discussed in Section 4.2.4, the company's model structure differs from most cost-effectiveness models for PD available in literature in that it estimates hourly changes in OFF time, as opposed to categories of aggregated hour changes (typically quartiles of awake time). Due to this, the EAG could not undertake a direct comparison of utilities used in literature with the values estimated by the company.

With regards to the comparability of study populations in M15-736 and M15-741 (as M20-098 and M15-737 were follow-up studies of M15-736 and M15-741, respectively), the company stated that the baseline characteristics across studies were generally well-matched and that the baseline normalised OFF time was well matched between the two populations, with patients experiencing a mean of [redacted] hours in M15-736 and [redacted] hours in M15-741. Nonetheless, the EAG notes that baseline utility values reported in Table 53 show a paramount lack of comparability across mean utility values for the same OFF states at baseline in the two studies. For example, for the OFF state 5, the mean utility value at baseline in M15-736 and M15-741 was [redacted] and [redacted] respectively. This suggests that patients' quality of life was considerably [redacted] in M15-741 than in M15-736 at baseline, and/or that trying to capture the granular impact of hourly OFF changes in patients' quality of life is not appropriate. Clinical expert opinion provided to the EAG reported that patients' quality of life is less

likely to be impacted by the total number of OFF hours experienced by patients, but more by how predictable the patterns of OFF hours are, and when they happen in the day.

The clinical rationale for patients' quality of life being more impacted by predictability than number of OFF hours in a day could also explain the lack of a trend in mean utility values at baseline as OFF hours increase in Table 53 (for example, within the M15-741 study, patients with 6 OFF hours have a mean utility of [redacted] while patients with 7 OFF hours have a mean utility of [redacted]). It could also explain why, in general, in the follow-up studies, patients experienced a considerably higher utility for the same OFF state as patients in M15-736 and in M15-741, as it is expected that in the follow-up studies patients with the same number of OFF hours as in the initial studies will have their pattern of OFF hours more stabilised and under control for a longer period of time.

During clarification, the company also reported that the only variables tested in the utility regression models were: total hours of OFF hours per day; PDSS-2 score; whether a patients woke up in an OFF state or not; treatment arm; and interaction terms combining the previous variables, of which only total hours of OFF hours per day was included as a variable in the final model. The company also confirmed that age, sex and baseline OFF hours were not tested as variables in the regression models. The EAG is unclear why such variables (with obvious correlation to quality of life) were not tested. Furthermore, the EAG notes that M15-736 and M15-741 had different durations, and that patients in M20-098 and M15-737 had been receiving treatment with foslevodopa-foscarbidopa for 12 days-3 months and 12 months at study baseline. Therefore, the EAG considers that treatment duration also should have been tested in the regression models.

The EAG notes that the underlying rationale to the company's approach that quality of life only depends on total hours of OFF time (by hourly increments) seems at odds with the data used to run the utility analysis. If treatment arm was found to not be statistically significant in predicting patients' quality of life, then the company should have used utility data from both treatment arms in every study where this was available, therefore increasing the sample size and robustness of the analysis.

In conclusion, the EAG considers that the utility values used in the company's base case analysis to carry a high degree of uncertainty and are unlikely to be robust for decision making. It also seems apparent that hourly changes in OFF time are not well correlated to changes in patients' quality of life. Most of the available cost-effectiveness studies available in literature seem to capture changes

in patients' quality of life within broader intervals of OFF hours (usually quartiles of daily time awake), split by changes in H&Y outcomes. Nonetheless, M15-736 and M15-741 did not capture H&Y outcomes, as such, is not possible to incorporate these directly in the utility analysis. As an alternative, the EAG suggests the following:

1. Attempt to convert the MDS-UPDRS data to an estimate for H&Y states of patients or use the MDS-UPDRS as a health state directly if plausible.
2. The company should investigate the impact of variables such as age; OFF hours at baseline; and treatment duration on patients' quality of life. The company should also include the utility data available in comparator arms of the relevant studies.
3. The company should investigate the possibility of analysing changes in mean utility by categories of OFF hours - For example, Table 51 and Table 52 show that aggregating changes in OFF hours by 0% to 25%; 31% to 50% and 50% to 100% categories could provide more robust sample sizes and therefore, potentially more robust utility estimates.
4. If step 1 and 2 do not lead to more consistent mean utility values within the same OFF states across studies, the company could investigate the possibility of using an individual study, instead of aggregating studies to estimate utility values in the model.
5. The company should use the data from the UK population with severe PD from the real-word Adelphi study to estimate utility values for the same OFF categories as those chosen in step 2, in order to validate the estimates used in the updated analysis.

Table 51. Number of patients treated with foslevodopa-foscarbidopa with EQ-5D-3L data available at baseline in all studies used by the company

Change in OFF hours*	OFF hours	M15-736		M20-098		M15-741		M15-737		Total combined		
		N	%	N	%	N	%	N	%	N	%	% patients by change in OFF hours by categories
Total population												
-	Missing											
0%	0											
6%	1											
13%	2											
19%	3											
25%	4											
31%	5											

38%	6	[redacted]										
44%	7	[redacted]										
50%	8	[redacted]										
56%	9	[redacted]										[redacted]
63%	10	[redacted]										
69%	11	[redacted]										
75%	12	[redacted]										
81%	13	[redacted]										[redacted]
88%	14	[redacted]										
94%	15	[redacted]										
100%	16	[redacted]										
*change in OFF hours estimated as total OFF hours/16 hours												

Table 52. Number of patients treated with foslevodopa-foscarbidopa with EQ-5D-3L data available at end of study in all studies used by the company

Change in OFF hours*	OFF hours	M15-736 (3 months)		M20-098 (3 months)		M15-741 (12 months)		M15-737 (24 months)		Total combined		
		N= [redacted]	%	N= [redacted]	%	N= [redacted]	%	N= [redacted]	%	N= [redacted]	%	% patients by change in OFF hours by categories
-	Missing	[redacted]										[redacted]
0%	0	[redacted]										[redacted]
6%	1	[redacted]										
13%	2	[redacted]										
19%	3	[redacted]										
25%	4	[redacted]										
31%	5	[redacted]										[redacted]
38%	6	[redacted]										
44%	7	[redacted]										
50%	8	[redacted]										
56%	9	[redacted]										[redacted]
63%	10	[redacted]										
69%	11	[redacted]										
75%	12	[redacted]										
81%	13	[redacted]										[redacted]
88%	14	[redacted]										
94%	15	[redacted]										
100%	16	[redacted]										
*change in OFF hours estimated as total OFF hours/16 hours												

Table 53. Mean utility values at baseline in all studies used by the company

OFF hours	M15-736		M20-098		M15-741		M15-737	
	Frequency (n=[redacted])	Mean (SD)	Frequency (n=[redacted])	Mean (SD)	Frequency (n=[redacted])	Mean (SD)	Frequency (n=[redacted])	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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Finally, after clarification the company provided the age adjustment in the model using Ara and Brazier, as per the EAG's request.[38] The results using the EAG-preferred source are reported in Section 6.3 and 6.4 of the EAG report.

4.2.10.2 Disutilities used in the model

The disutilities associated with adverse events in the model are reported in Table 62 of the CS.

4.2.11 Resource use and costs

4.2.11.1 Drug acquisition costs

The drug acquisition costs for foslevodopa-foscarbidopa and LCIG used by the company are shown in Table 54. Foslevodopa-foscarbidopa is administered as a continuous subcutaneous infusion, 24 hours/day. The recommended starting infusion rate of foslevodopa-foscarbidopa is determined by converting the daytime levodopa intake to levodopa equivalents and then increasing it to account for a 24-hour administration. The CS states that the dose may be adjusted to reach a clinical

response that maximises the functional ON time and minimises the number and duration of OFF episodes and ON episodes with troublesome dyskinesia. The maximum recommended daily dose of foslevodopa-foscarbidopa is 6000 mg (or 25 mL of foslevodopa-foscarbidopa per day, equivalent to approximately 4260 mg of levodopa per day). If enabled by their healthcare professional, patients may self-administer an extra dose to manage acute OFF symptoms experienced during continuous infusion. Foslevodopa-foscarbidopa and LCIG have a patient access scheme (PAS) as reported in Table 54.

Table 54. Drug acquisition costs for foslevodopa-foscarbidopa and LCIG with PASs included

Drug	Costs per package (£)	Units per package	List price per unit (£)	Net price per unit (£)	Source
Foslevodopa-foscarbidopa	[redacted]	7 units of 10ml doses	[redacted]	[redacted]	AbbVie
LCIG	539.00	7 units of 10ml doses	77.00	[redacted]	AbbVie

BNF: British National Formulary; LCIG: levodopa-carbidopa intestinal gel; NHS: National Health Service.

The basket of treatments and respective costs composing BMT are shown in Table 66 of the CS. The company reports using data from 700 patients on BMT from the Adelphi data to estimate the proportion of treatments (and respective doses) composing BMT. The Adelphi study, a real-world study commissioned by the company, collected 3 years of data on costs and quality of life data for PD patients across different countries. During clarification the company confirmed that only UK data from the study were used in the estimation of costs.

The unit acquisition costs for the basket of drugs included in the BMT arm were primarily sourced from the British National Formulary (BNF). Some of the drugs included in the BMT basket are subject to commercial arrangement discounts. Results including these discounts are provided in a confidential appendix to this EAG report.

The company did not model wastage as part of their base case analysis; however, it included scenario analyses where a percentage (5% and 10%) of wastage of vials for LCIG, due to unused (i.e., non-administered) medication was considered. The company reported that wastage is only applicable to LCIG as the infusion needs to be stopped overnight, in comparison with foslevodopa-foscarbidopa which is a 24-hour continuous infusion.

The total drug acquisition costs per three months (excluding wastage) for the intervention and comparators are shown in Table 55.

Table 55. Summary of drug costs per patient per three months

Drug	Costs per three months, list price (£)
Foslevodopa-foscarbidopa	[redacted]
BMT (best medical therapy)	428
LCIG (levodopa-carbidopa intestinal gel)	[redacted]

4.2.11.2 Drug management costs

The company also included management costs associated with treatment in the model (unit costs provided in Table 72 of the CS and frequency of resource use provided in Table 73). Costs were sourced from the NICE guideline [NG71],[39] care guidelines from the Wirral University Teaching Hospital, [40] and a previous cost-effectiveness study by Chaudhuri *et al.*[14]

The treatment management cost was assumed to be the same for all treatment arms (£276 for 3 months of treatment in the first year of treatment and £89 for 3 months of treatment from the second year of treatment onwards), with the exception of an additional cost of PEG tube removal for patients who discontinued LCIG.

4.2.11.3 Adjunctive therapies and administration costs

The company estimated adjunctive costs for LCIG based on the 2017-2019 Adelphi data, amounting to [redacted]. Details for the proportion and doses of adjunctive therapies are given in Table 68 of the CS. The company suggested adjunctive treatments would be given at night for LCIG patients to manage symptoms while the pump is off. However, since foslevodopa-foscarbidopa is continuously administered, adjunctive treatments are considered to not be needed.

The resource use and proportion of patients requiring administration costs in the LCIG and foslevodopa-foscarbidopa arms are shown in Table 56. The CS reports that the administration costs are based on the NICE guideline [NG71],[39] trial data from M15-741, and the cost-effectiveness study by Chaudhuri *et al.*[14] Administration costs were included as one-off costs at the start of the first model cycle, and amounted to £[redacted] for foslevodopa-foscarbidopa and £5,960 for LCIG.

Table 56. Treatment-specific quantities and proportion of patients to which treatment administration cost apply

Drug	Quantity		Proportion of patients (%)		Unit cost (£)	Source
	Foslevodopa-foscarbidopa	LCIG	Foslevodopa-foscarbidopa	LCIG		

NG tube insertion	N/A	1	N/A	80	1,464	NHS National Cost Collection data DRG code FF05Z [41]
Cost per treatment	-	£1,464	-	-	-	-
PEG tube insertion	N/A	1	N/A	100	1,116	NHS National Cost Collection data DRG code FE12A [41]
Cost per treatment	-	£1,116	-	-	-	-
Titration and monitoring (1 day)	[redacted]	5	[redacted]	100	726.60	Chaudhuri et al.,[14] inflated to 2021 costs
Cost per treatment	[redacted]	£3,633	[redacted]	-	-	-
Total cost	[redacted]	£5,960	[redacted]	-	-	-

Abbreviations: LCIG: levodopa-carbidopa intestinal gel; N/A: not applicable; NG: nasogastric; PEG: percutaneous endoscopic gastrostomy.

4.2.11.4 EAG comment

The model assumes a daily dose of 10 mL of foslevodopa-foscarbidopa throughout the entire time horizon of the analysis, nonetheless, patients in the M15-736 received a mean of [redacted] per day during the optimisation phase of the study (initial 4 weeks) and [redacted] per day during the remaining 8 weeks of the study. Therefore, the EAG replaced the dose assumed in the first cycle of treatment and subsequent ones in the model by the dose observed in the study. Changing the dose of foslevodopa-foscarbidopa in the model to reflect that received in M15-736 increased the costs associated with treatment by £2,139, while the ICER for foslevodopa-foscarbidopa vs BMT remained dominant; and the ICER against LCIG decreased to [redacted] (foslevodopa-foscarbidopa remained less costly and less effective than LCIG).

During clarification, the EAG requested that the company included a scenario analysis where wastage, as well as adjunctive therapies associated with foslevodopa-foscarbidopa were included in the model as clinical expert opinion provided to the EAG reflected that wastage (and thus the need for adjunctive therapies) is associated with the individualised titrated maintenance dose of treatment. The company did not undertake the scenarios requested by the EAG. During clarification, the EAG also asked that the company explain if treatment initiation with foslevodopa-foscarbidopa will take place in the hospital setting, which the company confirmed to be the case. In response to

the EAG request, the company added that initial treatment initiation costs in the hospital were already considered in the model as [redacted] hospital visits at a unit cost of £727 were included in the administration cost of foslevodopa-foscarbidopa (Table 56).

The EAG has several issues relating to the estimation of treatment administration and management costs in the model:

1. It is unclear to the EAG how the £727 cost was estimated given that it was taken from Chaudhuri *et al*., where no cost code was specified, and where the cost was categorised as the daily cost in the total of 5 days of "*titration and monitoring*".[14] Given that clinical expert opinion provided to the EAG was that LCIG patients require a day case to insert the PEG tube, followed by 5 days in-hospital for monitoring of dopamine levels, the EAG assumes that the £727 cost from Chaudhuri *et al*., reflects a daily cost of inpatient stay, as opposed to hospital visits as stated by the company.

2. Therefore, the administration costs for LCIG are likely to be overestimated as the company costed five days at a £727 each, in addition to the inpatient stay cost of inserting a PEG tube (£1,116, cost code FE12A), which reflects a short hospital stay, leading to a total cost of £4,789. Furthermore, the company added the cost of a NG tube insertion (£1,464) which the EAG's clinical experts advised no longer occurs in the UK. Nonetheless, during clarification, the company included a scenario analysis removing the cost of a NG tube insertion from the model.

   The EAG preference, is therefore, to use the cost associated with administering LCIG included in the 2016 NICE guideline for PD (NG71), updated to 2021 costs, amounting to a total of £2,929.[39] This includes PEG tube insertion resource use represented by HRG FZ93A "*elective inpatient endoscopic Insertion of Gastrostomy Tube, 19 years and over*" weighted by the proportion of patients who had the procedure as a day case (48%) and as an inpatient stay (62%), and an additional 5-day stay estimated as excess bed days (HRG FZ71) at £306.43 per day. Changing the administration costs of LCIG in the model decreased the costs associated with treatment by approximately £3,000, while the ICER for foslevodopa-foscarbidopa vs LCIG decreased to [redacted] (foslevodopa-foscarbidopa remained less costly and less effective than LCIG).

The treatment management costs associated with LCIG are also likely to be overestimated as the company included the cost of PEG tube removal for patients who discontinued LCIG, which was based on a day case cost for inserting a PEG tube (cost code FE12A) and amounted to £718. The EAG is unclear why the company assumed that the cost of removing the PEG tube would be the same as the cost of inserting the tube, when in the NICE guidelines for PD (NG71) removal of PEG tube was assumed to require a gastroenterology non-consultant led outpatient appointment, costing £110 (price updated from 2016 to 2021). Therefore, the EAG replaced the cost of PEG tube removal in the model by £110. Changing this parameter in the model decreased the costs associated with treatment with LCIG by approximately £3,500, while the ICER for foslevodopa-foscarbidopa vs LCIG decreased to [redacted] (foslevodopa-foscarbidopa remained less costly and less effective than LCIG).

3. Lack of clarity around the administration costs of foslevodopa-foscarbidopa: given the lack of clarity around the hospital day cost of £727, and the company's explanation that foslevodopa-foscarbidopa is intended to be initiated in hospital with four following hospital visits, the EAG notes that it is possible that treatment administration costs associated with foslevodopa-foscarbidopa are overestimated in the model. The EAG's clinical experts advised that treatment with foslevodopa-foscarbidopa was expected to require one outpatient visit.

Therefore, the EAG recommends that during TE the company:

1. Clarifies the use of the £727 daily cost and if this reflects a hospital daily stay.
2. Clarifies the resource use needed, and the setting required to initiate treatment with foslevodopa-foscarbidopa.

4.2.11.5 Health state costs

The company estimated a cost associated with each OFF state in the model. In order to estimate health state specific resource utilisation, the company fitted regression models to resource use data from the Adelphi study. The resource use included in the health state cost estimates consisted of:

- Hospitalisations,

- A&E visits,
- GP appointments,
- Consultant appointments,
- PD nurse appointments,
- Scans (computerised tomography [CT]; functional magnetic resonance imaging [fMRI]; and dopamine transporter [DaT] scans),
- Respite care,
- Professional care (nursing home staff, physiotherapist, social worker and home help).

The company estimated the total resource use in two steps:

- Estimating the proportion of patients using the specific resource in each OFF state,
- Among users, estimating the frequency of resource use.

For step 1, binary probit models were fitted to the Adelphi data. For step 2, Poisson models were fitted. The resource use related to consultant appointments and professional care were estimated by using an inverse Gaussian model fitted to the observed Adelphi data.

Multiplying the results from step 1 with the results from step 2 (Table 76, Table 77, and Table 78 of the CS) and the unit specific cost (reported in Table 75 of the CS) resulted in the total health state costs used for each OFF state in the model (Table 57). Total health state costs differ substantially between the different health states, ranging from [redacted] for OFF 0 to [redacted] for OFF 16.

Table 57. Total health state specific costs included in the model

Health state	Total yearly costs (£)
OFF 0	[redacted]
OFF 1	[redacted]
OFF2	[redacted]
OFF 3	[redacted]
OFF 4	[redacted]
OFF 5	[redacted]
OFF 6	[redacted]
OFF 7	[redacted]
OFF 8	[redacted]
OFF 9	[redacted]
OFF 10	[redacted]
OFF 11	[redacted]

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

4.2.11.6 EAG comment

During clarification, the EAG asked that the company confirm if the Adelphi data used in the cost analysis was restricted to UK patients with advanced PD (and that the early stage and intermediate stage patients with PD included in the study had not been included in the company's analysis). The company confirmed that only UK data from the study were used in the estimation of costs; however, it also clarified that the data used was not restricted to patients with advanced PD. The company reported that the decision to include early and intermediate stage patients with PD was made due to the limited sample size of patients in the Adelphi dataset who presented with advanced PD ([redacted]) in relation to the wider cohort ([redacted]).

The EAG does not consider that the sample size for patients with advanced PD ([redacted]) was small as it included nearly [redacted] as many patients as the treatment arm for M15-736. Crucially, including patients with early and intermediate PD misrepresents the population in the foslevodopa-foscarbidopa SmPC, which restricts the use of the drug to the advanced PD population. The Adelphi study shows that even though in general patients with advanced PD required a higher use of resources, this was not the case for all resources. For example, [redacted] of patients with early-stage PD required a DaT scan, whereas [redacted] of patients with advanced PD required the same scan. Another example is home help, where [redacted] patients with early and intermediate PD, respectively, required home help, whereas [redacted] patients with advanced PD required home help, but instead required higher nursing home staff. By combining all patients in the cost analysis, the company likely overestimated the total cost of some resources.

During clarification, the EAG also requested that the company discussed the comparability of the Adelphi population with the population in M15-736. The company reported that patients in the Adelphi study were slightly older, with a higher proportion of female patients with a slightly lower BMI. The company also noted that time since diagnosis was longer in the M15-736 than in the

Adelphi study. The EAG is not surprised that time since diagnosis was shorter in the Adelphi population given that the company used the study population with early and intermediate PD.

The EAG requested that in case the company had included patients with early and intermediate PD from the Adelphi study, an analysis was re-run where only patients with advanced PD were included in the estimation of costs. The company refused to conduct such analysis due to the sample size of this population. However, given the reasonably robust sample size of patients with advanced PD in the Adelphi study, and the likely overestimation of resource use in the company's base case approach, the EAG recommends that the company reconsider removing patients with early and intermediate PD.

The EAG also asked the company why a regression analysis was necessary to estimate resource use in the model given that the Adelphi data reported the proportion of patients utilising resources, together with mean time of visits and/or mean duration of episodes for 1 year. The company reported that regression analysis was needed due to a lack of available data for several OFF states in the model (Table 58). As discussed in Section 4.2.4, the EAG notes that the lack of data for each hour of OFF time is a problem arising from the company's choice of modelling approach, which requires a granularity that might not be appropriate to capture the cost-effectiveness of foslevodopa-foscarbidopa. Similar to the issue discussed in the utility analysis (Section 4.2.10.1), aggregating changes in OFF hours by categories could provide more robust sample sizes and therefore, allow the company to use observed cost data instead of having to rely on regression models.

During clarification, the EAG requested that the company:

1. Used the observed data from the Adelphi study, instead of the fitted data, using the UK population with advanced PD in the study in a scenario analysis
2. Reported the resource use, per OFF state, for each cost item included in the analysis, observed in the UK population with advanced PD in the study in a scenario analysis

The company did not provide results for any of the EAG's requests. Instead, the company provided the observed data from the study for the entire UK population.

Table 58. Number of observations by OFF state in Adelphi data, UK patients

OFF state	Number of patients
0 OFF hours	[redacted]
1 OFF hours	[redacted]

2 OFF hours	[redacted]
3 OFF hours	[redacted]
4 OFF hours	[redacted]
5 OFF hours	[redacted]
6 OFF hours	[redacted]
7 OFF hours	[redacted]
8 OFF hours	[redacted]
9 OFF hours	[redacted]
10 OFF hours	[redacted]

The EAG notes that according to the Adelphi data provided by the company (and according to Table 58) there were no observations in the study for patients with more than 10 hours of OFF time. The company did not provide any explanation for this; however, the EAG concludes that the reason for this is that in the Adelphi study there were no patients with more than 10 hours of OFF time. This is consistent with the number of patients in the M15 studies for which quality of life data was available, where a very small number of patients had more than 10 hours of OFF time. This means that all the costs estimated for the 11+ OFF states were based on fitted data, rather than observed data.

As reported in Table 57, the costs estimated for the 11+ OFF states (based on fitted data) increase substantially compared to the costs estimated for the 10 OFF state, with the total costs for OFF state 16 being 50% higher than that estimated for the 10 OFF state ([redacted] vs [redacted]). The EAG investigated what were the highest contributors to the total health state costs and concluded that the highest contributor is the professional care cost, followed by hospital costs and by respite care. Subsequently, the EAG investigated the estimated professional care and hospitalisation and respite costs in the model in comparison to the observed costs in the Adelphi UK population used to estimate the same costs.

As shown in Table 59, the costs of professional care estimated by the company result in a considerable overestimation of the professional care costs observed in the Adelphi study for the corresponding population for all OFF states (with the exception of OFF 0 and OFF 1). Furthermore, the EAG is unclear why the observed data provided by the company (Table 47 of the clarification response) was based only on [redacted] patients, when the Adelphi study provided data for [redacted] patients requiring professional care when the entire UK population was considered.

The same is observed in Table 60, where the costs of hospitalisation estimated by the company overestimate the hospitalisation costs observed in the Adelphi study for the corresponding population for all OFF states (with the exception of OFF 0 and OFF 1). Furthermore, the EAG is unclear why the observed data provided by the company (Table 41 of the clarification response) was based on [redacted] patients, when the Adelphi study only provided data for [redacted] patients requiring hospitalisation when the entire UK population was considered.

The EAG also notes the same issue of overestimation of costs for respite care, where the estimated proportion of patients needing respite care in the model was considerably higher than that observed in the Adelphi population (Table 61). The EAG notes that in the Adelphi study, [redacted] of patients in the OFF states 6, 7, and 10 needed respite care, whereas the model estimated that 23%, 28%, and 49% of patients, respectively, needed respite care in these states, demonstrating the poor fit of the company's regression models to the observed data.

Overall, the EAG considers that the company's approach to estimating health state costs in the model is flawed and leads to an overestimation of costs. The regression analysis used by the company does not provide an accurate prediction of the health state costs for which there was observed data. Professional care and hospitalisation costs (the key drivers of health state costs) are overestimated for every OFF state (with the exception of OFF 0 and OFF 1) when compared to the observed Adelphi data used to estimate the respective costs in the model. Furthermore, the EAG notes that the overestimation in costs for the last available OFF state (OFF 10) carries on until the OFF 16 state, for which there were no data available in the Adelphi study.

Due to time constraints, the EAG did not have time to conduct the same investigation into all the other resource use composing health state costs in the model (A&E visits; GP and consultant appointments; PD nurse appointments; and scans); however, it anticipates that similar issues will be present in these analyses.

As an exploratory analysis, the EAG replaced the hospitalisation; the professional care; and the respite care costs estimated by the company by the observed costs in the Adelphi study. The EAG caveats this analysis by the fact that the entire UK population from the Adelphi study was used (instead of patients with advanced PD only). For the OFF states with no observations available, the EAG assumed the same cost as that of the previous OFF sate (Table 62).

Results of the EAG's exploratory analysis increased the ICER for foslevodopa-foscarbidopa vs BMT from dominant (in favour of foslevodopa-foscarbidopa) to [redacted] with BMT being less costly than foslevodopa-foscarbidopa and generating less QALYs. For the comparison of foslevodopa-foscarbidopa with LCIG, the company's base case ICER of [redacted] (with LCIG being more costly than foslevodopa-foscarbidopa but generating higher QALYs) increased to [redacted] (with LCIG continuing to be more costly than foslevodopa-foscarbidopa and generating higher QALYs).

Table 59. Professional care costs (observed vs estimated)

Health state	Total yearly costs in the model	Professional care (% of total cost)	Professional care cost estimated in the model	% patients* in the model	% patients* in Adelphi	Time^ in the model	Time^ in Adelphi	Total yearly costs in Adelphi	Difference
OFF 0	[redacted]	71.7%	£2,496	9%	[redacted]	41	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	75.8%	£4,765	16%	[redacted]	45	[redacted]	[redacted]	[redacted]
OFF 2	[redacted]	78.6%	£8,255	26%	[redacted]	49	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	80.3%	£13,057	37%	[redacted]	53	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	81.3%	£18,991	50%	[redacted]	57	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	81.8%	£25,608	64%	[redacted]	61	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	81.7%	£32,325	75%	[redacted]	65	[redacted]	[redacted]	[redacted]
OFF 7	[redacted]	81.2%	£38,599	84%	[redacted]	69	[redacted]	[redacted]	[redacted]
OFF 8	[redacted]	80.2%	£44,096	91%	-	73	-	-	-
OFF 9	[redacted]	79.0%	£48,731	95%	-	77	-	-	-
OFF 10	[redacted]	77.4%	£52,618	98%	[redacted]	81	[redacted]	[redacted]	[redacted]
OFF 11	[redacted]	75.8%	£53,428	99%	-	85	-	-	-
OFF 12	[redacted]	74.2%	£58,982	100%	-	90	-	-	-
OFF 13	[redacted]	72.6%	£61,818	100%	-	94	-	-	-
OFF 14	[redacted]	71.1%	£64,570	100%	-	98	-	-	-
OFF 15	[redacted]	69.8%	£67,286	100%	-	102	-	-	-
OFF 16	[redacted]	68.7%	£69,990	100%	-	106	-	-	-

*proportion of patients using professional care within each OFF state (in the model vs observed).
^time (hours per week) of used professional care (in the model vs observed)
Observed values were taken from Table 47 of the company response to clarification.

Table 60. Hospitalisation costs (observed vs estimated)

Health state	Total yearly costs in the model	Hospital (% of total cost)	Hospital costs estimated in the model	% patients * in the model	% patients * in Adelphi	Hospitalisations in the model	Hospitalisations in Adelphi	Total yearly costs in Adelphi	Difference
OFF 0	[redacted]	16.1%	£559	11%	[redacted]	1.6	[redacted]	[redacted]	[redacted]

OFF 1	[redacted]	14.4%	£907	18%	[redacted]	1.6	[redacted]	[redacted]	[redacted]
OFF 2	[redacted]	12.9%	£1,356	28%	[redacted]	1.5	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	11.6%	£1,878	39%	[redacted]	1.5	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	10.4%	£2,423	52%	[redacted]	1.5	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	9.4%	£2,932	64%	[redacted]	1.4	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	8.5%	£3,352	75%	[redacted]	1.4	[redacted]	[redacted]	[redacted]
OFF 7	[redacted]	7.7%	£3,654	84%	[redacted]	1.4	[redacted]	[redacted]	[redacted]
OFF 8	[redacted]	7.0%	£3,833	91%	-	1.3	-	-	-
OFF 9	[redacted]	6.3%	£3,907	95%	-	1.3	-	-	-
OFF 10	[redacted]	5.7%	£3,901	97%	[redacted]	1.3	[redacted]	[redacted]	[redacted]
OFF 11	[redacted]	5.2%	£3,669	99%	-	1.2	-	-	-
OFF 12	[redacted]	4.7%	£3,756	100%	-	1.2	-	-	-
OFF 13	[redacted]	4.3%	£3,654	100%	-	1.1	-	-	-
OFF 14	[redacted]	3.9%	£3,545	100%	-	1.1	-	-	-
OFF 15	[redacted]	3.6%	£3,433	100%	-	1.1	-	-	-
OFF 16	[redacted]	3.3%	£3,320	100%	-	1.0	-	-	-

*proportion of patients using professional care within each OFF state (in the model vs observed)
Observed values were taken from Table 41 of the company response to clarification.

Table 61. Respite costs (observed vs estimated)

Health state	Respite care costs estimated in the model	% patients* in the model	% patients* in Adelphi	Total yearly costs in Adelphi	Difference
OFF 0	£141.92	3%	[redacted]	[redacted]	[redacted]
OFF 1	£293.20	5%	[redacted]	[redacted]	[redacted]
OFF 2	£542.27	7%	[redacted]	[redacted]	[redacted]
OFF 3	£928.02	10%	[redacted]	[redacted]	[redacted]
OFF 4	£1,494.60	13%	[redacted]	[redacted]	[redacted]
OFF 5	£2,287.67	17%	[redacted]	[redacted]	[redacted]
OFF 6	£3,349.94	23%	[redacted]	[redacted]	[redacted]
OFF 7	£4,715.01	28%	[redacted]	[redacted]	[redacted]
OFF 8	£6,401.84	35%	-	-	-
OFF 9	£8,410.36	42%	-	-	-
OFF 10	£10,718.89	49%	[redacted]	[redacted]	[redacted]
OFF 11	£12,682.47	57%	-	-	-
OFF 12	£16,049.34	64%	-	-	-
OFF 13	£18,940.95	70%	-	-	-
OFF 14	£21,886.02	76%	-	-	-
OFF 15	£24,814.86	82%	-	-	-

OFF 16	£27,669.02	86%	-	-	-

Table 62: 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
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

In conclusion, the EAG considers that the company's approach to estimating health state costs in the model is flawed and leads to an overestimation of costs. The results of the regression analyses used by the company to estimate health state costs demonstrate a poor fit and an overestimation of the costs observed in the Adelphi study. The EAG disagrees with the company's assessment that a regression analysis was needed due to a lack of available data for several OFF states in the model and notes that the lack of data for each hour of OFF time is more likely to be a problem arising from the company's choice of modelling approach.

The EAG also disagrees with the company's decision to include patients with early and intermediate PD in the analysis and notes that there is a reasonably robust sample size of patients with advanced PD in the Adelphi study. Furthermore, including patients with early and intermediate PD misrepresents the population in the foslevodopa-foscarbidopa SmPC , which restricts the use of the drug to the advanced PD population.

Therefore, the EAG recommends that during TE the company:

1. Explains the differences identified by the EAG in the sample size of patients reported for hospitalisation and professional care costs in the company's reply to clarification questions and the respective number of patients reported in the Adelphi study;
2. Uses the observed data from the Adelphi study, instead of the fitted data;
3. Uses the UK population with advanced PD only;
4. Investigates the possibility of analysing resource use by categories of OFF hours - for example, the Adelphi data suggests that it would be more robust to assume the same resource use for 10+ OFF hours.

4.2.11.7 Adverse event costs

The costs associated with adverse events in the model are reported in Table 80 of the CS. The EAG is generally satisfied with the cost estimates, however, as discussed in Section 4.2.8, the EAG is concerned the impact of troublesome dyskinesia is not currently captured in the model.

5 Cost effectiveness results

5.1.1 Company's base case cost effectiveness results

During the clarification stage, the company revised their base case analyses. The changes made by the company include:

- Duration of AEs have been updated in line with data from M15-736;
- Changes to dyskinesia values;
    - The incidence of dyskinesia in the foslevodopa-foscarbidopa arm of the model has been corrected from [redacted] to [redacted];
    - The disutility for dyskinesia has been updated from 0.076 to 0.07;
    - The probability of dyskinesia for LCIG has been corrected from 0.07% to 7.0%;
- The drug acquisition costs for Levodopa + carbidopa (e.g. sinemet) 110 mg, pramipexole 0.7 mg and rasagiline 1mg and ropinirole 2mg (84 pack) have been updated to eMIT prices;
- Costs for PET, SPECT and MRI scans have been removed from the health state-related costs;
- The proportion of female patients has been corrected from [redacted] to [redacted], in line with the correct value from the M15-736 trial;
- Health state costs were previously mistakenly omitted from PSA, they are now included.

All results in this section include these changes. The company originally only provided probabilistic with-PAS base case results but at the EAGs request in CQs both probabilistic and deterministic with-PAS results have been provided.

In the company's probabilistic and deterministic base case, foslevodopa-foscarbidopa is associated with lower costs and lower quality-adjusted life years (QALYs) compared to levodopa-carbidopa intestinal gel (LCIG), resulting in a bottom left quadrant incremental cost-effectiveness ratio (ICER) of [redacted] and [redacted] costs saved per QALY forgone. The reason the PSA results significantly differed from the deterministic base case results was due to an error discussed in further detail in section 6.1. Foslevodopa-foscarbidopa is dominant versus Best Medical Therapy (BMT). Probabilistic base case results are given in Table 63 and deterministic base case results are in Table 64.

Table 63. Company's probabilistic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	-	5.22	-	-	-	-
LCIG	[redacted]	-	5.31	[redacted]	-	−0.09	[redacted]
BMT	[redacted]	-	4.53	[redacted]	-	0.70	Foslevodopa-foscarbidopa dominant

[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 64. Company's deterministic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	9.072	5.327	-	-	-	-
LCIG	[redacted]	9.072	5.430	[redacted]	-	−0.10	[redacted]
BMT	[redacted]	9.072	4.527	[redacted]	-	0.80	Foslevodopa-foscarbidopa dominant

[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 company used the probabilistic sensitivity analysis (PSA) to provide a base case that accounts for the joint parameter uncertainty around the deterministic results. Probabilities and proportions were generally varied using a beta distribution, except for transition probabilities which were varied with

Dirichlet, due to the values interdependence. Costs and frequencies were varied with the gamma distribution. Baseline characteristics were not varied as part of the PSA.

The PSA results provided by the company, arising from 1,000 simulations, was provided in combination with a PSA scatter plot shown in Figure 15 and CEAC shown in Figure 16. The inclusion of health state costs in the PSA following CQs has resulted in a significant increase in the variability of incremental costs for BMT, as expected. Most simulations for LCIG lie in the south-west quadrant where foslevodopa-foscarbidopa is cheaper and less effective, whilst all simulations for BMT lie in the south-east quadrant where foslevodopa-foscarbidopa is dominant. According to the CEACs, foslevodopa-foscarbidopa is the cost-effective option at all tested WTP thresholds.

Figure 15. cost effectiveness plane for foslevodopa-foscarbidopa versus comparators, PAS price (copy of figure 7 in CQ response document)

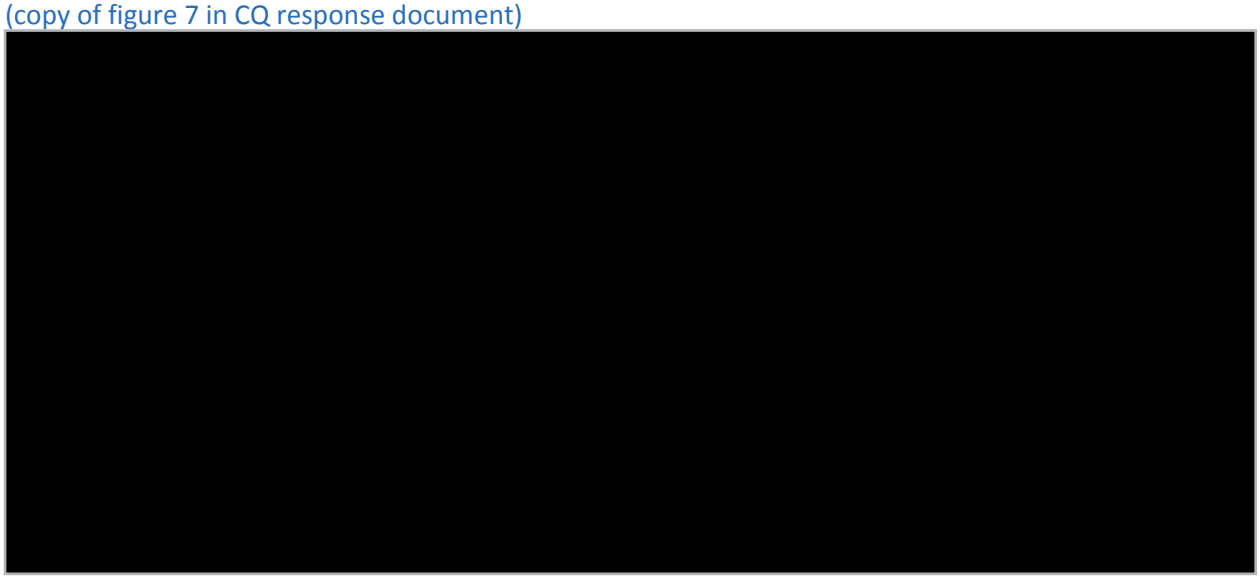


Figure 16. cost effectiveness acceptability curve for foslevodopa-foscarbidopa versus comparators, PAS price (copy of figure 8 in CQ response document)

The EAG re-ran the company's PSA, to validate the results produced by the company, these ICERs are reported in Table 65. The EAG's PSA had very similar results to the company. The EAG notes that there is a significant difference between the costs and QALYs for LCIG and foslevodopa-foscarbidopa between the PSA and the deterministic results. The difference in ICER may be partly driven by the impact of the risk ratio which appears to result in lower incremental costs and higher incremental QALYs vs LCIG when varied, as demonstrated in section 5.1.2.

Table 65. Company's probabilistic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	-	5.22	-	-	-	-
LCIG	[redacted]	-	5.31	[redacted]	-	−0.09	[redacted]
BMT	[redacted]	-	4.52	[redacted]	-	0.70	Foslevodopa-foscarbidopa dominant

[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.

5.1.2 Company's deterministic sensitivity analyses

The company carried out OWSAs to assess the impact of varying the key parameters between ±20% of the mean value or, if SEs were available, 95% CIs were used. The 10 most influential parameters on NHB resulting from the OWSA, comparing foslevodopa-foscarbidopa with LCIG and BMT, are displayed in the tornado diagrams; Figure 17 and Figure 18.

Figure 17. Updated tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus LCIG, PAS price (reproduced from figure 9 in CQ response document)

ABBV-951 = foslevodopa-foscarbidopa. Duodopa = LCIG

Abbreviations: LCIG, levodopa-carbidopa intestinal gel; NHB: net health benefit; NMA, network meta-analysis; PAS, patient access scheme; PEG, percutaneous endoscopic gastrostomy; RR, relative risk.

Figure 18. Updated tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus BMT, PAS price (reproduced from figure 10 in CQ response document)

Abbreviations: BMT, best medical therapy; NHB, net health benefit; PAS, patient access scheme.

5.1.3 Company's scenario analyses

The company undertook scenario analysis to explore the effect of utilising alternative assumptions for key model parameters. The results for these analyses are displayed in Table 69. BMT remained dominated across all of these scenarios. As LCIG is in the SW quadrant, a decrease in ICER represents

a move towards results being less cost effective. The largest decrease in ICER came from using higher rates of discontinuation for the foslevodopa-foscarbidopa, sourced from alternative trial data. Several EAG scenarios were also provided as part of this table, following CQs. These are discussed in further detail in Section 6.3.

Table 66: Probabilistic scenario analyses cost effectiveness results, PAS price (copy of table 57 from CQs)

#	Description	Foslevodopa-foscarbidopa		LCIG				BMT			
		Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHBa (QALY)	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHBa (QALY)
Base case (probabilistic)		[redacted]	5.22	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
Model time horizon											
1	10 years	[redacted]	4.28	[redacted]	−0.07	[redacted]	[redacted]	[redacted]	0.60	Dominant	[redacted]
2	15 years	[redacted]	4.97	[redacted]	−0.08	[redacted]	[redacted]	[redacted]	0.68	Dominant	[redacted]
3	30 years	[redacted]	5.28	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
Wastage											
4	5% standard wastage for LCIG	[redacted]	5.23	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
5	10% standard wastage for LCIG	[redacted]	5.23	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
Foslevodopa-foscarbidopa and LCIG efficacy estimates											
6	Months 3-24: LOCF Months 24+: Natural history	[redacted]	5.15	[redacted]	−0.06	[redacted]	[redacted]	[redacted]	0.63	Dominant	[redacted]
Foslevodopa-foscarbidopa discontinuation rates											
7	Months 0-3: M15-736 Months 3-24: M15-741 and M15-737 (Full cohort)	[redacted]	5.14	[redacted]	−0.17	[redacted]	[redacted]	[redacted]	0.61	Dominant	[redacted]

#	Description	Foslevodopa-foscarbidopa		LCIG				BMT			
		Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHBa (QALY)	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHBa (QALY)
	Months 24+: "standard rate"										
8	Months 0-12: M15-741 (sample 1) Months 12-24: M15-737 Months 24+: "standard rate"	[redacted]	5.14	[redacted]	−0.17	[redacted]	[redacted]	[redacted]	0.62	Dominant	[redacted]
9	Months 0-12: M15—741 (full cohort) Months 12-24: M15-737 Months 24+: "standard rate"	[redacted]	5.18	[redacted]	−0.14	[redacted]	[redacted]	[redacted]	0.64	Dominant	[redacted]
Mortality rate											
10	Standard mortality rate	[redacted]	6.46	[redacted]	−0.11	[redacted]	[redacted]	[redacted]	0.84	Dominant	[redacted]
Baseline characteristics											
11	Baseline age 61.4 years (−5 from baseline)	[redacted]	5.88	[redacted]	−0.10	[redacted]	[redacted]	[redacted]	0.77	Dominant	[redacted]
12	Baseline age 71.4 years (+5 from baseline)	[redacted]	4.18	[redacted]	−0.07	[redacted]	[redacted]	[redacted]	0.57	Dominant	[redacted]
Carer disutilities											
13	Include carer disutilities	[redacted]	4.83	[redacted]	−0.11	[redacted]	[redacted]	[redacted]	0.93	Dominant	[redacted]
EAG clarification questions scenarios											
B6	6-month transition probabilities	[redacted]	5.22	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.69	Dominant	[redacted]

#	Description	Foslevodopa-foscarbidopa		LCIG				BMT			
		Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHBa (QALY)	Inc. costs (£)	Inc. QALYs	ICERs (£)	NHBa (QALY)
	for foslevodopa-foscarbidopa and LCIG during LOCF period										
B7a	Equal efficacy between foslevodopa-foscarbidopa and LCIG	[redacted]	5.23	[redacted]	−0.11	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
B19	Ara and Brazier[38] source for utility adjustment for age and gender	[redacted]	5.15	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.69	Dominant	[redacted]
B25	No patients receiving NG tube insertion	[redacted]	5.22	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]
B32	17% of patients receiving respite care	[redacted]	5.23	[redacted]	−0.09	[redacted]	[redacted]	[redacted]	0.70	Dominant	[redacted]

5.1.4 *Model validation and face validity check*

In the CS, the company stated that extensive technical verification was undertaken by an independent modelling team. This involved a detailed review of programming and extreme value testing. This was primarily done to ensure accuracy in calculations and programming logic.

The company also noted that their external expert's role in validating model assumptions throughout the development of the model and drafting of the company submission document. Furthermore, during clarifications the company, at the request of the EAG, validated the relative risk

approach against real data for LCIG. Although it led to slightly lower OFF hours by month 24 the gap difference between the model and real world data was small and the trend was as expected.

The EAG considers that the company's model validation and face validity checks of the model were generally extensive and robust.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The EAG identified three potential errors in the company's model. One is in the source for the dyskinesia AEs for LCIG. This appears to be based on the value for oral levodopa in patients with <5 years treatment experience and not LCIG. There are no alternative data for the EAG to utilise, although the company has access to trial data for LCIG which likely contains information for this input.

The second error was in the NMA where the company used observed mean for the M15-736 trial data and least square mean for DYSCOVER. To maintain consistency the EAG has updated the NMA using least square mean and applied the updated NMA results as a correction to the model. This was calculated using the fixed effects difference in decrease in OFF time between LCIG and foslevodopa-foscarbidopa found in Table 34. This was then applied to the companies RR calculation: [redacted]. Note, that the RR has gone from being above one to below one due to the updated NMA results showing LCIG to result in a greater reduction in OFF time. Results from using this updated RR are shown in Table 67.

Table 67. Company's deterministic base case results following corrected RR

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	-	5.33	-	-	-	-
LCIG	[redacted]	-	5.47	[redacted]	-	-0.14	[redacted]
BMT	[redacted]	-	4.53	[redacted]	-	0.80	Foslevodopa-foscarbidopa dominant

[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 third error was found in the application of the Dirichlet distribution in the probabilistic sensitivity analysis. The company's error was in column H of the "Inputs" worksheet for all transition probability PSA calculations. The result of this error was that variation in the stochastic value appeared to be untied to the mean value, effectively reducing the effectiveness of both LCIG and foslevodopa-foscarbidopa. Due to LCIG's higher effectiveness in the base case this resulted in making LCIG appear artificially less cost effective. Results of the corrected model can be seen in Table 68.

Table 68. Company's probabilistic base case results following corrected Dirichlet distribution

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	-	5.32	-	-	-	-
LCIG	[redacted]	-	5.43	[redacted]	-	-0.10	[redacted]
BMT	[redacted]	-	4.52	[redacted]	-	0.80	Foslevodopa-foscarbidopa dominant

[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.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

The company was asked to perform several scenarios during the clarification stage. The scenarios provided by the company include:

- Adjusting the transition probabilities sourced from the three-month trial data, during the LOCF period, so they fit the 6-month cycle length (see section 4.2.6.1);
- Assume no difference in efficacy between foslevodopa-foscarbidopa and LCIG (see section 4.2.6.2);
- Use Ara and Brazier, 2010[38] for age related utility (see section 4.2.10.1);
- Excluding the cost of NG tube insertion (see section 4.2.11.4);
- Assuming 17% of patients receive respite care (see section 4.2.11.6).

However, several scenarios requested by the EAG were not provided, these include:

- Patients can discontinue foslevodopa-foscarbidopa to LCIG;
- The initial distribution of patients by OFF state modelled with a distribution curve (i.e. zero-inflated negative binomial, beta-binomial, negative binomial, Poisson);
- Decrease the cycle length during the trial period to 1 month and use month to month data to inform transitions, using the final data between month 2 and 3 to inform the LOCF period;
- Fix health states for the LOCF period;
- Apply the trial comparator transition probabilities from M15-736 to the BMT arm and use the LOCF assumption for the following two cycles;

- Apply AE costs and disutilities for the model time horizon;
- Adjunctive therapies are used in conjunction with foslevodopa-foscarbidopa;
- Include wastage for foslevodopa-foscarbidopa;
- Include only UK patients with severe PD disease from the Adelphi study used for costs.

The EAG still considers that these scenarios warrant further exploration. Where possible, the EAG has attempted to construct and add these scenarios as part of or section 6.4.

6.3 EAG scenario analysis

Results of the EAG's probabilistic scenario analysis for the PAS price, based on the corrected model are given in Table 69. Using the direct health state resource use data had the most significant impact on the BMT ICER. This resulted in foslevodopa-foscarbidopa no longer being cost effective versus the treatment due to the dramatic reduction in costs for high OFF states associated with BMT. Making patients who discontinue treatment (either LCIG or foslevodopa-foscarbidopa) have equivalent outcomes to patients in the BMT arm had the most significant impact on the ICER versus LCIG, resulting in LCIG becoming dominant. This was as it significantly increased the reduction in efficacy caused by the additional discontinuations in the foslevodopa-foscarbidopa arm.

Table 69. Results of the EAG's scenario analyses

	Results per patient	Intervention	BMT	LCIG	Incremental value BMT	Incremental value LCIG
0	Company's corrected base case					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.33	4.53	5.47	0.80	-0.14
	ICER (£/QALY)				Dominant	[redacted]
1	No change in efficacy during the LOCF period					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.15	4.53	5.26	0.63	-0.11
	ICER (£/QALY)				Dominant	[redacted]
2	Use 736 discontinuations, 741 cohort 2 and 737					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.25	4.52	5.46	0.72	-0.22
	ICER (£/QALY)				Dominant	[redacted]
3	Turn off injection related AEs for BMT, injection related AEs continue for life for foslevodopa-foscarbidopa and LCIG recurring AEs adjusted by percentage of cohort on treatment					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.30	4.52	5.47	0.78	-0.17

	ICER (£/QALY)				Dominant	[redacted]
4	Foslevodopa-foscarbidopa dose as per trial					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.33	4.52	5.47	0.80	-0.14
	ICER (£/QALY)				Dominant	[redacted]
5	LCIG administration cost					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.33	4.53	5.47	0.80	-0.14
	ICER (£/QALY)				Dominant	[redacted]
6	LCIG tx management cost					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.33	4.53	5.47	0.80	-0.14
	ICER (£/QALY)				Dominant	[redacted]
7	Use direct data to inform resource use for health state cost					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.33	4.52	5.47	0.80	-0.14
	ICER (£/QALY)				[redacted]	[redacted]
8	Patients who discontinue have equivalent outcomes to natural disease progression arm					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.01	4.53	5.22	0.48	-0.21
	ICER (£/QALY)				Dominant	Dominated

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

6.4 EAG preferred assumptions

Table 70 summarises the EAG's preferred assumptions and the cumulative impact these assumptions have on the ICER. Table 71 and Table 72 provides the breakdown of costs and QALYs associated with the EAGs probabilistic and deterministic base case respectively. Foslevodopa-foscarbidopa is associated with lower costs and lower QALYs than the LCIG (i.e., a south-west quadrant ICER). Based WTP thresholds of £20,000 or £30,000 per QALY, foslevodopa-foscarbidopa would be considered cost-effective compared to LCIG as the ICER is above these WTP thresholds. However, compared to BMT, foslevodopa-foscarbidopa is associated with higher costs and lower QALYs and would not be considered cost effective based on the WTP threshold. This is in line with other literature as, of the four cost-effectiveness studies conducted from the UK perspective, three indicate that LCIG is not cost effective versus SOC/BMT.

Table 70. EAG's preferred model assumptions, probabilistic and deterministic results

Preferred assumption	Section in EAG report	Cumulative ICER vs LCIG probabilistic (£/QALY)	Cumulative ICER vs LCIG deterministic (£/QALY)	Cumulative ICER vs BMT probabilistic (£/QALY)	Cumulative ICER vs BMT deterministic (£/QALY)
Company base case	5.1.2	[redacted]	[redacted]	Dominant	Dominant
EAG corrections					
Corrected NMA results	6.1 and 3.4	[redacted]	[redacted]	Dominant	Dominant
Corrected PSA Dirichlet distribution	6.1	[redacted]	[redacted]	Dominant	Dominant
Company provided scenarios					
Change utility source to Ara and Brazier	4.2.10	[redacted]	[redacted]	Dominant	Dominant
Efficacy between foslevodopa-foscarbidopa and LCIG assumed equal	4.2.6.2	[redacted]	[redacted]	Dominant	Dominant
Adjust TP to match cycle length change from 3 months to 6	4.2.6.1	[redacted]	[redacted]	Dominant	Dominant
Exclusion of NG tube insertion cost	4.2.11.4	[redacted]	[redacted]	Dominant	Dominant
EAG additional preferred scenarios					
No change in efficacy during the LOCF period	4.2.6.4	[redacted]	[redacted]	Dominant	Dominant
Use 736 discontinuations, 741 cohort 2 and 737	4.2.7.1	[redacted]	[redacted]	Dominant	Dominant
Turn off injection related AEs for BMT	4.2.8.1	[redacted]	[redacted]	Dominant	Dominant
Injection related AEs continue for life/time horizon for foslevodopa-foscarbidopa	4.2.8.1	[redacted]	[redacted]	Dominant	Dominant
Adjust LCIG recurring AEs by the percentage of cohort on treatment	4.2.8.1	[redacted]	[redacted]	Dominant	Dominant
Foslevodopa-foscarbidopa dose as per trial	4.2.11.1	[redacted]	[redacted]	Dominant	Dominant
LCIG administration cost	4.2.11.4	[redacted]	[redacted]	Dominant	Dominant

LCIG tx management costs	4.2.11.4	[redacted]	[redacted]	Dominant	Dominant
Health state costs	4.2.11.6	[redacted]	[redacted]	[redacted]	[redacted]
Patients who discontinue have equivalent outcomes to natural disease progression arm	4.2.4.3	[redacted]	[redacted]	[redacted]	[redacted]

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

Abbreviations: EAG, evidence review group; ICER, incremental cost-effectiveness ratio; NG, nasogastric; QALY, quality adjusted life year; TP, transition probability;

Table 71. EAG's probabilistic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	-	4.73	-	-	-	-
LCIG	[redacted]	-	4.96	[redacted]	-	-0.23	[redacted]
BMT	[redacted]	-	4.46	[redacted]	-	0.27	[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 72. EAG's deterministic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	9.072	4.734	-	-	-	-
LCIG	[redacted]	9.072	4.971	[redacted]	-	-0.24	[redacted]
BMT	[redacted]	9.072	4.460	[redacted]	-	0.27	[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

6.5 Conclusions of the cost effectiveness sections

The company submitted a cost-utility analysis comparing foslevodopa-foscarbidopa to BMT and LCIG for the advanced treatment of adults with Parkinson's disease in patients responsive to levodopa, with symptoms not adequately controlled by their current medical therapy and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control. Partly

because of this narrow treatment population, the submission is driven by a large number of strong assumptions about the nature of this condition, made in absence of data.

There are no previous NICE appraisals in this area, so the company has constructed a *de novo* state-transition model in Excel consisting of 17 live health states. The 17 health states consist of daily OFF time normalised to a 16-hour day in cumulative 1-hour increments, from 0h OFF time to 16h OFF time. While choosing to represent OFF time at such a granular level could allow the model to capture changes in patient health more precisely, the reality is both the available utility data and resource use data does not show significant changes at each hour increment of OFF time, resulting in the company needing to fit linear regressions to these data, to avoid situations where patients in lower OFF states results in higher resource use and lower utility. In addition, the size and distribution of the trial population meant that 8 out of 17 of the OFF states have no data to inform them and so, based on this absence of data, the company's base case assumed patients who transition to these health states, cannot change their health state, while those that move to health states that did contain patients at baseline can. All previously published models evaluating LCIG in the same relevant patient population, that were based around OFF time, used broader OFF time per day categories.

In addition, previous LCIG models tended to use H&Y in combination with OFF time to represent health states. This is because OFF time, while important, does not on its own accurately reflect the heterogeneity of treatment. What a patient considers OFF/ON time will vary depending on the stage and severity of their condition. Assuming, OFF time represents all aspects of the disease also fails to consider the effect of troublesome dyskinesia, which is associated with patient ON time. The current model structure seems likely to be overlooking certain key outcomes of the condition resulting in a higher degree of uncertainty around the cost effectiveness evidence.

In the company's base case, there are four key flawed assumptions that bias the ICER in favour of foslevodopa-foscarbidopa. One is the last observation carried forward assumption where the company assumed the transition matrix from month 0 to 3 continues for 3 years. This is despite all the significant decrease in OFF time occurring observed in the M15-736 trial occurring in the first month and the trial data also showing an increase in OFF time between month 2 and month 3. The second is that the company has chosen to discard the BMT data from M15-736 due to it demonstrating an improvement with BMT. The company asserts that the benefit with BMT is clinically implausible and is likely due to the additional interaction with the healthcare system

because of trial conditions; however, the same argument would equally apply to some of the benefit received by foslevodopa-foscarbidopa. Thirdly, the company uses the lower rate of discontinuations from M15-741, despite using the efficacy data and baseline characteristics from M15-736, which showed significantly more improvement in OFF time. The fourth assumption is that patients who discontinue do so into the health state they were in while on treatment. In practice this assumption had the biggest benefit to foslevodopa-foscarbidopa as it meant the higher rate of discontinuations had less of an impact due as discontinuing patients retained a significant benefit of treatment over patients who were always treated with BMT. This final assumption is the most significant, as when patients who discontinue are assumed to obtain the same OFF time outcomes as patients who were always treated with BMT, LCIG becomes dominant over foslevodopa-foscarbidopa.

The EAG considers the model structure flawed and a number of key model assumptions inappropriate. The EAG base case addresses most of the key model assumptions that would lead to obvious bias, but structural issues remain with: the derivation of utilities, implementation of such a high number of health states given the data available, and not taking into account the heterogeneity of the condition. The company also needs to account for the benefit observed in the BMT arm during the M15-736 trial.

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8 Appendices

8.1 OFF time data M15-736

Table 73: Number of patients receiving foslevodopa-foscarbidopa with 0 to 16 hours of OFF time at baseline, 4 weeks, 8 weeks, and 12 weeks in M15-736

NROFF	BASELINE	DAY 29	DAY 57	DAY 85	Total
OFF 0	*	**	**	**	**
OFF 1	*	*	*	*	**
OFF 2	*	*	*	*	**
OFF 3	*	*	*	*	**
OFF 4	*	*	*	*	**
OFF 5	**	*	*	*	**
OFF 6	*	*	*	*	**
OFF 7	**	*	*	*	**
OFF 8	*	*	*	*	**
OFF 9	*	*	*	*	*
OFF 10	*	*	*	*	*
OFF 11	*	*	*	*	*
OFF 12	*	*	*	*	*
OFF 13	*	*	*	*	*
OFF 14	*	*	*	*	*
OFF 15	*	*	*	*	*
OFF 16	*	*	*	*	*
Total	**	**	**	**	***

Table 74. Number of patients receiving oral treatment with 0 to 16 hours of OFF time at baseline, 4 weeks, 8 weeks, and 12 weeks in M15-736

NROFF	BASELINE	DAY 29	DAY 57	DAY 85	Total
OFF 0	*	*	*	*	**
OFF 1	*	*	*	*	**
OFF 2	*	*	*	*	**
OFF 3	*	*	*	*	**
OFF 4	**	*	*	*	**
OFF 5	**	*	*	*	**
OFF 6	**	**	*	*	**
OFF 7	*	*	*	**	**
OFF 8	*	*	*	*	**
OFF 9	*	*	*	*	**
OFF 10	*	*	*	*	*
OFF 11	*	*	*	*	*

NROFF	BASELINE	DAY 29	DAY 57	DAY 85	Total
OFF 12	*	*	*	*	*
OFF 13	*	*	*	*	*
OFF 14	*	*	*	*	*
OFF 15	*	*	*	*	*
OFF 16	*	*	*	*	*
Total	**	**	**	**	***

Figure 19. Distribution of patients receiving foslevodopa-foscarbidopa with 0 to 16 hours of OFF time at baseline, 4 weeks, 8 weeks, and 12 weeks in M15-736

Figure 20. Distribution of patients receiving oral treatment with 0 to 16 hours of OFF time at baseline, 4 weeks, 8 weeks, and 12 weeks in M15-736

8.2 Company's updated NMA results of limited network of trials

Table 75. Difference in mean ON time without troublesome dyskinesia change from baseline (95% CrI)

Treatment	RE (DIC = 16.4)	FE (DIC = 15.8)
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]

Abbreviations: BMT: best medical therapy; CrI: credible interval; DIC: deviance information criteria; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.

Table 76. Difference in mean OFF time change from baseline (95% CrI)

Treatment	RE (DIC = 16.4)	FE (DIC= 15.8)
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]

Abbreviations: BMT: best medical therapy; CrI: credible interval; DIC: deviance information criteria; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.

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

Assessment of severity

April 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135647.

1 Severity modifier

As outlined in the NICE methods guide,[1] "*the committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS*". The thresholds of QALY weightings for severity are reported in Table 1.

Table 1. QALY weighting for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18.
Abbreviations: QALY, quality-adjusted life-year		

The EAG calculated the absolute and proportional QALY shortfall using a published calculator by Schneider *et al*. 2021.[2] The tool calculates the expected total QALYs for the general population matched to baseline age and sex distribution included in the economic model. The source of the general population EQ-5D data used in the calculator is from a study by Hernandez *et al*. 2020.[3]

The EAG also altered the company model: applying the maximum time horizon of 30 years and removing the mortality and utility decrements associated with Parkinson's disease, in order to produce an estimate of general population QALYs.

Table 2 presents the EAG's preferred assumptions for the general population QALY shortfall estimates.

Table 2. Summary of preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Rationale
Sex distribution - % female	30%	Matches value used in EAG and company base case model
Starting age	[redacted]	Matches value used in EAG and company base case model
Expected total QALYs for the general population (QALY calculator)	[redacted]	Schneider *et al*. 2021.[2] Estimate based on starting age and sex distribution at baseline
Expected total QALYs for the general population (HE model)	11.90	HE model with general population utility/mortality
Discount rate	3.5%	Matches value used in EAG and company base case model
Abbreviations: QALY, quality-adjusted life-year		

To calculate the absolute and proportional QALY shortfall, the EAG used the company and EAG base case predicted total QALYs for the BMT and LCIG arms. The results of the EAG's QALY shortfall analysis for the company's base case model results is presented in Table 3 and the results using the EAG's illustrative base case model results is presented in Table 4.

Based on the QALY shortfall analysis, no severity modifier should be applied in the model.

Table 3. EAG's QALY shortfall analysis (company base case model results)

Category	Estimated QALYs	Absolute shortfall	Proportional shortfall
Schneider *et al.* general population QALY estimate ([redacted])			
With the disease - patients on BMT	[redacted]	[redacted]	[redacted]
With the disease – patients on LCIG	[redacted]	[redacted]	[redacted]
HE model general population QALY estimate (11.90)			
With the disease - patients on BMT	[redacted]	[redacted]	[redacted]
With the disease – patients on LCIG	[redacted]	[redacted]	[redacted]
Abbreviations: BMT, best medical therapy; LCIG, levodopa-carbidopa intestinal gel; QALY, quality adjusted life year			

Table 4. EAG's QALY shortfall analysis (EAG illustrative base case model results)

Category	Estimated QALYs	Absolute shortfall	Proportional shortfall
Schneider *et al.* general population QALY estimate ([redacted])			
With the disease - patients on BMT	[redacted]	[redacted]	[redacted]
With the disease – patients on LCIG	[redacted]	[redacted]	[redacted]
HE model general population QALY estimate (11.90)			
With the disease - patients on BMT	[redacted]	[redacted]	[redacted]
With the disease – patients on LCIG	[redacted]	[redacted]	[redacted]
Abbreviations: BMT, best medical therapy; LCIG, levodopa-carbidopa intestinal gel; QALY, quality adjusted life year			

2 References

1. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual, 2022. Available from: www.nice.org.uk/process/pmg36. Date accessed: 26 Jul 2022.
2. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. 2021.
3. Hernandez Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English Population Study. 2020.

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 1 November** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Section 1: Factual inaccuracies

Executive summary

Issue 1 Relative unit price of foslevodopa-foscarbidopa and BMT

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 18, Section 1.2: "Its lower unit price compared to BMT, […]"	Please amend this sentence to: "Its **higher** unit price compared to BMT, […]"	Foslevodopa-foscarbidopa has a higher unit price than BMT.	The EAG thanks the company for highlighting this error. The text has been updated.

Issue 2 Changes in cost-effectiveness related to EAG's key issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 1.3: Throughout the EAG's summary of its key issues, the EAG refers to increasing and/or decreasing ICERs.	Please amend the summary of the EAG's key issues by referring to increasing and/or decreasing **cost-effectiveness**, rather than ICERs.	Given the presence of SW ICERs (costs saved per QALY forgone) in a number of the analyses, the Company considers that it is misleading to refer to increasing and/or decreasing ICERs, as this can result in a misinterpretation of the cost-effectiveness results.	The text has been updated in all "what is expected effect" boxes in key issues.

Issue 3 Accounting for dyskinesia in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 25, Section 1.3 "While not as significant a decrement to patient quality of life as OFF-time, troublesome dyskinesia represents a common health related impact from PD that is unaccounted for in the model."	Please amend this sentence to: "While not as significant a decrement to patient quality of life as OFF-time, troublesome dyskinesia represents a common health related impact from PD."	Troublesome dyskinesia is accounted for in the model in the form of a dyskinesia adverse event, as reported in clinical trials.	The EAG considers that, while the company has account for dyskinesia defined as an AE, it hasn't accounted for troubling dyskinesia related to ON-time. AE dyskinesia and troublesome dyskinesia are not the same.

Issue 4 Higher OFF state costs advantaging treatments with lower efficacy

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 26, Section 1.3 "Reduces the cost effectiveness of foslevodopa-foscarbidopa versus BMT and improves it versus LCIG as an overestimate of higher OFF state costs will advantage the treatments that have lower efficacy."	Please amend this sentence to: "Reduces the cost effectiveness of foslevodopa-foscarbidopa versus BMT and improves it versus LCIG as an overestimate of higher OFF state costs will advantage the treatments that have **higher** efficacy."	Treatments with lower efficacy result in greater OFF time state occupancy in the model. An overestimation of high OFF time health state costs therefore advantages those treatments with higher efficacy able to reduce high OFF time state occupancy, rather than those with lower efficacy.	The EAG thanks the company for highlighting this discrepancy. The text has been changed to, "Reduces the cost effectiveness of foslevodopa-foscarbidopa versus BMT and improves it versus LCIG as **a correction to** an overestimate of higher OFF state costs will advantage

			the treatments that have lower efficacy.”

Introduction and background

Issue 5 Positioning of LCIG in the treatment pathway

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 31, Section 2.1: “If apomorphine and DBS are unsuitable for a person, or if they are ineffective , then the next treatment offered is LCIG.”	Please amend this sentence to: “If apomorphine and DBS are unsuitable for a person, **or for whom DBS has failed**, then the next treatment offered is LCIG.”	The current wording does not accurately reflect the NHS clinical commissioning guideline’s recommended use of LCIG.	The EAG thanks the company for highlighting this error. The wording has been updated.

Issue 6 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 37, Section 2.3.3: “The comparators specified in the NICE final scope[3] include best medical therapy (BMT), apomorphine, DBS and LCIG.**(ref)**”	The EAG may wish to amend this sentence to include the correct reference.	This is a typographical error.	The EAG thanks the company for highlighting this error. The text has been updated.

Issue 7 Description of BMT

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 38, Section 2.3.3: "The comparator in the key clinical trial, M15-736, was oral CD/LD, which can be considered as BMT."	Please amend this sentence to the following: "The comparator in the key clinical trial, M15-736, was oral CD/LD, **which forms the main component of BMT**.	In clinical practice, BMT is highly individualised and involves different combinations of treatments for different patients. It is therefore important to not generalise BMT as solely comprising oral CD/LD.	The EAG thanks the company for highlighting this error.. The wording has been updated.

Issue 8 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 38, Section 2.3.3: "• have contraindicated to further reasonable drug therapeutic options due to co-morbidities or late-PD disease complications;"	Please amend this sentence to the following: "• **are** contraindicated to further reasonable drug therapeutic options due to comorbidities or late-PD disease complications;"	This is a typographical error.	The wording has been updated.

Issue 9 M15-741 trial eligibility regarding prior DBS

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 39, Section 2.3.5: "The EAG requested data for this subgroup at the clarification stage but prior apomorphine use was not captured in the trials and both trials excluded patients with prior DBS."	Please amend this sentence to the following: "The EAG requested **baseline characteristics** data for this subgroup at the clarification stage. **Prior continuous daily infusion** apomorphine use was not captured **in M15-736 as such patients were excluded**. **M15-736 excluded patients with prior DBS, whilst M15-741 allowed patients with prior DBS to participate in the trial.**"	The M15-741 trial did not exclude patients with prior DBS use. The exclusion criterion for prior continuous daily infusion apomorphine has been clarified. Language for the data request has been updated to reflect Clarification Question A1.	The EAG thanks the company for highlighting this error. The text has been edited.

Clinical effectiveness

Issue 10 Typographical errors relating to cross-references

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 62, Section 3.3.2.1: "As described in Section 0, [...]" Page 64, Section 3.3.3.1:	The EAG may wish to amend these sentences with cross-references to the correct section of the EAG report.	This is a typographical error.	The cross-reference has been updated

“As highlighted in Section 0, […]” Page 71, Section 3.4.3.4: “As pointed out in the critique of M15-736 (Section 0), […]” Page 136, Section 6.2: “[…] as part of section 0 or section 6.4.			

Issue 11 Missing percentage sign

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 64, Section 3.3.3.1: “ […] and [redacted] had discontinued treatment.”	Please amend as follows: “ […] and [redacted] had discontinued treatment.”	The percentage sign for these data is missing.	The percentage sign has been added.

Issue 12 Missing footnote description

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 29, Page 65, Section 3.3.3.1: “24 months*”	Please add in the footnotes what the asterisk represents.	This is a typographical error.	The footnote has been added.

No footnote is provided for this asterisk.			

Issue 13 Incorrect labelling of TEAEs as AEs

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 66, Section 3.3.3.2.2: "As in M15-736, AEs in M15-741 were mostly mild or moderate in severity. However, during the 12-month trial period [redacted] of patients had a serious AE, compared with [redacted] at three months in M15-736 (Table 32)."	Please amend this sentence as follows: "As in M15-736, **TE**AEs in M15-741 were mostly mild or moderate in severity. However, during the 12-month trial period [redacted] of patients had a serious **TE**AE, compared with [redacted] at three months in M15-736 (Table 32)."	For consistency with the clinical study reports, please label these as TEAEs as opposed to AEs.	The text has been updated.

Issue 14 Relative risk of bias between the M15-736 and DYSCOVER trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 71, Section 3.4.3.3: "However, the DYSCOVER trial was open label and therefore at an increased risk of bias, similar to M15-736."	Please amend the sentence as follows: "However, the DYSCOVER trial was open label and therefore at an increased risk of bias."	This sentence is misleading and could imply that M15-736 was an open-label trial.	Not a factual inaccuracy. No change required.

Cost effectiveness

Issue 15 Description of SW quadrant outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 77, Section 4 and Page 125, Section 5.1.1: "In the company's probabilistic and deterministic base case, foslevodopa-foscarbidopa is associated with lower costs and lower quality-adjusted life years (QALYs) compared to levodopa-carbidopa intestinal gel (LCIG), resulting in a bottom left	Please amend this sentence as follows: "In the company's probabilistic and deterministic base case, foslevodopa-foscarbidopa is associated with lower costs and lower quality-adjusted life years (QALYs) compared to levodopa-carbidopa intestinal gel (LCIG), resulting in a bottom left quadrant incremental cost-effectiveness ratio (ICER) of £[redacted] and £[redacted] **costs saved** per QALY **forgone**."	The description of the base case results has been rephrased to avoid misinterpretation of the outcomes. Please note that each outcome should be marked as CIC (also see Section 3 of this document); this had not been marked as such in the draft EAG Report.	The EAG thanks the company for highlighting this error. The text has been updated.

quadrant incremental cost-effectiveness ratio (ICER) of £[redacted] and £[redacted] per QALY gained.”			

Issue 16 Generalisability of trial data to UK population

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 38, Page 81, Section 4.2.1: The EAG comment takes the position that neither M15-736 nor M15-741 are generalisable to UK clinical practice, based on the relative lack of UK patients included in both trials.	Please amend the response to a more accurate representation of the generalisability of both trials to the UK population.	Whilst it is true that [redacted] UK patients were included in the M15-736 trial and [redacted] were included in the M15-741 trial, the baseline characteristics of both trials have been judged to be generalisable to UK clinical practice by clinicians consulted as part of an advisory board conducted as part of the CS. Furthermore, the EAG itself notes that clinical experts advising the EAG “consider both trial populations to be broadly generalisable to patients with PD eligible for advanced therapy in UK clinical practice”. The EAG’s assessment in this particular table is therefore contradictory and should be updated to	The EAG thanks the company for highlighting this error. The text has been updated.

		more accurately reflect the generalisability of both trials to UK clinical practice, in line with expert clinical advice received by both the Company and the EAG.	

Issue 17 Cost-effectiveness comparison to apomorphine and DBS

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 81, Section 4.2.2: "The justification for the narrower population is that this is the group that foslevodopa-foscarbidopa would offer the best value for money, suggesting the treatment would not be expected to be cost-effective in a cost-utility analysis including apomorphine or DBS."	Please amend as follows: "The justification for the narrower population is that this is the group that foslevodopa-foscarbidopa would offer the best value for money."	No cost-effectiveness analyses have been presented comparing foslevodopa-foscarbidopa to either apomorphine or DBS. It is therefore inappropriate to speculate about foslevodopa-foscarbidopa's cost-effectiveness in relation to these therapies.	The text has been updated.

Issue 18 Misrepresentation of Company response to clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 83, Section 4.2.2.1: "The company has somewhat contradicted itself in response to CQs, stating that the requested scenario of utilising a modelled distribution for initial OFF time would have limited impact but also be significant enough to result in problematic bias."	Please remove this sentence.	The wording currently misrepresents the Company's response to clarification question B.4. The Company response argues that given that the fitting of distribution to the trial data had limited impact, the most appropriate data source was the unmanipulated trial data. Had the distribution models shown significantly different results, their use in the cost-effectiveness model would have been considered further in case one data source were more appropriate than the original trial data. These are not contradictory positions.	The EAG thanks the company for clarifying their contradictory statement in their clarification response. However, it appears that the company has not run the requested analysis that they speculated on in the clarification response so it cannot be confirmed that this analysis had limited impact. Initially, at CQs, the company predicted this scenario would likely have little impact, yet they went on to stress that bias here could affect all subsequent transmissions. The EAG requests that the company provide this analysis at technical engagement for appropriate review. This request has been added to the text of the report: "The EAG have requested the results of this analysis be provided at technical engagement."

Issue 19 Description of foslevodopa-foscarbidopa

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 83, Section 4.2.3.1: "The economic analysis investigates the cost-effectiveness of foslevodopa-foscarbidopa (ABBV-951); a combination of monophosphate and carbidopa monophosphate administered subcutaneously."	Please amend this sentence to the following: "The economic analysis investigates the cost-effectiveness of foslevodopa-foscarbidopa (ABBV-951); a combination of **levodopa** monophosphate and carbidopa monophosphate administered subcutaneously."	The description of foslevodopa-foscarbidopa was missing levodopa as an active substance.	The text has been updated.

Issue 20 Description of LOCF period as arbitrary

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 90, Section 4.2.4.3: "Given the GLORIA trial[24] data demonstrating LCIG still is effective at 2 years the LOCF period duration of 3 years seems acceptable, if arbitrary."	Please amend the sentence as follows: "Given the GLORIA trial[24] data demonstrating LCIG still is effective at 2 years the LOCF period duration of 3 years seems acceptable."	In response the clarification question B.4, the Company provided justification for the choice of the 36-month cut-off chosen for the LOCF period, based on clinical expert feedback on the expected treatment effect duration of DATs in clinical practice. It is therefore inappropriate to	The text has been updated.

		describe this choice as “arbitrary”.	

Issue 21 Description of half-cycle correction in the Company model

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 90, Section 4.2.5: “The cycle length in the model was 3 months for the first two cycles to match the follow up time of M15-736 and the pivotal RCTs for LCIG. Beyond these two cycles the cycle length is six months with a half cycle correction applied.”	Please amend this paragraph as follows: “The cycle length in the model was 3 months for the first two cycles to match the follow up time of M15-736 and the pivotal RCTs for LCIG. Beyond these two cycles the cycle length is six months. **A half-cycle correction is applied to all cycles throughout the model time horizon**.”	The current wording could be interpreted to mean that a half-cycle correction was not applied to the first two model cycles. It should be made clear that a half-cycle correction was applied to all model cycles.	The text has been updated.

Issue 22 Discounting rate scenario

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 90, Section 4.2.5: “In scenario analysis, an annual discount rate of 1.5% was applied.”	Please remove this sentence.	No scenario analysis varying the discounting rate was conducted or presented in the Company submission.	The text has been updated.

Issue 23 Start of the LOCF period

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 91, Section 4.2.6.1: "[…] meaning when the cycle length changes to six months (from month 3 onwards) the rate of patients transferring between states per cycle remains the same until the end of the LOCF period."	Please amend this sentence as follows: "[…] meaning when the cycle length changes to six months (from Month **6** onwards) the rate of patients transferring between states per cycle remains the same until the end of the LOCF period."	The cycle length changes to six months after the first two model cycles, which are three months in duration. The cycle length therefore changes from Month 6 onwards, rather than Month 3 onwards as currently reported.	The text has been updated.

Issue 24 Statistical significance of M15-741 results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 97, Section 4.2.6.4: "• The decline in OFF time was not [redacted] after week 26;"	Please remove this bullet point.	Reductions in OFF time observed in M15-741 were [redacted] at all timepoints measured.	This has been reworded to clarify the point: "The difference in OFF time from week 26 to later time points was not [redacted]" This was not intended to mean the decline was not significant from baseline after week 26 this is referring to the

			difference between OFF time at w26 and future timepoints.

Issue 25 Incorrect cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 99, Section 4.2.6.4: "As can be seen in Figure 6 the company effectively assumes all patients under 25% OFF and over 25% OFF time had the same time on treatment (i.e. no relationship) and then assumes there's an exponential relationship."	Please amend this sentence as follows: "As can be seen in Figure 11 the company effectively assumes all patients under 25% OFF and over 25% OFF time had the same time on treatment (i.e. no relationship) and then assumes there's an exponential relationship."	This is a typographical error.	The text has been updated.

Issue 26 Relative sample size of M15-736 and aPD Adelphi data

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 117, Section 4.2.11.6: "The EAG does not consider that the sample size for	Please amend as follows:	M15-736 included [redacted] patients with advanced PD, therefore the EAG's comment about the relative size of each	Text updated to, "The EAG does not consider that the sample size for

patients with advanced PD (n=[redacted]) was small as it included nearly [redacted] as many patients as M15-736."	"The EAG does not consider that the sample size for patients with advanced PD (n=[redacted]) was small."	study is not accurate. If the sentence relates to patients in individual trial arms, this should be clarified in the text.	patients with advanced PD (n=[redacted]) was small as it included nearly twice as many patients as the treatment arm for M15-736."

Issue 27 Clarification over the probability of dyskinesia correction

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 124, Section 5.1.1: "The probability of dyskinesia has been corrected from 0.07% to 7.0%;"	Please amend as follows: "The probability of dyskinesia has been corrected from 0.07% to 7.0% **for LCIG**;"	The correction to the probability of dyskinesia as an AE in the model should be clarified. This is to avoid any doubt over which treatment that this applicable to.	The text has been updated.

Issue 28 Inclusion of deterministic results in company submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 125, Section 5.1.1: "The company originally only provided probabilistic base case results but at the EAGs request in CQs both probabilistic and	Please amend this sentence as follows: "The company originally only provided probabilistic**, with-PAS** base case results but at the EAG's request in CQs both probabilistic and deterministic **with-PAS** results have been provided."	List price deterministic base case results were provided in Appendix J.2 of the CS. It is therefore inaccurate to suggest that no deterministic base case results were provided in the original CS.	The text has been updated.

deterministic results have been provided.”			

Issue 29 Model population

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 140, Section 6.5: “The company submitted a cost-utility analysis comparing foslevodopa-foscarbidopa to BMT and LCIG for the advanced treatment of adults with Parkinson’s disease in patients responsive to levodopa, with symptoms not adequately controlled by their current medical therapy.”	Please amend this sentence as follows: “The company submitted a cost-utility analysis comparing foslevodopa-foscarbidopa to BMT and LCIG for the advanced treatment of adults with Parkinson’s disease in patients responsive to levodopa, with symptoms not adequately controlled by their current medical therapy **and for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control**.”	The model population presented by the EAG does not take into account the criteria for either previous failure or unsuitability for apomorphine or DBS. This is therefore a misrepresentation of the Company’s modelled population and proposed positioning of foslevodopa-foscarbidopa.	The text has been updated.

Section 2: Data amendments

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 51, Section 3.3.1.1: "Treatment with foslevodopa-foscarbidopa resulted in a clinically meaningful [redacted] increase in ON time without troublesome dyskinesia from baseline when compared with oral CD/LD ([redacted])."	Please amend this sentence as follows: ""Treatment with foslevodopa-foscarbidopa resulted in a clinically meaningful [redacted] increase in ON time without troublesome dyskinesia from baseline when compared with oral CD/LD ([redacted])."	The SD for the LS mean difference was incorrectly reported as [redacted].	The number has been updated.
Page 51, Section 3.3.1.1: "At the end of the trial (12 weeks), patients in the foslevodopa-foscarbidopa arm experienced a mean improvement from baseline of [redacted] hours on the average ON time without troublesome dyskinesia compared with [redacted] hours for patients in the oral CD/LD group (Table 18)."	Please amend this sentence as follows: "At the end of the trial (12 weeks), patients in the foslevodopa-foscarbidopa arm experienced an **LS** mean improvement from baseline of [redacted] hours on the average ON time without troublesome dyskinesia compared with [redacted] hours for patients in the oral CD/LD group (Table 18)."	Clarifying that these data are LS mean change avoids confusions with raw mean change data which are different.	The text has been updated.
Page 51, Section 3.3.1.1:	Please amend this sentence as follows: ""The ANCOVA analysis, imputing missing	The data from the primary MMRM analysis were quoted	The numbers have been updated.

"The ANCOVA analysis, imputing missing values based on the LOCF, resulted in an increase in from baseline in ON time without troublesome dyskinesia of [redacted] hours (p-value [redacted]) for foslevodopa-foscarbidopa compared with oral CD/LD."	values based on the LOCF, resulted in an increase in from baseline in ON time without troublesome dyskinesia of [redacted] hours (p-value [redacted]) for foslevodopa-foscarbidopa compared with oral CD/LD."	here instead of the ANCOVA analysis.	
Page 53, Section 3.3.1.2: "Treatment with foslevodopa-foscarbidopa resulted in a [redacted] and clinically meaningful reduction in OFF time from baseline when compared with oral CD/LD ([redacted])"	Please amend this sentence as follows: "Treatment with foslevodopa-foscarbidopa resulted in a [redacted] and clinically meaningful reduction in OFF time from baseline when compared with oral CD/LD ([redacted])."	This correction clarifies that the data quoted is the LS mean difference.	Not a factual inaccuracy. No change required.
Page 53, Section 3.3.1.2: "At the end of the trial (12 weeks), patients in the foslevodopa-foscarbidopa arm experienced a mean reduction from baseline of [redacted] hours in OFF time compared with a reduction of [redacted] hours for patients in the oral CD/LD arm (Table 19)."	Please amend this sentence as follows: "At the end of the trial (12 weeks), patients in the foslevodopa-foscarbidopa arm experienced an **LS** mean reduction from baseline of [redacted] hours in OFF time compared with a reduction of [redacted] hours for patients in the oral CD/LD arm (Table 19)."	Clarifying that these data are LS mean change avoids confusions with raw mean change data which are different.	The text has been updated.

Table 57, Page 116, Table 59, Page 121, Table 60, Page 122 and Table 62, Page 123, Section 4.2.11: The total yearly costs in the company's base case for OFF 11 are incorrectly reported as "£[redacted] £[redacted]"	Please amend this value in these tables as follows: "£[redacted]"	These data are incorrectly reported.	The tables have been updated.
Page 61, Section 3.3.2.1: "The mean change from baseline to Week 12 was an increase of [redacted] and a decrease of [redacted] hours in ON time without troublesome dyskinesia and OFF time, respectively. The equivalent data from M15-736 at the same timepoint was an increase of [redacted] and a decrease of [redacted] hours in ON time without troublesome dyskinesia and OFF time, respectively."	Please amend these sentences as follows: ""The mean change from baseline to Week **13** was an increase of [redacted] and a decrease of [redacted] hours in ON time without troublesome dyskinesia and OFF time, respectively. The data from M15-736 at **Week 12** was an increase of [redacted] and a decrease of [redacted] hours in ON time without troublesome dyskinesia and OFF time, respectively."	These data from M15-741 are reported at Week 13 while M15-736 reported these data at Week 12.	The text has been updated.
Page 63, Section 3.3.2.2 "The mean change from baseline to Week 12 was an increase of [redacted] in M15-741,	Please amend this sentence as follows: ""The mean change from baseline to Week **13** was an increase of [redacted] in M15-741. The mean change from baseline to	The change from baseline data for M15-741 and M15-736 were incorrectly reported, and the timepoints are Week	The text has been updated.

compared with an increase of [redacted] in M15-736 at the same timepoint."	Week **12** was an increase of [redacted] in M15-736."	13 and Week 12 for the studies, respectively.	
Page 65 Section 3.3.3.2.1: "The most common AEs leading to discontinuation of foslevodopa-foscarbidopa were infusion site AEs: infusion site erythema ([redacted]), infusion site pain ([redacted]), infusion site cellulitis ([redacted]), and infusion site oedema ([redacted])."	Please amend this sentence as follows: "The most common AEs leading to discontinuation of foslevodopa-foscarbidopa were infusion site AEs: **infection site cellulitis ([redacted]), infusion site pain ([redacted]), infusion site oedema ([redacted]), infusion site bruising ([redacted]), and infusion site haemorrhage ([redacted]).**"	The data reported are for AEs overall, not for AEs leading to treatment discontinuation. The proposed amendments report data on the most common AEs leading to treatment discontinuation.	The text has been updated.
Table 44, Page 93, Section 4.2.6: The scenario results presented in this table are incorrect.	Please replace this table with the data in Table 15 of the Company's clarification responses and ensure the CIC highlighting aligns with this also.	These data are incorrectly reported and missing CIC highlighting.	The tables have been updated.
Table 51, Page 108 and Table 52, Page 109, Section 4.2.10: The first value reported in the "total combined % patients by change in OFF hours by categories" column incorrectly includes the	Please amend these values in both tables to remove the patients with missing EQ-5D-3L data from the first value in the "total combined % patients by change in OFF hours by categories" column.	These data are incorrectly reported.	The tables have been updated.

percentage of patients with missing values.			
Page 116, Section 4.2.11.5: "Total health costs differ substantially between the different health states, ranging from £[redacted] for OFF 0 to £[redacted] for OFF 16"	Please amend these values as follows: "Total health costs differ substantially between the different health states, ranging from **£**[redacted] for OFF 0 to **£**[redacted] for OFF 16" AIC highlighting is also missing from these values in the current version of the EAG report; please add AIC highlighting to these data.	These data are incorrectly reported and missing AIC highlighting.	The tables have been updated.
Table 67, Page 134, Section 6.1 The cost-effectiveness results for LCIG following amendment of the relative risk value in the model are incorrect.	Please amend the values reported for LCIG to the following: Total costs: £[redacted] Incremental costs: -£[redacted] ICER: £[redacted]	The results for this EAG scenario analysis conducted on the company base case are inaccurate.	The EAG thanks the company for highlighting this error. However, the EAG points out that only the LCIG cost was incorrect as it should have been £[redacted]. This text has been updated This has been tested by rerunning the analysis in a version of the model the company sent at CQs. The model will be uploaded with this response.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 8 December**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

About you

Table 1: About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AbbVie UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Potential overestimation of treatment benefit for foslevodopa-foscarbidopa Report sections: 2.3.1, 3.2, and 3.3	No	**AbbVie recognise that patients could "guess" their treatment allocation. However, this is inherent to all double-blind randomised controlled trials (RCTs), particularly placebo-controlled trials, and the M15-736 trial was conducted to the highest possible standard, minimising the risk of potential unblinding. The EAG's concern is speculative, and AbbVie maintain that the M15-736 trial represents the most robust source of clinical evidence available to inform the estimate of treatment effect for foslevodopa-foscarbidopa.** In the summary of this key issue in their report, the EAG note the appropriateness of the trial's conduct. However, the EAG note that differences in treatment effect between the intervention and control arm in the trial, in particular relating to morning akinesia, may have allowed patients to correctly "guess" treatment allocation, potentially leading to unblinding and bias to have been introduced in the trial. Accordingly, the EAG note that patient reported outcomes in diaries could be at risk of bias. As previously detailed in AbbVie's response to the EAG's clarification question A4, M15-736 was a robustly conducted clinical trial, and no flaws in the protocol exist that would have directly resulted in unblinding. As part of AbbVie's response to this issue, AbbVie have conducted three interviews in which clinicians were asked about the validity/conduct of the trial. Each clinician interviewed confirmed that M15-736 is a

		robust trial and that a double-blind, double-dummy study is the correct study design approach, with no better alternatives for evaluating interventions in Parkinson's disease (PD). According to clinical opinion, the use of patient diaries as an instrument to collect 'Off' time data remains the gold standard in PD trials. One clinician also noted that they could not envisage how the trial could have been designed in a way to alleviate the EAG's concerns. Finally, during an advisory board conducted with clinical experts as part of this appraisal, clinicians did not raise any concerns regarding the trial design and potential unblinding of participants. Whilst AbbVie recognise that patients could correctly "guess" their treatment allocation in the M15-736 trial, this should not be considered a source of uncertainty in the cost-effectiveness analysis of foslevodopa-foscarbidopa. This is a possibility in any RCT, in particular placebo-controlled trials, and this is a position that the EAG agreed with during the Technical Engagement meeting. Given the validity of the M15-736 trial design, which clinicians have validated along with its outcomes, AbbVie consider it speculative to draw conclusions on blinding given the lack of data to show a direction or size of any potential bias. The EAG have additionally questioned to what extent the effectiveness of foslevodopa-foscarbidopa differs between the population specified in the scope, the patient population in M15-736, and the narrower population the company is seeking recommendation in. The EAG mentioned that "*in M15-736, prior deep brain stimulation (DBS) was not allowed, and it is unclear how many patients had prior apomorphine and if patients who hadn't received these treatments prior to the trial were unsuitable for them*". In line with the company response to the EAG's clarification question A2, AbbVie maintain that there is expected to be limited impact on the clinical efficacy of foslevodopa-foscarbidopa based on whether patients have been previously treated with apomorphine or DBS. Clinicians consulted as part of this submission confirmed that prior use of apomorphine is not expected to affect efficacy of subsequent therapies. Indeed, as can be seen 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 CSCI apomorphine or DBS in M15-741 were similarly matched to the full trial populations who were enrolled in M15-736 and M15-741 study. Accordingly, outcomes for these patients are not expected to be different from the broader trial populations. As such, AbbVie consider the effectiveness of foslevodopa-foscarbidopa to not differ between the population in M15-736 and the narrower population the company is focusing on, and that the results of the M15-736 trial are applicable to the patient population of interest.
Key Issue 2: Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG Report sections: 3.4 and 4.2.6.4	Yes	**AbbVie acknowledge that there is uncertainty in the indirect treatment comparison (ITC) of foslevodopa-foscarbidopa and LCIG, and in order to address the issue of heterogeneity in the analysis, AbbVie have reconducted the network meta-analysis (NMA) using a consistent approach of observed means from all trials.** The EAG have noted some limitations with the original ITC performed by AbbVie, which was required due to the lack of head-to-head trial data for foslevodopa-foscarbidopa versus LCIG. AbbVie accepts that heterogeneity in the data used in the methods of the NMA, which used both estimates of least squares (LS) means and observed means, may result in uncertainty in the comparison of foslevodopa-foscarbidopa and LCIG. While uncertainty may exist in any ITC approach taken due to the paucity of available clinical data, AbbVie disagree with the EAG's preferred approach of assuming clinical equivalence between foslevodopa-foscarbidopa and LCIG. During clinician interviews conducted as part of this appraisal, clinical experts agreed that it is not justified to simply assume equivalence between the two treatments, and there are benefits of foslevodopa-foscarbidopa that can plausibly translate into superior efficacy. In particular, clinicians noted that foslevodopa-foscarbidopa's sleep benefits support a superior efficacy profile. Foslevodopa-foscarbidopa's novel 24-hour administration

		provides patients with improvement in sleep problems, which is an important aspect of the symptoms of PD. Additionally, patients who receive non-continuous PD medications, such as LCIG, may commonly experience early morning 'Off' times following treatment wearing off overnight. Alternatively, some patients receiving LCIG experience biphasic dyskinesia on starting or ending a dose (atypical biphasic dyskinesia),[1, 2] with one clinician suggesting that the florid nature of biphasic dyskinesia greatly impacts patients' quality of life (QoL). This is unlikely to occur with continuous foslevodopa-foscarbidopa; the overnight administration of foslevodopa-foscarbidopa allows for greater symptom control during and following sleep, which was demonstrated in the M15-736 trial. Clinical opinion also suggested that this could translate to improved cognitive functioning after waking. One clinician noted that the wait time for LCIG surgery, if not postponed or cancelled, is between 6–9 months; consequently, patients are maintained on existing treatment that is insufficient for controlling motor fluctuations, impacting QoL until surgery. According to NHS England figures, 49% of patients were waiting for more than 18 weeks to start treatment within a neurosurgical service.[3] Approximately 42% of surgical postponements and cancellations are due to "clinical issues", which mostly include not being able to place the percutaneous endoscopic gastrostomy (PEG) tube required for treatment, for instance due to patient anatomy.[4] Surgery for LCIG may also yield complications including wound/stoma infection, abdominal pain, erythema and tube dislocation,[5] further impacting QoL. This highlights the meaningful alternative foslevodopa-foscarbidopa can provide for patients, given there is no requirement for surgical intervention. Therefore, based on the lack of clinical data supporting the assumption, clinician feedback indicating plausibility for a superior efficacy profile for foslevodopa-foscarbidopa, and ongoing constraints for neurosurgical services in the NHS, AbbVie consider it inappropriate to assume clinical equivalence between the treatments.

		Despite this, the issue of heterogeneity in the NMA remains. To address this heterogeneity, AbbVie have updated the NMA using only observed means data from all the original available trials (DYSCOVER, M15-736, Olanow 2014), an approach which may not run the risk of biased parameter estimates associated with using LS means data. The results of this NMA are presented in Table 7 (Appendix A). These results indicate that mean change from baseline in 'Off' time relative to BMT was the largest for [redacted]. Indeed, both the originally conducted NMA and the updated analysis using only observed means, [redacted], have demonstrated that [redacted]. As the new analysis aims to address heterogeneity in the original NMA, the relative risks derived from the updated NMA have been implemented in the model. The cost-effectiveness results of this change to the base case are presented in Table 4.
Key Issue 3: 'Off' states 0–16 is inadequate at capturing the range of health effects of advanced Parkinson's, given the data available Report sections: 4.2.4.3, 4.2.6.4 and 4.2.10.1	No	**'Off' time provides the most representative outcome to model changes in symptom control and is widely reported in clinical trials in PD, providing a robust source of data to inform the model. Incorporating the Hoehn and Yahr (H&Y) scale as proposed by the EAG would add further complexity and increase uncertainty. While recognising that there are limitations with each of the possible structural approaches to modelling PD, AbbVie maintain that the chosen model structure is suitable for decision making.** The model developed to support this appraisal is the first to evaluate the cost effectiveness of foslevodopa-foscarbidopa, LCIG and BMT based on a systematic review of evidence, and has adopted a *de novo* structure to reflect the novel aspects of foslevodopa-foscarbidopa including its 24-hour continuous infusion. 'Off' time is the most appropriate outcome to include in the model, as it best captures the progression and predictability of symptom control, outcomes which are of high importance to patients with PD. The suitability of 'Off' time to model advanced PD has been extensively validated by clinical expert feedback. Significant structural changes to

		incorporate H&Y stages or group 'Off' health states are neither beneficial nor feasible, for reasons outlined below. During development of the model, secondary research was conducted to evaluate potential model structures based on previous cost-effectiveness models in advanced PD. The feasibility to evaluate the cost-effectiveness of foslevodopa-foscarbidopa against potentially relevant comparators with a number of potential model structures was assessed; previous model structures were evaluated, and these were used as the basis for developing *de novo* model structures. The conclusions of this exercise were that 'Off' time was the most appropriate health state to include in the model, and provides the best balance of appropriately capturing disease progression whilst maintaining a simple structure. The results of this secondary research were presented in Appendix N of the original CS. The EAG have questioned the appropriateness of only using 'Off' time health states in the model, arguing that this does not adequately capture the heterogeneity associated with PD. To address this, the EAG have suggested adopting a model structure involving health states driven by both 'Off' time and H&Y stage. AbbVie consider that H&Y does not accurately reflect disease progression and that the inclusion of H&Y health states is therefore inappropriate. During an advisory board with clinical and health economics experts conducted as part of the original submission, there was general consensus that H&Y states should not be included, both from a clinical and modelling standpoint. They highlighted that presence or absence of any changes in the H&Y scale would not accurately reflect disease progression within the model; H&Y is a measure primarily of subjects' mobility and gait imbalance, and is not an appropriate proxy measure for PD disease progression, as it only captures one aspect of motor symptoms. It was also noted by clinicians that patients were unlikely to achieve transitions between discrete H&Y states. This limitation of using H&Y states to model PD was also highlighted in the economic report conducted by NICE as part of its publication of clinical guidelines 71 in PD.[6] From a modelling perspective, it was also noted during the advisory board that adding H&Y states to the model would

		substantially increase the complexity of the model and the size of the model traces. Further clinician feedback was obtained through additional interviews during the technical engagement period, which aligned with previously received feedback. Clinical experts noted that H&Y does not take into account QoL, which is predominantly driven by 'Off' time, and in clinical practice H&Y is not a relevant measure of a patient's experience of their disease; instead, 'Off' time better reflects both motor-symptoms and non-motor symptoms, which patients are typically most concerned about. The consulted experts were clear that 'Off' time is the gold standard parameter for measuring the progression of symptoms of PD. Overall, AbbVie consider that based upon the secondary research and clinical feedback, 'Off' time is the most appropriate outcome for inclusion in the model, and H&Y would not provide a beneficial addition, resulting instead in unneeded complexity. The EAG's suggested alternative model structure involves a combination of 5 'Off' states and 5 H&Y states leading to 25 overall health states. As well as adding further complexity to the model with increased health states, H&Y and 'Off' time are intrinsically linked and unable to be appropriately modelled separately, leading to potential double counting of transitions within the model.[6] The EAG additionally cited various previous models to support inclusion of H&Y, including the CADTH submission,[7] Kalabina et al. 2019,[8] Walter and Odin 2015,[9] Chaudhuri et al. 2022,[10] Lowin et al. 2011,[11] and Lowin et al. 2017.[12] However, all of these models were explored as part of the secondary research conducted and each of these models have limitations of their own. • Lowin et al. 2011 is derived from an earlier model version based on a decision tree, and the rationale for such a jump from a simple decision tree to a 12-health state model is lacking. Kalabina et al. 2019, Lowin et al. 2017 and Chaudhuri et al. 2022 implemented the same model structure as Lowin et al. 2011, with slight differences in modelling assumptions; each of these publications note data availability and robustness of data available to inform

		health state transitions as important limitations of these models, which represents a general obstacle in a challenging disease area such as PD.[8, 10-12] • The CADTH submission model instead utilised a larger number of 'Off' state categories (OFF1–4) but did not capture H&Y states. CADTH did refer to Walter and Odin 2015 as a potential solution. In Walter and Odin 2015, patients with advanced PD receiving standard of care (SoC) experienced no treatment effect but followed disease progression;[9] treatment benefit is expressed as delayed disease progression due to improvement in the first two cycles (1 year). If AbbVie's model adopted this approach, the disease progression rate modelled for the active arms would differ to the one used for SoC (BMT), which could potentially result in greater benefits in terms of QoL for LCIG and foslevodopa-foscarbidopa. Additionally, this model relied heavily on pooled data from studies which were predominantly open-label studies, and, for one comparator data is derived from an RCT. However, it is unclear how OFF time was derived as this outcome is not an explicitly reported endpoint in the RCT of this comparator. The authors do not provide information on how the data were synthesised; this raises concerns on the appropriateness of the study, and its applicability to this appraisal. The EAG have additionally highlighted the granularity of the company's model, meaning data from only a small number of patients inform a large number of health states in the model. AbbVie acknowledge that this level of granularity is associated with the limitation of relatively small numbers of patients informing certain transitions. However, 1-hour increments in 'Off' time were chosen to account for the continuous administration of foslevodopa-foscarbidopa, and the more stable hour-to-hour symptom control associated with this method of administration, as described in section B.3.2.2 of Document B of the CS. Furthermore, 1-hour reductions in 'Off' time have been shown to be clinically meaningful, and would otherwise not be captured in a model in which 'Off' times are grouped.[13] Therefore, AbbVie maintain that the current

		approach is an appropriate balance of granularity versus limiting the amount of uncertainty introduced to the modelled transitions. It is important to highlight that AbbVie's model is the first to compare foslevodopa-foscarbidopa, LCIG and BMT based on a systematic review of evidence, with effectiveness evidence drawn from appropriately identified and synthesised RCTs. In this respect, the model utilises the best available evidence, which previous attempts at modelling this disease area have failed to do. This model focuses on modelling symptom control captured by 'Off' time (as NICE scientific advice suggested), and provides the necessary granularity to allow the benefit of foslevodopa-foscarbidopa's 24-hour infusion to be captured. A modelling validation exercise was conducted to assess how 'Off' time evolves over time in the revised company model and that of the Chaudhuri et al. 2022 model. The results, presented in Appendix B, demonstrate consistency for both BMT and LCIG. Finally, AbbVie recognise the EAG's concerns, though consider the current modelling approach to also be a conservative one. Clinician feedback suggested patients receiving foslevodopa-foscarbidopa could maintain cardiovascular fitness and overall health benefits that lead to a more mobile lifestyle, potentially reducing deterioration compared with BMT. Overall, AbbVie do not consider it feasible to conduct significant model structure changes during the timescales of the Technical Engagement period. The EAG noted in their report that "most aspects of the model would need a significant overhaul to accommodate the structural changes"; AbbVie agree that the addition of H&Y health states to the model would require significant model adaptations not possible at this stage, with their inclusion only resulting in greater complexity and uncertainty being introduced into the model. Overall, 'Off' time is the most appropriate outcome to include in the model, based on the available data from the RCTs, and reflects an appropriate balance of granularity and simplicity. This model is able to capture relevant data from the synthesised evidence-base to represent relevant events in the experience of people living with advanced PD.

Key Issue 4: Patients are assumed to retain a lasting benefit from treatment following discontinuation Report sections: 4.2.4.3	Yes	**AbbVie acknowledge that the original approach to treatment discontinuation may have overestimated lasting benefits for foslevodopa-foscarbidopa and LCIG. However, the EAG's proposed approach, in which patients immediately revert to contemporaneous natural disease health states upon discontinuation, is not reflective of treatment benefits that would be expected in practice. Indeed, this assumption would overlook improvements to functioning, mobility, and overall health while receiving active treatment. AbbVie have revised their approach to account for a loss of treatment effect upon discontinuation, with patients who discontinue treatment being distributed across OFF states according to the baseline OFF state distribution.** The EAG note that patients discontinuing active treatments in the model remain in the health states which they occupied at the point of discontinuation, at which point transition probabilities for the BMT arm are applied. AbbVie accept that the way in which efficacy was modelled following treatment discontinuation did not fully align with clinical practice, and the long-term efficacy following treatment discontinuation may be an overestimation in the company's original model. This assumption was made due to a lack of long-term data to inform disease progression following discontinuation on advanced treatments such as foslevodopa-foscarbidopa and LCIG. However, AbbVie disagree with the EAG's suggestion that immediately after discontinuation patients have equal outcomes to patients receiving BMT. In application, the EAG's approach explicitly assumes the proportion of the modelled cohort who discontinue "active" treatment are distributed across 'Off' states according to the contemporaneous BMT 'Off' state distribution, in the following cycle. This appears to be clinically implausible; it would be improbable for patients to immediately appear as though they had never received previous treatment, and to have equivalent clinical experiences as those who have been receiving BMT already. Clinician interviews suggested that this assumption would mean that patients would forgo the QoL, functioning and mobility, and cardiovascular benefits that lead to a more active

		lifestyle, as well as overall health benefits such as potentially being less susceptible to comorbidities. Whilst it is true that decreases in 'Off' time would likely be seen immediately, clinician feedback indicated that physical health benefits such as cardiovascular fitness could be retained in patients having discontinued foslevodopa-foscarbidopa or LCIG, as compared with patients receiving BMT over the same time period. In other words, AbbVie agree with the timing of the decrease in 'Off' time, but not with its magnitude. There are no data to inform the number of 'Off' hours that patients may be expected to have, however it is clinically unlikely for patients to immediately mirror those receiving BMT, as though they never received previous advanced therapy. Indeed foslevodopa-foscarbidopa treatment imparts progressive, not immediate, improvement in 'Off' time; one expects the same progressive changes to apply when discontinuing treatment. Clinician feedback has indicated that the most likely clinical situation for patients discontinuing treatment would be to return to baseline. In light of this, and the fact that the magnitude of the change in 'Off' time proposed by the EAG is implausible, the most appropriate approach is for patients who discontinue treatment to be redistributed to the BMT arm based on the baseline distribution rather than the contemporaneous BMT distribution as proposed by the EAG. This change has been implemented into the updated model, and the impact on the company's original cost-effectiveness estimates are presented in Table 4.
Key Issue 5: The LOCF assumption does not align with the trial data Report sections: 4.2.6.4	Yes	**AbbVie agree that the current LOCF assumption may be misrepresentative of the available clinical evidence, and therefore have aligned with the EAG's suggestion of assuming patients remain in their health states for the LOCF period in the updated model.** The EAG questioned the implementation of the LOCF assumption in the model, arguing that it does not align with long-term efficacy data from M15-736 and M15-741,

		suggesting that the main treatment benefit occurs only within the first three months and therefore this LOCF assumption is an overextrapolation of the data. In the company's original model, for the LOCF period (Months 3–36), the transition probabilities calculated for the trial period (Month 0–3) were applied due to supporting evidence from M15-741 which does demonstrate some sustained long-term effect for foslevodopa-foscarbidopa. M15-741 demonstrated that control of motor symptoms is maintained over 52 weeks, and [redacted] improvements in 'Off' time were observed at all time points measured during the trial. This LOCF assumption was applied to LCIG as well as foslevodopa-foscarbidopa. Despite this, AbbVie acknowledge that it may be inappropriate to carry forward the transition probabilities that occur in the first three months of the M15-736 trial throughout the following three years. AbbVie agree that the trial data from M15-736 and M15-741 indicate that treatment benefit predominantly occurs in the months following treatment initiation, and the current LOCF assumption may be an overestimation of the long-term efficacy of foslevodopa-foscarbidopa and LCIG. Therefore, the EAG's recommendation of assuming that patients remain in their health states for the LOCF period appears to be a more appropriate approach to estimating long-term efficacy. It should be noted that data from M20-098, the M15-736 trial extension, are not yet available to inform the LOCF period transitions and therefore cannot be incorporated into the model. This change has been implemented in the model and the updated cost-effectiveness results are presented in Table 4.
Key Issue 6: Problems with the use of Palmer *et al.* 2002 in informing BMT Report sections: 4.2.6.4	No	**AbbVie agree that the use of two data points from Palmer et al. 2002 to inform the transitions for the full time horizon of the BMT arm and the transitions of all patients is associated with limitations.[14] However, as discussed during the Technical Engagement call, AbbVie understand that the EAG no longer consider**

		this to be a key issue, in light of the lack of more appropriate data available to inform such these transitions. The approach of using the data reported in Palmer et al. 2002 was taken as literature to directly populate natural disease transition probabilities was not available, as noted by the EAG. Indeed, the use of constant transition probabilities derived by fitting an exponential model to data from Palmer et al. 2002 is consistent with the approach taken by Kalabina et al.[8] An exponential model, rather than a linear model, was fitted to the data because it would be expected that patients in higher 'Off' states would be less likely to move to the next worse 'Off' state than patients in the lower 'Off' states. To inform this technical engagement response, AbbVie explored the data in the Palmer et al. 2000 paper as suggested by the EAG, however it was concluded that there are no appropriate data from this study to inform BMT transitions.[15] This study aimed to derive utilities and understand how patients with PD value their own current health and outcomes associated with medical treatment of PD, and does not report any data relating to rates of natural disease progression. This issue was discussed between AbbVie and the EAG during the Technical Engagement meeting, during which AbbVie explained the lack of usable data in the Palmer et al 2000 study. It was agreed that in the absence of any other more recent relevant papers, the most appropriate data source remains Palmer et al. 2002.
Key Issue 7: The company did not use the trial M15-736 trial data on the comparator arm Report sections: 4.2.6.4	No	**AbbVie maintain that modelling a treatment effect for a population uncontrolled on current treatment (i.e. BMT) is not appropriate. Any "trial effect" observed in the BMT arm of the M15-736 trial, is likely the result of the increased clinical interaction that patients received in the trial compared with expected clinical practice; using trial data in the model would therefore overestimate clinical benefit of BMT. As the patient population being considered would previously**

		have been treated with BMT, and would no longer be controlled on BMT, any approach which models a treatment effect for BMT lacks face validity. The EAG have raised concerns with the company's approach of not using trial data from the comparator arm of M15-736 to model BMT treatment effect. The EAG agree with AbbVie that the reduction in OFF time seen in the comparator arm of the M15-736 trial is most likely due to increased exposure to the healthcare system. However, they add that this would be equally true for patients receiving foslevodopa-foscarbidopa. AbbVie note that whilst this kind of "trial effect" is likely to apply to the intervention arm also, advanced device-aided therapies (DATs) are associated with greater exposure to the healthcare system, as reflected by the higher modelled administration and management costs for foslevodopa-foscarbidopa and LCIG and which is more closely reflective of the healthcare interaction observed in the M15-736 trial. In contrast, patients receiving BMT in clinical practice would not experience the same levels of healthcare support as in the trial. The EAG agree that patients receiving BMT in practice would be unlikely to see any such reductions in OFF time in clinical practice; therefore, the BMT arm of the trial cannot be considered an appropriate source of efficacy for BMT in UK clinical practice. Patients enrolled in the M15-736 trial were required to be using oral carbidopa/levodopa (CD/LD) at study entry, and be uncontrolled on current treatment. Patients in the control arm were continued on oral CD/LD, with any non-permitted concomitant treatments converted to levodopa equivalent dose. Patients in the BMT arm therefore continued to receive treatment which they were uncontrolled on prior to study entry. Any improvement in OFF time observed in the control arm of the M15-736 trial therefore is inappropriate to be attributed to a direct treatment effect, but rather resulting from the increased exposure to the health care system and positive impact of being involved in the trial, and should not therefore inform the efficacy of BMT in the model.

		AbbVie consider any observed benefit to patients receiving BMT in M15-736 are impacted by being in a trial setting with increased exposure to the healthcare system. Based on clinical expert opinion received as part of this response, the disease trajectory of patients who had previously failed BMT would more closely reflect natural disease progression. Indeed, continuing to give BMT to a patient who had previously failed BMT will likely not change the outcome of their treatment as the patient might experience increasingly more motor fluctuations at an advanced stage with oral therapy. Clinical feedback highlighted that patients were enrolled in M15-736 precisely because BMT was failing them, and even if a patient had benefited from BMT, it is not expected that this will last long given the advanced stage of PD and the fact that they were already failing on oral therapy. Importantly, given that the patient population being considered would previously have been treated with BMT, and would no longer be controlled on BMT, any approach which models a treatment effect for BMT would lack face validity. Whilst AbbVie note the discrepancy in using trial data to model foslevodopa-foscarbidopa and not BMT, AbbVie do not consider the efficacy data for BMT in the M15-736 trial to be reflective of UK clinical practice for these patients, given the differences in healthcare exposure in the trial versus standard care practices, with natural history data representing the most appropriate source of data. AbbVie have therefore maintained the original approach to modelling BMT using natural history data throughout the model time horizon.
Key Issue 8: The company uses efficacy data and discontinuation data from different sources Report sections: 4.2.7.1	No	**AbbVie maintain that cohort 2 of the M15-741 trial is the most appropriate source of discontinuation rates to reflect anticipated UK clinical practice.** The EAG considered the M15-736 trial to be the most appropriate source of discontinuation data for the first model cycle. The original company approach of using M15-741 in this model period was chosen in order to ensure a consistent use of discontinuation data across the period for which trial data were available. Given that M15-741 and its extension trial M15-737 reported two year discontinuation data, these

		were considered most appropriate to model this initial model period. M15-736 only reported discontinuation data for the first three months of the trial, meaning that a different source would have to be used, introducing heterogeneity of data within the discontinuation assumptions. Rates of discontinuation from M15-741 cohort 2 are likely the most predictive of expected discontinuation rates in clinical practice, with the use of the new infusion set, whereby training was provided on the correct use and application of the infusion set cannula including aseptic technique. Additionally, the follow-up (three months) of M15-736 would require making an assumption at an early-stage for discontinuation beyond three months. An option (which has already been presented as a scenario in the CS), is to use M15-736 data for the first three months followed by M15-741. However, it was deemed more robust to use the longer-term M15-741 discontinuation rates as the base case to provide discontinuation data from a continuous source and to use the data from cohort 2 to reflect the infusion set that will be the only intended infusion set for delivery of foslevodopa-foscarbidopa. To further alleviate any outstanding concerns surrounding the choice of discontinuation rates, clinical expert feedback obtained for this response indicated that discontinuation rates are expected to fall with continued use and training with foslevodopa-foscarbidopa in clinical practice, particularly as both clinicians and patients become more familiar with the treatment. When an innovative therapy like foslevodopa-foscarbidopa has not been previously used, there is an overabundance of caution from patients and physicians. Therefore, the discontinuation rates used in the model may in fact be above that expected to be seen in future clinical practice. It is worth noting that discontinuation of foslevodopa-foscarbidopa differs to other device-aided therapies. The convenience of foslevodopa-foscarbidopa and the lack of surgical requirement means that patients have the flexibility to easily discontinue treatment based on their preferences; treatment is reversible, and patients can easily initiate, and discontinue, foslevodopa-foscarbidopa. Further to this, in M15-736

		discontinuation rates are likely inflated compared with rates expected in future clinical practice due to a number of discontinuations due to difficulty in administering foslevodopa-foscarbidopa, rather than discontinuations due to AEs or lack of efficacy. In M15-736, among the primary reasons for the 31 treatment discontinuations in all patients, five (16.1%) were due to difficulty with the drug delivery system and eight (25.8%) were due to "withdrawal of consent".[16] The number of discontinuations of this nature are expected to reduce with appropriate training, and continued use and increased confidence with foslevodopa-foscarbidopa. The EAG also suggested use of discontinuation data from M20-098 (the open-label extension of M15-736) for the first year, however AbbVie note that data from M20-098 will not yet be available in time for presentation as part of the Technical Engagement response. Overall, AbbVie consider the data source used in the original company's base case to be the most appropriate data to use to most closely reflect anticipated experiences in UK clinical practice. The source of discontinuation has therefore been maintained in the company's base case economic analysis.
Key Issue 9: Troublesome dyskinesia appears to be a source of unaccounted for patient burden Report sections: 4.2.8.1	No	**AbbVie recognise that troublesome dyskinesia represents a burden in a minority of patients that the model does not account for. However, AbbVie consider troublesome dyskinesia to be uncommon and well-managed in practice, and its implementation in the model would be informed by very limited data, most likely leading to negligible changes in cost-effectiveness estimates. As such, a measure of troublesome dyskinesia has not been implemented in the company's revised base case analysis.** The EAG consider that troublesome dyskinesia represents a potentially important source of disutility for patients with PD and should be accounted for in the company's model. However troublesome dyskinesia, whilst an important consideration for patients, is relatively uncommon. In the M15-736 trial, the average number of hours of

		'On' time with troublesome dyskinesia patients experienced in the intervention and control arms at baseline was only 0.46 and 0.60 hours, respectively, based on the PD Diary (normalised to a 16-hour waking day averaged over three consecutive days).[16] At the end of the study, these values in the intervention and control arms had increased by only 0.05 (p value = [redacted]) and 0.08 hours (p value = [redacted]), respectively. Additionally, at each timepoint measured (Baseline and Days 8, 15, 22, 29, 57, and 85) there was [redacted] between the foslevodopa-foscarbidopa and oral CD/LD groups in LS mean change from baseline in average daily normalised 'On' time with troublesome dyskinesia.[17] Similarly, in the Olanow 2014 study, mean 'On' time with troublesome dyskinesia at baseline was only 1.00 and 1.20 hours in the LCIG and control arms, respectively.[18] These values only changed by 0.11 and 0.03, respectively, with the treatment difference not being statistically significant.[18] In the DYSCOVER trial, treatment difference between LCIG and control in normalised 'On' time with troublesome dyskinesia again did not reach statistical significance.[19] Therefore, it is unlikely that implementation of troublesome dyskinesia will have a significant impact on the model outcomes. The above data indicate that troublesome dyskinesia is an uncommon outcome of treatment for advanced PD, and unlikely to be significantly different between alternative treatment options. This has been confirmed by clinical expert feedback received as part of this response, and has been ascribed to levodopa-sparing strategies often seen in UK clinical practice. Furthermore, knowledge, awareness, and management of troublesome dyskinesia has improved; treatment can be adjusted and anti-dyskinetic treatment such as amantadine prescribed to ease and reduce incidences of dyskinesia. Alternative approaches include consistent use of small doses of oral levodopa to keep patients in a state of 'On' Time without troublesome dyskinesia. It should be noted that the approach of not including troublesome dyskinesia may be considered conservative, for two reasons. Firstly, whilst not reaching statistical significance, the point estimates from M15-736 indicate foslevodopa-foscarbidopa may

		provide better control of troublesome dyskinesia when compared with oral CD/LD. Secondly, whilst troublesome dyskinesia is uncommon, patients receiving LCIG may experience biphasic dyskinesia due to its non-continuous nature,[1, 2] a burden unaccounted for in the model's approach to dyskinesia. AbbVie recognise that troublesome dyskinesia represents a burden in a minority of patients, however it is not expected to have a major impact on cost-effectiveness outcomes. For the reasons outlined above, AbbVie do not consider the structural incorporation of troublesome dyskinesia to be necessary, both practically and clinically, and have therefore not implemented any such changes in their revised approach.
Key Issue 10: The regressions used for health state cost by 'Off' time appear inappropriate Report sections: 4.2.4.3	No	**In the absence of more robust data, the Adelphi data remain the most appropriate source to estimate health state costs in the model. The benefit of using data from the advanced population is outweighed by the limitation of its small sample size, and the use of observed data from the overall population suggested by the EAG yields clinically implausible estimates. The use of regression analysis to the overall Adelphi population is therefore reasonable to estimate health state costs, given these limitations.** The EAG commented on AbbVie's approach to estimating health state costs, and the results of this approach informing the model, and considered that these overestimated costs in the model. The EAG instead proposed using the observed data directly to estimate health state costs in the model as opposed to AbbVie's regression analysis, and have presented this as an exploratory analysis in their report. However, the health state costs resulting from this analysis yield entirely clinically implausible results. For example, OFF state 4 is modelled as incurring the greatest cost, whilst OFF states 7–9 are now associated with the fewest costs. OFF state 0, associated with greatest symptom control, is assigned a health state cost three times greater than that of OFF state 16 in the EAG's analysis. These health state cost estimates lack face validity, and therefore cannot be considered appropriate for use in the economic model. The company's approach of using regression analysis accounts for the challenges

		observed by the EAG's approach resulting from the small data set and yields more clinically plausible estimates in which health state costs increase with increasing patient 'Off' time. Clinical feedback obtained in response to this issue agreed that in general more resource use occurs with patients with more advanced PD; it was noted that more 'Off' time is generally seen in patients with unmanaged symptoms and, accordingly, they require more support to manage their symptoms. The EAG also disagreed with the company's use of the overall Adelphi dataset, as opposed to restricting the analysis to the population of patients included in the Adelphi data who had been diagnosed with advanced PD. As noted in response to the EAG's clarification question B27, the Adelphi data for the advanced population are weakened by the limited sample size and may not be appropriate to reliably inform health state costs estimates, whether using directly observed data or via regression analysis. Whilst the use of the overall population is associated with some limitations relating to the generalisability of the data. AbbVie maintain that making use of all of the available Adelphi data has advantages over focussing on the narrower population. In conclusion, AbbVie maintain that the health state costs presented in the original submission are informed by the most robust data available, and the overall Adelphi population is appropriate to estimate health state costs.
Key Issue 11: The utility values used in the company's base case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making Report sections: 4.2.4.3	No	**AbbVie maintain that pooling EQ-5D data from different trials investigating foslevodopa-foscarbidopa is the most appropriate approach to estimating health state utility values in the model. The alternatives proposed by the EAG are not applicable and would likely result in less robust estimates of utility in the model.** The EAG have suggested converting the MDS-UPDRS data to an estimate for H&Y states of patients or use the MDS-UPDRS as a health state directly. The EAG have also suggested analysing changes in mean utility by categories of 'Off' hours, rather than hourly increments in 'Off' time, to inform utility values by a greater number of data points. For the reasons outlined in our response to Issue 3 above, AbbVie maintain the

		existing model structure is appropriate for decision making, and it is not appropriate to convert MDS-UPDRS to H&Y data. Therefore, these suggestions have not been implemented in the context of estimating utility. The EAG have raised concerns with the linear mixed model used to estimate utility values for each of the health states, and have questioned why variables such as age and sex were not tested. AbbVie have since tested including these additional variables as covariates in the linear mixed model. Whilst sex had a significant impact on utility (p=[redacted]), the coefficient for NROFF remained similar to that of the analysis excluding these additional covariates ([redacted] versus [redacted], respectively). Inclusion of age and sex in the linear regression model is therefore unlikely to have a significant impact on health state utility values. This has been confirmed by clinical expert feedback obtained in relation to this issue, which indicated that QoL differences are not expected between males and females. The assumption of linearity and use of a linear mixed model to estimate utility values is supported by a study by Thach et al. 2021, which utilised data from the US-specific 2017 and 2019 Adelphi Real World Disease Specific Programme for PD.[20] The regression analysis performed in this study of hourly daily 'Off' time and EQ-5D was adjusted for age, sex, body mass index, and the number of concomitant conditions related or unrelated to mobility. Their findings showed a linear regression coefficient of −0.018 (95% CI; −0.025, −0.011). The linear regression coefficients derived from the EQ-5D data from the foslevodopa-foscarbidopa clinical trials are all within the 95% confidence interval of the Thach et al. 2021 result (M15-741: [redacted]; M15-737: [redacted]; M15-736: [redacted]; M20-098: [redacted]). While this study utilises a US population, another study conducted using data from five European countries (France, Germany, Italy, Spain, and the UK) found that presence of 'Off' time is associated with reduced HRQoL, as assessed by PDQ-39 and EQ-5D; the impact on HRQoL increased incrementally as average 'Off' time increased.[21] Moreover, this regression shows a sensible trend, whereby fewer QALY gains are associated with more 'Off' time for patients with advanced PD. Clinician feedback obtained in response to this issue has

		confirmed this trend, indicating that it is expected that patients with more 'Off' time have a lower QoL. Additionally, the health state utilities in the model are adjusted for age (Document B, Table 61) by multiplying the utility per cycle by the relative age-related utility adjustment based on the mean age of the trial population in that cycle. To further support the current approach taken, the fit statistics for each individual foslevodopa-foslevodopa trial are presented in Appendix C, which demonstrate that the data are a good fit. As an alternative to converting the MDS-UPDRS data to an estimate for H&Y states and grouping patients by categories of 'Off' time, the EAG suggested using just a single study to inform utility values. The EAG note differences in EQ-5D values for 'Off' states reported by patients in the different studies. They suggest that this heterogeneity in HRQoL data across the studies means that the pooling of trial data is inappropriate, and that just a single study should be used in order to eliminate heterogeneity in the analysis. The company consider that this approach would not make use of all available foslevodopa-foscarbidopa data, and would use only a limited number of patients to inform health state utility values. Whilst AbbVie acknowledge that the approach taken introduces heterogeneity, a limitation of the analysis, it does make use of all available trial data. Nevertheless, to explore the impact of using single studies to inform utility values, scenario analyses have been conducted using M15-736 and M15-741 data alone. The results of these scenarios are presented in Table 6. It was also proposed by the EAG to use the data from the UK population with severe PD from the real-word Adelphi study to estimate utility values for those same 'Off' categories, in order to validate the estimates used in the updated analysis. This suggested approach is not appropriate due to the sample sizes available with EQ-5D data. Only [redacted] patients in the overall PD cohort, and [redacted] patients in the advanced PD cohort, have EQ-5D values reported. Further to this, the majority of patients ([redacted]) in the advanced PD cohort have OFF 0, with no EQ-5D data available for OFF 5+.

		Overall, AbbVie consider pooling data from the M15-736, M15-741, M20-098, and M15-737 studies, which represent comprehensive and robust sources of HRQoL data for patients receiving foslevodopa-foscarbidopa, the most appropriate approach to estimating utility values. Whilst this approach is associated with limitations, no better sources of utility data are available. The utility values in the company's original base case approach have therefore been maintained in the cost-effectiveness analyses presented in response to technical engagement.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3: Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The data source for discontinuations for LCIG appears to go on for 16 years but only 2 years of data was used.	4.2.7.1	No	A long-term discontinuation per six-monthly cycle rate of 3.5% is applied to LCIG following 24 months (this standard rate is also applied to foslevodopa-foscarbidopa), which is aligned with the approach taken by Chaudhuri et al. 2022 for the LCIG cost-effectiveness model.[10] Chaudhuri et al. 2022 sourced the six-monthly 3.5% rate from Fernandez et al. 2018, which reports a 6.9% annual LCIG discontinuation rate.[22] This 6.9% rate was calculated by taking the number of patients discontinuing therapy each year (Years 2–5, as Year 1 is captured separately) for reasons other than mortality and applying a weighting based on the sample size at the beginning of each year. Patients discontinuing due to the withdrawal of consent were included in this calculation, as patients' reasons for consent withdrawal are expected to mirror reasons for patient treatment termination in clinical practice. Treatment discontinuations after 24 months are not expected to differ by advanced treatment, and

			therefore, the same six-monthly discontinuation rate (3.5%) is applied after 24 months for both foslevodopa-foscarbidopa and LCIG.
Additional issue 2: The source for the rate of dyskinesia in LCIG patients appears to relate to oral levodopa.	4.2.8.1	Yes	The EAG have highlighted that the source for the rate of dyskinesia in patients receiving LCIG, originally from Schrag and Quinn 2000, relates instead to patients receiving oral levodopa. AbbVie agree that this value is inappropriate for patients receiving LCIG. To address this, the rate of dyskinesia in LCIG patients has been updated in the cost-effectiveness model to 0%. This is in line with the rate of dyskinesia as a TEAE associated with product complaints that was reported for foslevodopa-foscarbidopa in M15-736.[17] It should be noted that the 0% rate of dyskinesia for LCIG is a conservative estimate; the Olanow 2014 LCIG RCT reported a rate of dyskinesia for the LCIG arm of 13.5%, and biphasic dyskinesia may be experienced by patients during LCIG treatment due to its non-continuous administration, as noted in response to Key Issue 2.[1, 2, 18] However, as noted by the EAG, dyskinesia rates for LCIG that are significantly higher than BMT and foslevodopa-foscarbidopa are clinically implausible given the mechanism of action. Further, as discussed above in Issue 9, troublesome dyskinesia is not a commonly reported AE in patients with PD in UK clinical practice; rates of dyskinesia are often minimised through the use of levodopa-sparing strategies and treatment with anti-dyskinetic medication such as amantadine. The rates of dyskinesia observed in the

			Olanow study are likely to overestimate the rate of dyskinesia associated with treatment with LCIG in UK clinical practice. AbbVie therefore consider the conservative approach of applying a rate of 0%, in line with the rate observed for foslevodopa-foscarbidopa, to be most appropriate. The results of updating the rate of dyskinesia for LCIG to 0% are presented in Table 4. In addition, a scenario analysis in which the dyskinesia rate for LCIG is aligned with the values reported in Olanow 2014 (13.5%),[18] is presented in Table 6, showing limited impact on the base case cost-effectiveness estimates.
Additional issue 3: Applying AEs only in the first cycle is inappropriate when most of these AEs would be expected to progress over time.	4.2.8.1	Yes	As part of clinician interviews conducted for this appraisal, clinical experts expressed that it is possible for infusion site reactions, nodules and infections to be controlled with appropriate hygiene and education. If patients are aware, and site rotation is applied appropriately, the risk of these AEs and the chance of progression can be minimised. Further, aside from injection site-related AEs, it can be argued that dizziness and falls may be features of disease progression and therefore likely to be accounted for by 'Off' time in the model. Nevertheless, in order to take a conservative approach and consider the possibility that these AEs may progress overtime in clinical practice, infusion site-related AEs have been applied continuously over the model time horizon for foslevodopa-foscarbidopa and

			LCIG, whilst dizziness and falls have been applied continuously over the model time horizon, for all treatments. In addition to this, in line with clinical feedback that injected-related AEs can be controlled, a scenario analysis where only dizziness and falls are applied continuously has been conducted, the results of which are presented in Table 6. Further to this, AbbVie agree with the EAG's suggestion of removing injection-related AEs for BMT. These had originally been added as the AE incidences were aligned with the M15-736 trial which had reported injection site-related AEs for BMT. However, AbbVie agree that these were likely due to the dummy injection patients in the control arm received, rather than any medications constituting BMT. These AEs have therefore been excluded from the BMT arm in the revised company base case. The results of both of these changes are presented in Table 4.
Additional issue 4: LCIG recurring AEs continue occurring at the same rate regardless of the percentage of patients on treatment	4.2.8.1	Yes	The EAG have questioned the implementation of the recurring AEs for LCIG. Recurring AEs relating to the need to replace and or reposition the infusion set used to administer LCIG were included in the model, and were applied on a per-cycle basis in the model. To address this issue, in the updated model, the recurring LCIG AEs are now applied based on the

			percentage of patients receiving treatment in the cohort, and the results of this of presented in Table 4.
Additional issue 5: The Dirichlet distribution applied to the health state transition probabilities for the PSA appears to have been calculated erroneously	6.1	No	AbbVie recognise that the Dirichlet distribution in the PSA was being applied erroneously. As a result of this error, variation in the stochastic value appeared to be untied to the mean value, which essentially reduced the effectiveness of both LCIG and foslevodopa-foscarbidopa. AbbVie have examined the way in which the EAG have corrected the Dirichlet distribution, and agree that the changes made are accurate and this is now applied in the model correctly. The EAG's correction has therefore been maintained in the updated model.
Additional issue 6: LCIG administration and treatment management costs appear to be overestimated	4.2.11.4 and 4.2.11.6	Yes	AbbVie agree that the administration costs associated with LCIG in the model may represent an overestimate. The costs associated with the administration of LCIG have been updated as per the EAG's recommendations of aligning with the 2016 NICE guideline for PD (NG71), updated to 2021 costs, amounting to a total of £2,929.[6] The model has also been updated in relation to the treatment management costs of LCIG. The EAG recommended using the costs of one gastroenterology non-consultant led outpatient appointment to model the cost of PEG tube removal, in line with the NICE guidelines for PD (NG71);[6] this cost has now been updated to £141.41 based on the 2019/20 NHS

			reference costs for this appointment. The results of these updates are presented in Table 4. AbbVie would additionally like to note that the EAG's estimates may not entirely capture the full administrative burden associated with treatment with LCIG. Initiation of treatment with LCIG requires a hospital appointment for surgery to insert the PEG feeding tube and requires another appointment to be removed upon treatment discontinuation. However, these surgical appointments are subject to the pressures faced by the NHS, leading to appointments for PEG surgery appointments being delayed or cancelled. As noted in Issue 2, as of August 2022 just under 50% of patients were waiting for over 18 weeks to start treatment within a neurosurgical service in NHS England.[3] Approximately 42% of surgical postponements and cancellations were due to "clinical issues",[4] which normally are a result of not being able to place the PEG tube (e.g. due to patient anatomy); this is where foslevodopa-foscarbidopa represents a meaningful alternative for patients, given the lack of surgery requirement. Additionally, 21% of surgical postponements and cancellations have been ascribed to NHS workforce issues, 4% ascribed to no beds being available, and a further 2% due to issues with gastric services.[4] These figures provided are likely under-representations, as patients not yet progressing to a booking due to lack of bed availability or gastro service availability are not captured in these data. These delays

			and cancellations are associated with increased costs to the NHS. The costs associated with LCIG treatment administration presented as part of these responses do not capture these additional administrative costs, and are therefore likely to underestimate the true cost to the NHS of treating patients with LCIG. The EAG have additionally suggested that the costs of administering foslevodopa-foscarbidopa may be overestimated in the model. These are currently modelled as [redacted] outpatient visits for titration and monitoring purposes. Each such visit is estimated to cost £726.60, based on previously published literature.[10] However, AbbVie recognise that this approach may overestimate costs associated with the administration of foslevodopa-foscarbidopa. This has therefore been updated, with the administration of foslevodopa-foscarbidopa now being associated with two non-consultant led appointments, one associated with titration, and another with monitoring; each appointment is based on the cost of one hour of non-consultant doctor time in the latest PSSRU costs (£120). This is considered a conservative approach; the EAG suggested a single outpatient visit should be needed, though AbbVie consider that a second could be expected to account for treatment optimisation with foslevodopa-foscarbidopa. A scenario analysis has therefore been conducted in which only one non-consultant led appointment is modelled as an

			administration cost for foslevodopa-foscarbidopa, the results of which are shown in Table 6. The results of these changes to the administration costs of treatments in the model are shown in Table 4.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4: Changes to the company's cost-effectiveness model

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Changes non-related to EAG issues			
Foslevodopa-foscarbidopa dosing	Patients received 10 mL foscarbidopa-foslevodopa	As per the M15-736 trial, the EAG updated the foslevodopa-foscarbidopa dose to 10.4 mL for the first month, followed by 10.2 mL. This has been updated and corrected to patients receiving 10.4 mL for exactly 28 days	See Table 5 below
Source for utilities adjustments	Janssen et al. 2019 used to adjust utility values by age and gender	During clarification questions this source was requested to be changed to Ara and Brazier 2010	See Table 5 below
Key issues			
Key Issue 2: Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG	Use of relative risks derived from the NMA using a mix of observed and LS means for foslevodopa-foscarbidopa and LCIG efficacy	Use of relative risks derived from the NMA using only observed means	See Table 5 below

Key Issue 4: Patients are assumed to retain a lasting benefit from treatment following discontinuation	Patients discontinuing active treatments in the model remained in the health states which they occupied at the point of discontinuation, at which point transition probabilities for the BMT arm were applied	Patients discontinuing active treatments in the model are redistributed to the BMT arm based on baseline distribution	See Table 5 below
Key Issue 5: The LOCF assumption does not align with the trial data	For the LOCF period (Months 3–36), the transition probabilities calculated for the trial period (Month 0–3) were applied	Patients remain in their health states for the LOCF period	See Table 5 below
Additional issues			
Additional issue 2: The source for the rate of dyskinesia in LCIG patients appears to relate to oral levodopa.	7.0% rate of dyskinesia in patients receiving LCIG	0% rate of dyskinesia in patients receiving LCIG	See Table 5 below
Additional issue 3: Applying AEs only in the first cycle is inappropriate when most of these AEs would be expected to progress over time.	AEs applied only in the first cycle, and injection-related AEs were applied for BMT based on M15-736	Infusion site-related AEs, dizziness, and falls applied continuously over the model horizon, and removed injection-related AEs for BMT	See Table 5 below
Additional issue 4: LCIG recurring AEs continue occurring at the same rate regardless of the percentage of patients on treatment	The rate of recurring AEs for LCIG occurred at the same rate regardless of the percentage of patients receiving treatment in the cohort	Recurring AEs for LCIG are applied based on the percentage of patients receiving treatment in the cohort	See Table 5 below

Additional issue 6: LCIG administration and treatment management costs appear to be overestimated	LCIG administration costs: £4,789 LCIG management costs: £718 Four outpatient visits for titration and monitoring purposes for foslevodopa-foscarbidopa	LCIG administration costs: £2,929 LCIG management costs: £141.41 Two non-consultant led appointments for foslevodopa-foscarbidopa, one associated with titration, and another with monitoring	See Table 5 below

Abbreviations: AE: adverse event; BMT: medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; LOCF: last observation carried forward; LS: least squares; NMA: network meta-analysis.

Table 5 below shows the impact in isolation of individual changes made to the company base case cost-effectiveness analysis presented at clarification questions, as well as the revised base case cost-effectiveness results. All results shown include 3.5% discounting of both costs and QALYs as per the NICE reference case, with the PAS included for foslevodopa-foscarbidopa and LCIG.

Table 5: Updated base case results, with-PAS

	BMT			LCIG		
	Incremental QALYs	**Incremental costs**	**ICER (change from clarification questions ICER)**	**Incremental QALYs**	**Incremental costs**	**ICER (change from clarification questions 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]
Updates to the base case not relating to EAG issues (applied individually, deterministic)						
Foslevodopa-foscarbidopa dosing	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]

	BMT			LCIG		
	Incremental QALYs	Incremental costs	ICER (change from clarification questions ICER)	Incremental QALYs	Incremental costs	ICER (change from clarification questions ICER)
Source for utilities adjustments	0.79	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]
Updates to the base case relating to EAG issues (applied individually, deterministic)						
Key Issue 2: Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.09	[redacted]	[redacted]
Key Issue 4: Patients are assumed to retain a lasting benefit from treatment following discontinuation	0.60	[redacted]	Foslevodopa-foscarbidopa dominant	−0.21	[redacted]	Foslevodopa-foscarbidopa dominated
Key Issue 5: The LOCF assumption does not align with the trial data	0.63	[redacted]	Foslevodopa-foscarbidopa dominant	−0.03	[redacted]	[redacted]
Additional issue 2: The source for the rate of dyskinesia in LCIG patients appears to relate to oral levodopa.	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]

	BMT			LCIG		
	Incremental QALYs	Incremental costs	ICER (change from clarification questions ICER)	Incremental QALYs	Incremental costs	ICER (change from clarification questions ICER)
Additional issue 3: Applying AEs only in the first cycle is inappropriate when most of these AEs would be expected to progress over time.	0.78	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]
Additional issue 4: LCIG recurring AEs continue occurring at the same rate regardless of the percentage of patients on treatment	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.11	[redacted]	[redacted]
Additional issue 6: LCIG administration and treatment management costs appear to be overestimated	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]
Company's revised base case (deterministic)	0.46	[redacted]	Foslevodopa-foscarbidopa dominant	−0.11	[redacted]	[redacted]
Company's revised base case (probabilistic)	0.46	[redacted]	Foslevodopa-foscarbidopa dominant	−0.12	[redacted]	[redacted]

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

Abbreviations: AE: adverse event; BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; LOCF: last observation carried forward; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Sensitivity analyses around revised base case

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.

Scenario analyses

Table 6: Results of the scenario analyses, with-PAS

Description	Foslevodopa-foscarbidopa		BMT			LCIG		
	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	Inc. costs (£)	Inc. QALYs	ICERs (£)
Base case (deterministic)	[redacted]	4.91	[redacted]	0.46	Foslevodopa-foscarbidopa dominant	[redacted]	−0.11	[redacted]
Issue 11: Utility values sourced from M15-736 data	[redacted]	5.84	[redacted]	0.19	Foslevodopa-foscarbidopa dominant	[redacted]	−0.04	[redacted]
Issue 11: Utility values sourced from M15-741 data	[redacted]	4.73	[redacted]	0.40	Foslevodopa-foscarbidopa dominant	[redacted]	−0.09	[redacted]
Additional issue 2: 13.5% dyskinesia rate for LCIG	[redacted]	4.91	[redacted]	0.46	Foslevodopa-foscarbidopa dominant	[redacted]	−0.11	[redacted]
Additional issue 3: Dizziness and falls applied continuously over the model horizon	[redacted]	4.94	[redacted]	0.49	Foslevodopa-foscarbidopa dominant	[redacted]	−0.11	[redacted]

Description	Foslevodopa-foscarbidopa		BMT			LCIG		
	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	Inc. costs (£)	Inc. QALYs	ICERs (£)
Additional issue 6: One non-consultant led appointment for foslevodopa-foscarbidopa	[redacted]	4.91	[redacted]	0.46	Foslevodopa-foscarbidopa dominant	[redacted]	−0.11	[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 A

AbbVie have updated the NMA using only observed means data from all the original available trials (DYSCOVER, M15-736, Olanow 2014). The results of this NMA are presented below in Table 7.

Table 7: Difference in mean 'Off' time change from baseline (95% CrI) relative to BMT

Treatment	RE (DIC = [redacted])	FE (DIC= [redacted])	FE SUCRA
BMT	-	-	[redacted]
Foslevodopa-foscarbidopa	[redacted]	[redacted]	[redacted]
LCIG	[redacted]	[redacted]	[redacted]

Abbreviations: BMT: best medical therapy; CrI: credible interval; DIC: deviance information criteria; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.

Appendix B

A modelling validation exercise was conducted to assess how 'Off' time evolves over time in the revised company model and that of the Chaudhuri et al. 2022 model. The results, presented below, demonstrate consistency for both BMT and LCIG.

Figure 5: Proportion of patients in OFF 3 health state over time for BMT

951 = foslevodopa-foscarbidopa; Duodopa = LCIG
Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel.

Figure 6: Cumulative proportion of patients in OFF 3 health state over time for BMT

951 = foslevodopa-foscarbidopa; Duodopa = LCIG
Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel

Figure 7: Proportion of patients in OFF 4 health state over time for BMT

951 = foslevodopa-foscarbidopa; Duodopa = LCIG
Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel

Figure 8: Cumulative proportion of patients in OFF 4 health state over time for BMT

951 = foslevodopa-foscarbidopa; Duodopa = LCIG
Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel

Figure 9: Proportion of patients in OFF 3 health state over time for LCIG

951 = foslevodopa-foscarbidopa; Duodopa = LCIG
Abbreviations: LCIG: levodopa-carbidopa intestinal gel

Figure 10: Cumulative proportion of patients in OFF 3 health state over time for LCIG

951 = foslevodopa-foscarbidopa; Duodopa = LCIG
Abbreviations: LCIG: levodopa-carbidopa intestinal gel

Figure 11: Proportion of patients in OFF 4 health state over time for LCIG

951 = foslevodopa-foscarbidopa; Duodopa = LCIG
Abbreviations: LCIG: levodopa-carbidopa intestinal gel

Figure 12: Cumulative proportion of patients in OFF 4 health state over time for LCIG

951 = foslevodopa-foscarbidopa; Duodopa = LCIG
Abbreviations: LCIG: levodopa-carbidopa intestinal gel

Appendix C

The fit statistics for the individual and pooled foslevodopa-foscarbidopa trials utility regressions are presented below in Table 8.

Table 8: Fit statistics for the individual and pooled foslevodopa-foscarbidopa trials utility regressions

Fit statistics	M15-741	M15-737	M15-736	M20-098	Pooled trials
−2 Res Log Likelihood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC (Smaller is Better)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AICc (Smaller is Better)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC (Smaller is Better)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; AICC: corrected Akaike's information criterion; BIC: Bayesian information criterion.

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

Company response to EAG clarification questions

1) Confirm how to interpret the results of mean difference in 'OFF' time from the NMA presented in Appendix A, Table 7 of the company response to Technical Engagement as the EAG notes that the results in this table are [redacted] values whereas the results in Table 29 of the company submission (Difference in mean 'Off' time change from baseline (95% CrI) relative to BMT, base case analysis) are [redacted] values.

The values presented in Appendix A, Table 7 were mistakenly presented as positive in the company response to Technical Engagement, and should indeed be interpreted as negative, indicating greater reduction in 'Off' time relative to BMT.

The updated NMA results are provided in full below in Table 1, corrected to be consistent with the presentation in the original company submission, with the results for foslevodopa-foscarbidopa and LCIG relative to BMT. The last comparison is presented as foslevodopa-foscarbidopa relative to LCIG, as requested by the EAG.

2) Provide the results for the comparison of Foslevodopa-foscarbidopa vs LCIG from the updated NMA presented in the company response to technical engagement.

The full results of the NMA including the comparison of foslevodopa-foscarbidopa versus LCIG are provided in Table 1.

Table 1: Difference in mean 'Off' time change from baseline (95% CrI)

Treatment	RE (DIC = [redacted])	FE (DIC = [redacted])
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]

Abbreviations: BMT: best medical therapy; CrI: credible interval; DIC: deviance information criteria; FE: fixed effects; LCIG: levodopa-carbidopa intestinal gel; RE: random effects.

3) Provide the OpenBUGS files for the new network meta-analyses.

The updates analyses were run using bnma R package. Illustrative R code for fixed and random effects models are shown in Figure 1 and **Abbreviations:** NMA: network meta-analysis.

Figure 2, respectively.

Figure 1: R code for fixed effects NMA

Abbreviations: NMA: network meta-analysis.

Figure 2: R code for random effects NMA

Abbreviations: NMA: network meta-analysis.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **8th December 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Treating Parkinson's and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Camille Carroll
2. Name of organisation	University of Plymouth
3. Job title or position	Professor Clinical Neuroscience
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Parkinson's? ☒ A specialist in the clinical evidence base for Parkinson's or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for Parkinson's? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Alleviate the motor and non-motor symptoms, improve mobility and ability to undertake daily tasks, improve quality of life, prevent hospital admissions, maintain independence, prevent disease-related complications.
9. What do you consider a clinically significant treatment response?	Improvement in patient-reported outcomes, activities of daily living, quality of life.

(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in Parkinson's?	Yes – symptom control and slowing disease progression are two of the unmet needs. Also predictors of progression, predictors of events.
11. How is Parkinson's currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Treatment is mainly guided by NICE Guidance (2017). There are variations in practice between individual practitioners, services, organisations and regions. Parkinson's UK audit standard compliance varies. In general patients are seen by neurologists or geriatricians with interest in Parkinson's disease or movement disorders, but this is not always the case. Many patients are cared for by general neurologists or general geriatricians without subspecialty expertise. Most patients have access to a Parkinson's disease nurse specialist supporting their care in the community. The expertise of the nurses varies between organisations and regions. Many nurses are non-medical prescribers, but this is not always the case. Patients resident in nursing homes or too frail to attend clinic might be looked after by their GP, supported by a community PDNS. The level of input to care homes/nursing homes varies between regions, largely dependent on caseload of the PDNS and their level of expertise. If patients are admitted to hospital they may or may not have access to an in-patient Parkinson's specialist team. People with Parkinson's have higher rates of admission to hospital, longer length of stay and increased mortality than age-matched peers. Hospital admissions are usually related to falls (related to motor and balance problems, orthostatic hypotension), often complicated by hip fracture, and infections – particularly urinary tract infections (related to neurogenic bladder and constipation) and chest infections (related to immobility, impaired ventilatory capacity and swallow impairment). Hospital admissions are

	frequently complicated by delirium and decompensation of parkinsonism. This is compounded by patients not receiving their time-critical medications. In the event that swallow or oral intake is compromised, non-oral medication administration routes for dopamine replacement therapies need to be utilised. Care based on oral therapies is usually provided within a secondary care out-patient clinic setting. To treat significant motor (and non-motor) fluctuations, patients are considered for device-aided therapies. s/c apomophine infusion or injection is generally available within secondary care or community care based teams. Patients may not be suitable for s/c apomorphine infusion, for example if they have orthostatic hypotension or cognitive impairment. If patients require other device-aided therapies (eg LCIG or DBS) they are usually referred to a tertiary centre. The distances involved are a significant barrier to access for many patients. The technology would impact on the current pathway of care by increasing the accessibility of infusion therapies for those not suitable for apomorphine, for whom DBS is not an appropriate treatment option. It would also provide a more accessible treatment option for those suitable for DBS, and a less burdensome treatment option for those suitable for apomorphine. The therapy is easy to use and implement and could be available to patients via their local specialist service – whether secondary care or community based.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Current care for people with impactful motor and non-motor fluctuations despite optimisation of oral therapies is evaluation for device-aided therapies – s/c apomorphine, LCIG or DBS – depending on various criteria. The technology would be similar in terms of resource use to s/c apomorphine, except it would involve less in the way of safety checks and assessments (no ECG, no blood tests), and less monitoring (no requirement for blood tests). Patients would be able to be titrated up to a therapeutic dose very quickly within

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	a community/home setting. In contrast, apomorphine initiation involves either a clinic or hospital-based start or a slow titration at home. They could be effectively maintained on this technology as monotherapy. In contrast, patients on apomorphine usually require continuing levodopa oral doses. The technology should be used in any Parkinson's service – which could be secondary care, tertiary care or community-based. This could be initiated and managed by a prescribing PDNS. Investment needed – primarily training for staff supporting patients with the use of the technology.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – I expect this technology to result in a significant increase in health-related quality of life for the person with Parkinson's. Also a significant increase in carer quality of life and reduced carer burden.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I think most patients with levodopa dose-related fluctuations would find this therapy effective. Patients who live alone might find this more difficult, particularly if they have dexterity problems, visual impairment or cognitive impairment.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	The drug needs to be stored in a fridge, so storage space at home might be an issue for some. Travelling with the drug requires cool bags etc.

acceptability or ease of use or additional tests or monitoring needed)	This technology would be easier to use than s/c apomorphine infusion for both patients and healthcare professionals. The infusion site change is less frequent (every 72 hours), the adverse event profile is more favourable. The technology would also be less burdensome and carry less risk for patients than DBS and PEJ-insertion for LCIG. The technology does not require the hospital admissions and clinical assessments required to ascertain suitability for DBS or LCIG.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting and stopping rules would be informal. For starting, the same selection criteria would apply as for other device-aided therapies – impactful motor and non-motor fluctuations, with no contra-indications. Stopping would be in the event of adverse events or lack of tolerability/efficacy.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The technology will be much easier to administer than standard of care – either BMT or s/c apomorphine infusion. It will relieve the patient of significant pill burden. The much prolonged on time will alleviate carer burden and increase carer QoL, which will result in less institutionalised care. The unpredictability of motor state in the context of BMT will be alleviated with this technology, which could allow retention in the workforce. Improved motor and non-motor symptom control will result in reduced hospital admissions. Having this therapy option available as a non-oral alternative for in-patients will reduced missed time-critical medications and reduce length of stay and hospital-admission related morbidity.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	Yes – this is an innovative technology with the potential to make a significant and substantial impact on the lives of many people with Parkinson's. This is a step-change in Parkinson's management.

• Does the use of the technology address any particular unmet need of the patient population?	Yes – it allows access to impactful and effective device aided therapy to everyone with Parkinson's, as it is easily deliverable via community-based teams. This will address significant contributors to healthcare inequalities related to geographical location and tertiary-level service provision.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are dopamine-related and similar to those with other levodopa or dopamine agonist preparations. There is a potential for adverse effects related to infusion site reactions/infections. These are generally short-lived and would not impact too much on patient quality of life.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes – the trials reflect UK clinical practice. The most important outcomes are off time, activities of daily living and quality of life, and these were measured in the trials. Other benefits – such as effect on non-motor fluctuations, carer QoL/burden – were not measured in the trials. All adverse events were apparent in the trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	There is no real world data on this technology.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	Patients with physical or learning disability might find this technology more challenging, similar to current alternatives – LCIG and apomorphine. Pump-based therapies might be less acceptable in some cultural or ethnic groups.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Potential overestimation of treatment benefit for foslevodopa-foscarbidopa Report sections: 2.3.1, 3.2, and 3.3	The population addressed in the submission is a sub-population of the trial population, particularly those in 741, in which previous DBS was not an exclusion criterion. Patients who were experiencing significant fluctuations despite previous DBS were included. However, these patients were not included in 736. Although some ([redacted]) of 741 participants had previous apomorphine exposure, it is not known how many participants were unsuitable for apomorphine. The trial population was more representative of patients suitable for DBS and apomorphine than patients suitable for LCIG (those who have failed apomorphine and/or DBS or those in whom these therapies are contra-indicated). It is possible that this is particularly the case for those in whom the treatment was discontinued. There may have been an overestimation of the treatment benefit due to unblinding in the RCT. However, the findings are dramatic and consistent across several measures. Additionally, they are sustained and reproduced in the other studies reported.
Uncertainty in indirect treatment comparisons of	Nothing to add to this point.

foslevodopa-foscarbidopa and LCIG Report sections: 3.4 and 4.2.6.4	
OFF states 0-16 is inadequate at capturing the range of health effects of advanced Parkinson's, given the data available Report sections: 4.2.4.3, 4.2.6.4 and 4.2.10.1	Agree that H&Y can be easily derived from the MDS-UPDRS. There may be other contributors to OFF state-associated QoL, in addition to the duration of OFF time, such as the severity of the OFF state, predictability of the OFF state and timing of the OFF state, such as early morning OFF. There is heterogeneity in rate of disease progression, and this is related to factors such as age, sex and H&Y stage.
Patients are assumed to retain a lasting benefit from treatment following discontinuation Report sections:4.2.4.3	From my experience, changes in OFF time for patients who discontinue treatment are seen within hours. However, it is plausible that patients may have some longer-term benefit from their treatment. Whilst on treatment patients will have had better sleep and increased mobility, maintaining a better level of function, muscle strength and cardiovascular fitness than they would have had with progressively worsening and increasing duration OFF time. Some of these benefits might be sustained following treatment discontinuation.
The LOCF assumption does not	Nothing to add to this point. Agree the trial data do not support the LOCF assumption used in the model.

align with the trial data Report sections: 4.2.6.4	
Problems with the use of Palmer *et al.* 2002 in informing BMT Report sections: 4.2.6.4	Nothing to add to this point.
The company did not use the trial M15-736 trial data on the comparator arm Report sections: 4.2.6.4	If the purpose of the model is to demonstrate the potential value of the therapy in the NHS setting, then I agree that the benefit of that treatment is a combination of the treatment effect and the placebo effect. The comparator of BMT in the NHS setting would not have exposure to an infusion and therefore experience neither placebo nor treatment benefit.
The company uses efficacy data and discontinuation data from different sources	I don't think the participants in 741 and 736 are too dissimilar. The efficacy data are comparable. I think 741 cohort 2 data might be more reflective of the discontinuation rate were the therapy to be started within the NHS. The lessons learned from the earlier high discontinuation rate enabled practice to improve, in addition to utilising a new administration set. These learnings can be implemented in care services.

Report sections: 4.2.7.1	
Troublesome dyskinesia appears to be a source of unaccounted for patient burden Report sections: 4.2.8.1	Agree dyskinesia can be troublesome. As well as physically limiting (for a minority), it can also be socially stigmatising and impact social confidence. There is some rationale for how long term (ie >3 months) continuous dopaminergic stimulation may result in reduced dyskinesia – via neuromodulatory mechanisms. This effect might not be so apparent in the shorter term – up to 3 months.
The regressions used for health state cost by OFF time appear inappropriate Report sections: 4.2.4.3	Re: early and intermediate PD. I would be interested to know the definitions of these terms. One definition of 'advanced' is that it includes everyone with wearing off. If early and intermediate are defined according to other criteria – eg H&Y or disease duration, then these categories might well include patients with wearing off (and therefore be 'advanced' according to different criteria). However, these patients are likely to be those suitable for apomorphine and DBS, and therefore not within the scope presented (who have to be unsuitable or have failed apomorphine and DBS). From the report (section 4.2.4.3) it appears that advanced patients were more likely to be in a nursing home, for example, and therefore not represented by the trial participants. I suspect trial participants are more representative of intermediate severity patients. In summary – I suspect the Adelphi intermediate patients are most similar to the trial populations, and that Adelphi advanced are more advanced than the trial populations. The terms early, intermediate and advanced should be clearly defined. Are informal care costs/lost earnings (patient and carer) considered in the model?

The utility values used in the company's base case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making Report sections: 4.2.4.3	H&Y score can be easily derived from MDS-UPDRS part III. I have nothing further to add to this point.
Are there any important issues that have been missed in EAR?	Non-motor fluctuations – particularly of symptoms such as 'brain fog', anxiety and fatigue – can be hugely impactful on quality of life, for both patient and carer. These non-motor features of the OFF state would also be expected to improve with the reduction in OFF time. Some of the items captured in the trial outcomes will correlate with/predict events such as falls or infections – ie drivers of hospital admission, which would add to healthcare costs.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This is a game changing intervention.
Its ease of use should facilitate its being widely available, reducing healthcare inequalities related to geographical influences.
The trial populations are the populations that would benefit greatly from this therapy – those suitable for DBS and apomorphine.
The population within the submission is not well represented in the trial populations.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **8th December 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Treating Parkinson's and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	PATHIKONDA UMA NATH
2. Name of organisation	South Tyneside and Sunderland Foundation Trust
3. Job title or position	Consultant neurologist and Parkinsons disease specialist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? I am a local BMA representative for STSFT. I am a member of the Advisory group for Movement disorders which is part of the Association of British Neurologists. ☒ A specialist in the treatment of people with Parkinson's? ☐ A specialist in the clinical evidence base for Parkinson's or technology? ☒ Other (please specify): President local branch Sunderland Parkinsons UK
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE
8. What is the main aim of treatment for Parkinson's? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main hope for treatment is to prevent or reverse this neurodegenerative condition. There is much effort to try to find a drug to slow disease progression, as yet not successful. The main aim of currently available therapies is to provide

	symptomatic benefit and evenness of response ie continuous dopaminergic stimulation so that patients are not primed for dyskinesias or motor fluctuations.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	This is a complex question given PD heterogeneity. A reduction that is meaningful to patients is clinically significant. Objectively a reduction of 5 to 6 points on UPDRS is generally considered significant. It is generally accepted that clinical progression in PD is multidimensional. There is no clear consensus on how to best implement clinically meaningful endpoints that would reflect the way these complex interactions influence and impact on the evolution of global disability in PD. There are no good biomarkers to help measure treatment response. Broadly looking at placebo arms of clinical trials in PD, they show an 8-10 point rate of increase in UPDRS total scores annually, with 5-6 of these for the motor subsection of UPDRS. Given this magnitude of change in UPDRS , 5-6 points has been suggested as a threshold for clinically significant differences.
10. In your view, is there an unmet need for patients and healthcare professionals in Parkinson's?	Yes there is a significant unmet need for safe and effective therapies in Parkinson's patients who are not responding to or do not tolerate best medical (oral/transdermal) therapy. Over 6.1 million people worldwide have Parkinson's disease and the number of patients affected will increase over time due to the ageing population. At our local branch meetings (I am the President of the Sunderland Parkinsons disease association), every year the request for my annual lecture is for "new therapies to offer hope for PD patients". There is particular interest in those drugs for advanced PD as there are so few options in this group of patients at present, and there are a significant proportion who are not suitable for apomorphine infusions or deep brain stimulation.

	PD still has a poor prognosis. In one longitudinal study, after 15 years of disease duration, over 70% died and half of the remaining patients required nursing home care (Poewe 2009). Schrag and Banks et al found that up to 57% of PD patients retired early due to their PD and mean age of retirement was 55.8 years as opposed to the average retirement age of 62 years in the UK population. Patients are very keen to have more choices which use novel drug delivery systems or new drug formulations. Both motor and non motor symptoms contribute to disability. Not all symptoms of PD are levodopa responsive. The unmet need of PD patients with poorly levodopa responsive symptoms will still be an issue even with this infusion as it only addresses dopamine neurotransmitter and there are a variety of neurotransmitters involved in patients with PD. Axial symptoms such as posture, balance and gait difficulties will still not be likely to be significantly improved as they are poorly levodopa responsive in general. Best medical therapy also becomes less effective over time and with longer disease duration the narrower the therapeutic window. This is partly due to ageing and other factors but also the fact that gastric emptying becomes more erratic. There are some common general misconceptions around Parkinson's disease. For example, it may be felt that it is "just a tremor" whereas the symptom complex is far more than that. This patient group is heterogenous with some progressing at a very slow rate for many years. In all cases, there are a number of effective symptomatic treatments to help the different problems, both motor and non motor but additional treatments particularly late in the disease are needed. There is a need for more awareness and understanding of the condition. The disease though quite common is not as well understood as other long term conditions such as heart failure. The motor fluctuations and dramatic switching from dyskinesias (uncontrolled movements) to off states where patients are unable to move at all, can be occasionally mistaken for lack of effort and poor motivation. PD patients nearly all, sadly, eventually develop significant cognitive impairment.

	Patients being considered for Levodopa-carbidopa intestinal gel (LCIG) or deep brain stimulation (DBS) may be not accepted due to frailty or gastric problems, not able to travel up to a regional centre where the treatment is available or are unable to undergo surgery. Thus they are denied access to advanced therapy and often are not suitable for apomorphine which has several side effects (somnolence, nodules on skin and some mental health issues). Even when patients are referred to regional units the pressure on those services is high and waiting lists may be quite extensive. Making this drug available may reduce pressure on those waiting lists and also would be available to those who would not be suitable for the current advanced therapies. It is also possible that lack of awareness of available options for advanced disease and a negative perception of the treatability of this condition may mean that patients who might be considered for advanced therapies, are not referred or not referred early enough. It may be believed that any cognitive impairment means that they cannot be referred whereas this is not always the case. There are patients who are worried about having an operation in whom a subcutaneous infusion might be much more acceptable. Some patients may feel that the LCIG pump currently available is bulky and will be concerned about difficulty using due to dexterity issues. All these may benefit from this treatment.
11. How is Parkinson's currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	NG 71 guideline (2017) is one guideline that is used in treatment and management of Parkinson's disease There is broad consensus on treatment pathways for PD patients in the UK. The pathway of care is relatively well defined even given the clinical heterogeneity of this condition. I think this technology would have a huge impact on patients. It would reduce pressures centrally and support a truly local patient-centred service. Some of the factors limiting awareness and use of advanced therapies would be obviated; for example the ease of local use might increase accessibility of treatment compared to other device aided therapies. This may reduce admissions to hospital due to poor control and complications of medical therapy side effects and might reduce waiting list for other advanced therapies as well.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This treatment can be set up and administered more locally than LCIG and DBS. The new technology is more expensive than current standard best medical therapy. All therapies for patients with advanced disease are more expensive than best medical therapy. The important difference from LCIG and DBS is that it doesn't need an operation to start the new treatment. This means no anaesthetic is required. Involvement and workload for surgeons, anaesthetists, gastroenterologists who would be involved in some of the other therapies for patients with advanced PD would be lessened. The risk of displacement of the subcutaneous infusion is less than for LCIG. These factors may impact health care resource use, reducing its total cost to the health service compared to other advanced therapies. The clinical setting would likely be secondary care in district general hospitals with specialist nurse support. Perhaps it could be done with appropriate support and home visits in primary care once the technology is more familiar to PD teams across the UK. Investment is needed in the following areas: -training of PD specialist nurses and consultants/SpRs. -Facilities for storage and set up within hospital settings. -Training of hospital staff in case patients are admitted. -Training of pharmacists both in primary and secondary care. -Training to be given to relevant healthcare staff on picking up and managing skin problems, infections and nodules. -Support and staffing in the community for patients in care homes or their own homes who need support to set up and use the new therapy which is given overnight.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Please reference my responses to above questions to avoid duplication.

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Studies on whether Parkinson's disease affects mortality are quite complex to interpret. Certain subgroups such as tremor dominant disease themselves are said to have better survival than the gait difficulty- postural instability(PIGD) subtype. I think it unlikely that foslevodopa-foscarbidopa will increase length of life more than currently available therapies. I do expect it to increase health-related quality of life (HR QOL) more than best medical therapy. In that population who were not suitable for any other of the advanced therapies this new technology may reduce falls and avoid hospital admissions. If it does, it is thus likely to increase their QOL compared to best medical therapy. The magnitude of effect is difficult to be sure of in absence of head to head studies. Since it is much more convenient to administer than LCIG, this may positively impact quality of life in this case too. Skin related problems however may cause discontinuation. There is some evidence that LCIG could reduce caregiver burden and carer anxiety in Parkinsons disease and it is possible that this new technology could also achieve this. Further studies with this outcome measure included would be helpful.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are patients with symptoms of PD which are poorly or non levodopa responsive. These include freezing, falls and gait problems. These would not be expected to benefit significantly from this therapy. Patients with visual impairment or cognitive impairment or significant dexterity problems may find it difficult to use the device and would rely on carer support which may be limited. Patients with skin problems may not be suitable. Any allergies to component of drug may be relevant.

	The group of patients who are likely to benefit most are those with advanced PD mainly with motor symptoms which are responsive to levodopa and who are relatively cognitively preserved and who are able to manipulate the device as required.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Ease of use and administration compared to LCIG and surgery are big advantages of this new technology. Apomorphine infusions are currently delivered locally rather than in regional centres and similarly this new drug would not need to involve referral to a regional specialist centre. This infusion may have fewer side effects than apomorphine. There is no need for gastroenterology involvement as there is no requirement for a PEJ tube. The unpleasant nasogastric initiation phase for LCIG can be avoided. The therapy can be discontinued easily whereas deep brain stimulation carries a risk of stroke and is not reversible. The new technology does need to be stored in fridge. It needs to be administered continually so support will be required overnight if there are issues with the infusion such as blockage or dislodging of the cannula. Patients need adequate supplies and support if they run into any issues, so the drug is not stopped suddenly which could carry a risk of sudden and severe “off” period. Each patient would require an emergency protocol for this eventuality potentially involving reversion to oral medication.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is likely that regional and local pathways will be developed using the informal links and networks already set up by PD professionals to determine the appropriate referral pathway. This is likely to evolve as PD professionals both nurse specialists, community nurse teams and PD consultants become more familiar with foslevodopa-foscarbidopa. In the longer term the pathway for this therapy could be in secondary local care or even, with specialist support, in a primary care setting, Stopping criteria will need to similarly be determined. Testing and monitoring patients clinically and//or with UPDRS will be helpful. Neuropathy may be a side effect as with LCIG so it may be useful to monitor for B12 deficiency.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	It is difficult to include factors like ease of local use, convenience for patients and carers in QALY calculations. The QALY calculation should include risk of standard best medical therapy which is accompanied by deterioration over time and potentially more complications affecting QOL and number of hospital admissions. The treatment can be more easily started, adjusted and stopped than LCIG or surgery and with less risk to patients. The above answers already submitted make clear the substantial health related benefits of this technology.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is a novel approach to treatment using a subcutaneous infusible formulation of levodopa (prodrug). It is not a dopamine agonist like apomorphine so does not have the side effects of that class of drug. It does not require PEJ tube insertion or brain surgery as for deep brain stimulation. It could be given in a local centre quite possibly more near the patient's home. It could be set up and given from a district hospital base. It is given over 24 hours so is reasonable that the stabilisation in plasma levels might lower the future risk of dyskinesias. Other advanced therapies like LCIG or apomorphine are not 24 hour infusions so it is possible that better overall 24 hour control could be achieved. In all these ways the new technology is innovative. It seems to be a highly effective treatment which is simpler to administer than some other therapies for advanced PD.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are a number of listed side effects in trial M15 736. Trial data M15 736 shows that there was a high rate of discontinuation of the trial drug. There were also significant number of skin and infusion site reactions in the active group. There was a significant number of adverse events. Serious adverse events occurred in 25.4% of patients on the trial drug. Some led to drug discontinuation. TEAE associated with product complaints were much more

	common in the trial infusion group than the oral therapy group. Redness, pain and cellulitis were common in the treatment group. Patients with Parkinson's disease often become quite ill with intercurrent infections and take longer to recover back to their baseline than the normal population. Against this, there would be a likely reduction in oral drug-related side effects where the new drug allowed a reduction in concomitant oral medications. This could improve quality of life including, potentially, cognition as cognitive side effects of other oral therapies are common. Skin tolerability and nodules may prove to be problematic and limit the usefulness of this therapy. It will not always lead to discontinuation. Rotation and other measures such as ultrasound may help nodules. There are no head to head studies directly comparing this drug to other advanced therapies. Metaanalyses comparing other advanced therapies LCIG, apomorphine and surgery are rare. The comparisons are often difficult due to patient heterogeneity and different criteria for best medical therapy. Broadly speaking, what is reflected in clinical real world experience is that patients sometimes prefer apomorphine infusions over other advanced therapies like LCIG due to convenience and availability of local centres for Apo challenge and monitoring. Foslevodopa foscarbidopa shares this advantage with apomorphine.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes I feel it broadly does reflect current UK clinical practice. The most important outcomes were measured in the trials. These included change in "on" time without dyskinesia, reduction in "off" time both using diaries and UPDRS 2 measures. It also included early morning akinesia status which is clinically valuable as patients usually need to be active in the mornings to get ready for the day. Wearable devices provide additional relevant information and it would be useful to see this data if it were to become available. The use of PDQ 39 is a reasonable measure of quality of life in this group. Caregiver burden could be a useful additional measure in future studies

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	There is a reasonable correlation between real world experience and the trial data for other similar drugs such as LCIG. A review of safety and efficacy of LCIG over 24 months across 75 centres found that LCIG reduced "off" time, "on" time without dyskinesias, motor fluctuations and non-motor symptoms. A proportion of patients had sustained improvements in sleep and mood and cognition. Foslevodopa-foscarbidopa is based upon levodopa therapy and is using a novel administration approach over 24 hours with subcutaneous infusion. It is reasonable to consider that the side effect profiles and benefits might share some similarities to LCIG with the exception of the mode of delivery specific side effects. Given the entirely different approach to route of administration, a head to head direct study to compare the two would nonetheless be key information.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Patients with cognitive impairment, those who are older and frail, and those who are more isolated, for example without a carer, may find it more difficult to access and use this therapy than oral therapies. The use of the drug in pregnancy may not have been studied and as the disease normally occurs in those beyond childbearing age data may not be available. I am not aware if the drug contains any nut products if so, allergy sufferers would need to be informed. For those with visual or hearing impairment, patient information should be provided in accessible form and if necessary braille or audio, A signing interpreter may be needed to explain the drug to those with hearing impairment.

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Potential overestimation of treatment benefit for foslevodopa-foscarbidopa Report sections: 2.3.1, 3.2, and 3.3	The scope of the patients in the trial is a narrower population than the NICE scope overall. This smaller population of patients may be older, more frail and possibly with more cognitive issues rendering them unsuitable or intolerant of other treatments. Severe depression, cardiac disease, somnolence, autonomic dysfunction or significant impulse control disorders can all represent relative contraindications to other advanced therapies. Patients might have stopped apomorphine due to infusion site reactions or nodules or have problems with subcutaneous injections. Patients with gastric surgery may not be suitable for LCIG. The company might be able to provide more information on whether some patients in study M 15 736 had been on other advanced therapies, if so which therapy and the reason for discontinuation. Patient diaries are not a perfect way to record symptoms as they are necessarily somewhat subjective. It is not clear if there was a kinetograph or other wearable monitoring device as well in any of the patients; if so this might provide useful corroborative information to the available patient diaries. It is not clear to me whether patients were required to complete the diary daily and if not, there might be some recall bias or failure to recall symptoms. If patients find it difficult to write, a handwritten diary will pose its own issues and if they have apathy or cognitive issues this also compounds the difficulties with engagement with this

	process that can be burdensome. Patient diaries are however a commonly used source of useful direct patient information prospectively in other studies and can be very informative. Considerable efforts were made to have effective blinding between the study arms. The study M15 736 was a large multicentre study over 57 sites. Given the high proportion of side effects such as skin changes or nodules in the treatment group, and the effectiveness of the drug versus placebo at reducing morning akinesia, it is very likely that patients were effectively unblinded. Cellulitis and other infections were more common in the treatment group. There is often a tendency to overestimate treatment response in infusions so one can see a large placebo effect in many studies with infusions. It is difficult to estimate how large this overestimation effect would be. It is likely that it would be relatively greater for non motor symptoms such as quality of life, anxiety, mood rather than factors related to motor symptoms that are objectively easier to measure, such as falls. Perfectly blinded studies are often very difficult to achieve however good the blinding method due to obvious drug effects.
Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG Report sections: 3.4 and 4.2.6.4	There are no direct head to head comparator studies of foslevodopa-foscarbidopa and other treatments currently available for advanced Parkinsons disease. I am in broad agreement with EAG comments about the indirect treatment comparison methods chosen.

OFF states 0-16 is inadequate at capturing the range of health effects of advanced Parkinson's, given the data available Report sections: 4.2.4.3, 4.2.6.4 and 4.2.10.1	Broadly in agreement with EAG comments. The trial model is quite complex. A simpler model with broader categories for "off" states may be preferable. The complex model also has few data points for some of the health states.
Patients are assumed to retain a lasting benefit from treatment following discontinuation Report sections:4.2.4.3	Patients are, I think, unlikely to retain a lasting benefit from treatment with foslevodopa-foscarbidopa following its discontinuation. There is no current evidence of it having neuroprotective properties, indeed no therapeutic agent for Parkinson's disease has to date been convincingly proven to do so. There is normally a "washout period" before a drug that has been discontinued can be assumed to be completely out of the person's system. This may be longer for a subcutaneous than an oral preparation. The difficulty with Parkinson's disease trials is the lack of a clinical marker (or biochemical one) for slowing of disease progression as distinct from symptomatic benefit from the drug. UPDRS scales are not a perfect model to differentiate these. Parkinson's disease is a very heterogenous condition and the prognosis in each case can be variable. It may be that the company are commenting on the possible long term positive impact on patients who have had the foslevodopa-foscarbidopa therapy and during that time, benefitting from potentially greater mobility and less falls and more physical fitness than those not on the drug. Against this, patients with Parkinson's disease on the drug are perhaps more likely to have infections and skin site reactions which could be a cause of reduced physical fitness. Patients who have Parkinson's disease can require longer to recover from significant infections than the normal population.

The LOCF assumption does not align with the trial data Report sections: 4.2.6.4	Not able to comment
Problems with the use of Palmer *et al.* 2002 in informing BMT Report sections: 4.2.6.4	See below for comment
The company did not use the trial M15-736 trial data on the comparator arm Report sections: 4.2.6.4	Not able to comment The company may be able to provide more information on why it has chosen Palmer et al data which is a rather old dataset (2000) rather than the trial data M15 736 . Data from the M15 736 trial or a more recent data source would be useful to see and I think, important to have sight of, for the comparator arm
The company uses efficacy data and discontinuation data from different sources	Not able to comment The company may be able to provide a more detailed rationale for why they have used efficacy and discontinuation data from different sources.

Report sections: 4.2.7.1	
Troublesome dyskinesia appears to be a source of unaccounted for patient burden Report sections: 4.2.8.1	Troublesome dyskinesias are not included in the model. It is true that dyskinesias can develop over time but in general, oral medications are reduced or "pared down" over time to combat this problem. Dyskinesias are usually not troublesome to patients in my experience. Patients on the whole report a preference to be mobile and "on" with dyskinesias rather than immobile and off. They find the "off" state generally more disabling than the "on" state with dyskinesias. Dyskinesias can be socially embarrassing and are sometimes more noticeable to relatives and carers than to patients. A proportion of patients do get clinically troublesome and disabling dyskinesias and if the data is available it would be helpful to see it. Any available kinetograph data may help corroborate patient's impression. Troublesome dyskinesia can in some patients be a burden and can lead to falls. It tends to be more embarrassing than disabling. In my experience, the proportion of patients with this problem is relatively small so it may not impact the analysis greatly. If the data for troublesome dyskinesias for trials in this drug and also in LCIG trials is available it would be helpful to see it included in the model.
The regressions used for health state cost by OFF time appear inappropriate Report sections: 4.2.4.3	Not qualified to comment See below for comments relating to this report section.
The utility values used in the company's base case analysis carry	I am not expert in this field. I have reviewed and broadly agree with the comments made by EAG on this issue and their suggestions for resolution as follows:.

a high degree of uncertainty and are unlikely to be robust for decision making Report sections: 4.2.4.3	There are a large number of “off” states in the model used, some of which have little accompanying data. A simpler model using broader categories for off states might be more optimal and also more in line with previous studies. The exclusion of H and Y scale from the analysis is noted and I agree with EAG comment that if a method could be found to estimate/convert to H and Y score from the available MDS UPDRS scores this may provide additional useful information.
Are there any important issues that have been missed in EAR?	The EAG analysis is very comprehensive. There is a lack of a viable alternative for this group of patients. This can be very frustrating and disappointing for patients and their families. The availability of an effective and novel treatment approach is a very positive step forward in this relatively empty field. Patients are more likely to be willing to try this new drug and approach despite some risks of side effects. It is important to balance the lack of viable alternatives for patients in this group and the prospect of the expected inevitable decline in quality of life on best medical therapy, against its potential problems. Any measures of overall burden on patients, carers and families and health care systems with and without this therapy, are useful to bear in mind when considering its effectiveness. The comparative ease of use of foslevodopa-foscarbidopa (for example, not requiring admission to a regional specialist unit for LCIG, not requiring PEJ tube, and avoiding possible initial evaluation with nasogastric tube insertion which can be very uncomfortable) are all really beneficial to patients. This benefit which includes factors like convenience to patients, may be difficult to quantify particularly in the absence of direct comparative studies between these treatments. There are geographical inequalities in health care across the UK and not all patients may have equal access to the other advanced therapies available. There is a need for more awareness of and access to all the currently available advanced therapies for Parkinson’s disease.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is significant unmet need in the population of Parkinson's patients who require advanced therapies and for whom currently available therapies for advanced therapies (deep brain stimulation, apomorphine or LCIG) are unsuitable or not tolerated.
This group of patients have very few therapeutic options left as their therapeutic window is narrow and the progressive nature of the disease, alongside increasing complications of currently available best medical therapy, will mean their quality of life is likely to be significantly reduced and this has implications for those suffering from Parkinson's disease as well as their carers.
Foslevodopa-foscarbidopa subcutaneous infusion is an important step forward for this patient group with evidence of meaningful efficacy compared to placebo and it would also be likely to reduce the additional burden of oral medications.
There is a high rate of skin related complications and high discontinuation rates for this new therapy.
Longer term studies and studies directly comparing foslevodopa-foscarbidopa with other advanced therapies would be helpful.
Click or tap here to enter text.
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with Parkinson's or caring for a patient with Parkinson's. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **8th December 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Living with this condition or caring for a patient with Parkinson's

Table 1 About you, Parkinson's, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with Parkinson's? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Parkinson's? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Parkinson's? **If you are a carer (for someone with Parkinson's) please share your experience of caring for them**	Since being diagnosed in 2017 I have found that living with Parkinson's has become increasingly challenging. It is all encompassing in terms of the symptoms and pain affecting everyday life. No two days are ever the same and it's impossible to plan ahead as you never know how you will feel. The motor symptoms I have are stiffness, joint pain, severe dystonia (muscle spasms). I do not have a tremor. The non-moto symptoms are equally as problematic, a list of these by no way all of them include: anxiety, REM sleep disorder, bladder urgency, constipation, depression, brain fog, lack of appetite, loss of taste, loss of smell, apathy, feeling excessively tired. I feel a burden on my family who have to care for me and ensure I am safe and as well as I can be.
7a. What do you think of the current treatments and care available for Parkinson's on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**Current treatments tend to rely on patches (dopamine agonists) and tablets in the form of levodopa. There is a significant issue with all of these as you expeience severe on and off periods throughout the day. The tablets are very short acting and don't last in the system – remembering to take the tablets even with alarms, back up alarms and a wife chasing me around with them I still sometimes forget; this then means I am trying to function without the required medication. The patches can cause OCD tendacies, hallucinations, and other side effets which don't suit everyone. The optiosn for the duodopa pump are quite a procedure to have fitted, however, as a person with ulcerative colitis my intestines do not absorb any of the oral meds or duodupa pump or**

	if they do it's not to their full potential due to absorption issues. DBS is an option for me and if I hadn't had the opportunity to use the trial pump I would have arrived at the DBS route a lot sooner, in my opinion I have managed to delay the operation by at least two years. We have contact with a large group of people in the South West who are all on different medication regimes and everyone is either under medicated or find the oral regime difficult to manage due to the short acting nature of them. There haven't been any improvements in the drugs coming to the market over the years since I was diagnosed, this feels as though we have to put up with and make do with treatments which are not conducive to living our best lives with the condition. In fact, a significant proportion of parkinson's drugs were originally designed for other ailments and are now utilitised to treat PD. The drugs I take include pregabiliin for sleep and anxiety, clonazapem and diazepam for dystonia, rasagiline to protect the dopamine supply I do have.
8. If there are disadvantages for patients of current NHS treatments for Parkinson's (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Disadvantages are: Tablets are short acting – wear off quickly leaving me with increasing symptoms. Side affects of current treatment are extensive, mainly the on' off' periods which are like living on a roller coaster, with severe dips as the tablets wear off. During the night the slow release tablets are ineffective leaving me unable to turn over in bed, access the toietl on my own, I shuffle my feet to try and walk about and I am at risk of falls as I am so 'off' I can't function.
9a. If there are advantages of foslevodopa-foscarbidopa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	**My quality of life has been improved substantially whilst using the foslevadrope:foscarbidopa pump. This is because it is 24/7 delivery of the drug with just two changes of vial per day. Therefore I am not having to try to remember to take tablets, the fluctuations in on' off' periods have greatly been reduced. The night time issues with being**

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does foslevodopa-foscarbidopa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**unable to move, walk around or access the toilet have completely been remedied using this pump. It enables me to exercise and gives me freedom to have hobbies which I otherwise would not have been able to access on the previous medication regmine. I still require the additional medications to treat the non-motor symptoms ie, REM sleep disorder, anxiety, depression etc. but the pump delivers the leveadopa all day and all night which alleviates the issues previsouly described. It also gives me back my independence and control.**
10. If there are disadvantages of foslevodopa-foscarbidopa over current treatments on the NHS please describe these. For example, are there any risks with foslevodopa-foscarbidopa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	One disadvantage of the pump is I believe it would be difficult but not impossible for someone without a carer to administer the pump changes. Currently I use the back of my arm for my site and this is where my wife inserts the cannula. Without her help I would not be able to do this. The training given enabled us to be become confident in doing this but it would essential that people receive training to ensure that they have a good understanding of using a sterile environment to avoid infection of the site. Another disadvantage of the pump is that the 'site' area for the cannula can leave 'nodules'. These can be troublesome and stop that area from being reused as a site. Also the medication can 'pool' if too much is being pushed through at one time; for that reason I never use the 'boost' function as I believe it is ineffective and causes more harm than good.
11. Are there any groups of patients who might benefit more from foslevodopa-foscarbidopa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with	In my opinion anyone with a pre-existing condition such as Chrons, colitis or IBS would benefit from this medication as it doesn't rely on the stomach or intestinal tract to absorb the medication. For people with poor cognitive function and poor dexterity they would struggle potentially to do the site changes, however, a nurse led service

mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	would enable them to access the treatment. They would benefit as they would be 'on' more and therefore have a much better qualifty of life.
12. Are there any potential equality issues that should be taken into account when considering Parkinson's and foslevodopa-foscarbidopa? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I do not believe that there would be any equality issues.
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Potential overestimation of treatment benefit for foslevodopa-foscarbidopa Report sections: 2.3.1, 3.2, and 3.3	I believe that the treatment has delayed me having to access DBS operation by around 2 years. However, I also believe that if the treatment is stopped (ie the pump is stopped) for any time longer than half and hour I will experience an 'off' period which will take me a long time to get back 'on'.
Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and	

Patient expert statement

Levodopa-carbidopa intestinal gel Report sections: 3.4 and 4.2.6.4	
Cost-effectiveness model OFF states 0-16 are inadequate at capturing the range of health effects of advanced Parkinson's, given the data available Report sections: 4.2.4.3, 4.2.6.4 and 4.2.10.1	
Patients are assumed to retain a lasting benefit from treatment following discontinuation Report sections:4.2.4.3	In my opinion I would not experience a lasting benefit if I stopped the treatment and went onto the oral regime. The reason for this is because the medication doesn't last long in the body and therefore I would experience a severe 'off' if I stopped the medication.
The last observation carried forward	

Patient expert statement

(LOCF) assumption does not align with the trial data Report sections: 4.2.6.4	
Problems with the use of Palmer *et al.* 2002 in informing Best medical therapy effectiveness Report sections: 4.2.6.4	
The company did not use the trial M15-736 trial data on the comparator arm Report sections: 4.2.6.4	
The company uses efficacy data and discontinuation data from different sources	

Patient expert statement

Report sections: 4.2.7.1	
Troublesome dyskinesia appears to be a source of unaccounted for patient burden Report sections: 4.2.8.1	I do not suffer from dyskinesia as result of oral meds or use of the pump.
The regression analysis used for health state cost by OFF time appear inappropriate Report sections: 4.2.4.3	
The quality of life utility values used in the company's base case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making	

Patient expert statement

Report sections: 4.2.4.3	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The infusion pump has given me my freedom and independence back
- The infusion pump enables me to exercise more
- The infusion pump gives me a much better qualify of life, I do not experience severe ‘off’ periods over night.
- The infusion pump gives me confidence to do things I wouldn’t attempt on an oral regime.
- The infusion pump enables my care partner to have time to do other things instead of overseeing many oral tablet reminders!

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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Part 1: Living with this condition or caring for a patient with Parkinson's

Table 1 About you, Parkinson's, current treatments and equality

1. Your name	Marc van Grieken
2. Are you (please tick all that apply)	☒ A patient with Parkinson's? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Parkinson's? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Cure Parkinson's
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I am A EUPATI Fellow and frequently act as a patient expert or advocate. ☒ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Parkinson's? **If you are a carer (for someone with Parkinson's) please share your experience of caring for them**	Personally, I would describe living with Parkinson's as a slowly but inescapably progressive assault on quality of life and dignity. A kind of 'life sentence' one of my Parkinsonian friends calls it. Parkinson's slowly and continuously shrinks our world both physically, and for many also mentally. The relentless progression has a real undermining effect and may lead us to withdraw from the world around us. With increasing mobility limitations our confidence drops and instead self-consciousness of symptoms takes over. I believe we all fear the unknown, often asking what lies ahead. Rightly or wrongly, when meeting other people with Parkinson's we may wonder if the person you meet is further or less far advanced on what ultimately is the same path. As our condition progresses, we may try hide 'how bad things have got' so as not to upset family, friends and colleagues. Parkinson's can also be very embarrassing depending on the type and severity of symptoms. Urgent need to pass urine, constant and exceptional flatulence, looking totally lost, not being able to express oneself, freezing, falling stumbling and looking totally blank when someone asked you something to name a few examples. Effects experienced by people with Parkinson's may also include bad dystonia and bad hallucinations Nobody who does not have Parkinson's will ever know what it is like and likewise everybody with Parkinson's will not know what one's partner or family thinks about it. Fear of the unknown and worry about how family friends and colleagues sees you played a major role in how I responded to the diagnosis of Parkinson's. I expected to be cast aside by colleagues taken pity on by friends and becoming a burden on the family. Interpretation of language and body language and facial expressions is of course difficult for those without Parkinson's. 'You are doing well' might be interpreted as 'I take pity on you'.

	Living with Parkinson's also means taking vast amounts of medication and not only that, taking them at the right time and consistently every day. This may affect many other routines and in particular when to eat. If on oral medication, taking a tablet of levodopa will have no or little effect 15 minutes after eating your dinner. Likewise having dinner immediately after taking the tablet adversely affects the potential benefit of the drug.
7a. What do you think of the current treatments and care available for Parkinson's on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Currently available treatments are extremely limited, in my view not just the result of lack of funding of research into PD and other neurodegenerative diseases. From very early on I was aware of the likely 'symptoms management' path that lie ahead of me. Dopamine agonists, then add Levodopa-Carbidopa, then add COMT inhibitor to maximise effect/benefits of Levodopa, followed by increase in frequency of taking meds and later perhaps Apomorphine, DBS or Duodopa. As the doses of levodopa increases the risk of dyskinesia also increases and drugs countering some of the side effects will also become necessary. For example constipation may need the addition of laxatives to once-daily pill diet. As far as I can see the only difference between one person and the next is the brand name of the drugs. After all levodopa has been around for more than 60 years. I regret that I have to say that the current response within the NHS to supporting people with Parkinson's is in my view inadequate and outdated. One may say this is the consequence of limited funding but I don't think so. It is now widely and well known that Parkinson's symptoms can be much better managed by developing a person specific treatment plan. Such a plan needs to be developed by all health professionals involved in the treatment as well as his or her carers and most importantly the person living with Parkinson's. He or she should be encouraged to articulate what he or she thinks has worked most effectively since previous discussions and what may not have worked so well. All health professionals can then share their view with respect to ongoing management. The care or management plan developed in such a way will be collectively owned by the health service and the person with Parkinson's. This is of course in contrast with what I understand to be the approach from the health system at present. A typical

	treatment comprises an annual 10 or at best 15 minutes appointment with one's neurologist. In such short consultations it is not possible to create a meaningful discussion about a treatment plan because the neurologist has perhaps 5 minutes prior to the consultation to familiarise with the clinical file of the PWP and the PwP is often overwhelmed by the Consultant neurologist who should 'know best'. This was also my own experience, but I decided to send an email to my neurologist setting out what had gone well or not so well in the previous period. My consultant neurologist warmly welcomed this because it began to fill some of the canvas of me and PD. I think all people attending this important meeting about FosLevodopa-FosCarbidopa will agree that the holistic treatment picture I sketched above is much more effective and ultimately more cost effective. The current approach with separate interventions essentially pushes the patient from pillar to post and the financial cost or liability from one sector in the NHS to another. Parkinson's has many different guises, in fact everyone's Parkinson's is different and unique. I believe it is only a matter of time that thanks to scientific advancement different types and variants of Parkinson's will be identified, currently limited to 2 types, Idiopathic Parkinson's or in layman's terms "we don't know what causes it" Parkinson's and Parkinson's caused by faulty genes. If all different and in many cases very rare cancers were treated the same I expect that little progress would have been made in managing these cancers or even curing them. I know from personal experience that most people diagnosed with non-Hodgkin's lymphoma can now be very successfully treated which is some 25 years after early trials for new drugs. Yet in 60 years after Levodopa there is still no similarly significant new treatments in Parkinson's. There is also a huge lack of awareness of PD. Personally, I did know very little about Parkinson's at the time of my own diagnosis. In fact, most people don't know anything or very little about PD. Although the incidence of PD is rapidly increasing, most GP's, who are obviously at the front line of NHS response have little knowledge and in both my personal experience and the experience of others I have

	spoken with, this may significantly delay diagnosis. I understand however that research now firmly confirms that early diagnosis is vital to allow early disease management which in turn may improve quality of life of the PwP and at the same time potentially reduce costs to the NHS. Why does it take 9 to 12 months to see a qualified neurologist when referred by one's GP who suspects or wishes to exclude PD. As the fastest growing neurological condition with rapidly hugely growing lifetime costs it is not difficult to see priority should be granted to those with suspected Parkinsonism. When I am travelling in the UK and Europe through airport security and immigration, people don't have any difficulty in recognising I may not be able to stand for hours in the 'regular' que and staff will take me to the priority or special assistance channel. Is this perhaps one of two 'silver linings, the second being our blank facial expressions whilst playing home poker. In my experience the view I set out here are widely shared amongst PwP's. This can be checked against activities of PwP within patient organisations, Support groups, PD Avengers, EUPATI etc.
8. If there are disadvantages for patients of current NHS treatments for Parkinson's (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The efficacy of oral medication for PD is highly dependent on regular intake (eg at fixed intervals and time of day) and the interaction with daily eating. If you were to take your dopamine 15 minutes after your evening meal, you might as well not take the meds because the gut is busy digesting your food. Many PwPs have difficulty remembering taking Meds on time or they may not remember if they have taken a particular dose. Prior to stating FosL-FosC, I refused to eat less than two hours prior to taking my tablets. It was a forced curtailment of my families freedom to eat when the family wanted to eat. The greatest disadvantages of current BMT delivered by means of tablets are the clear and increasingly debilitating 'off' periods compared with 'on'. Or…virtually no movement during off periods intertwined with 'On' when our mobility may be much better but over time after prolonged use of L-dopa also leading to dyskinesia. .

9a. If there are advantages of foslevodopa-foscarbidopa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does foslevodopa-foscarbidopa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	For me there have been and there continue to be huge benefits derived from Foslevodopa-Foscarbidopa. **My Personal lived experience with FosLevodopa-Foscarbidopa:** Transformational This actually says it all. I started the trial on the 19th December 2019. I have a 'selfie' video clip taken at 6.30 am and look and sound terrible. I can share this if helpful. 23 hours later since I took that video and therefore at the start of my second day on the trial, I woke up at 5.30am and I simply could not believe the time: I had slept for a solid 5 and half hours for the first time in at least 3 years. I normally woke at least 3 times/night because I would have to try sit up in bed before I could turn over. This was the start of a good sleep pattern which has now been maintained for 3 years. However, during the following days and weeks the day pattern of my PD was not so good. I recall that the 31st of December, the all-important 'hogmany' in Scotland including in the village of Comrie where I live, was particularly bad. I had periods of repetitive freezing, a terrible posture, very week voice and was very self-conscious. Was this what my life was going to be like? No, it was not. It was because it took a few weeks to titrate, until mid January 2020. Since then my dose has only very minimally increased. By the end of January 2020 the early signs of benefit became visible. Just before lockdown I bought an electric Mountain Bike and thanks to the spectacular weather during spring and early summer of 2020 and the unique and wonderful environment around Comrie, I could cycle from home into the mountains on a daily basis. The continued delivery of the drugs had opened up a new (in this case outside world) which I could explore in the knowledge

	that ‘the pump would keep me going. However, COVID restrictions meant I could not engage with my favourite watersport. I have always loved watersport and since I moved to Comrie waterskiing had become my favourite summer sport. Not being allowed to waterski was demoralising because during the previous two summers waterskiing had become increasingly difficult for me. Many a time I needed multiple attempts to get out of the water and when succesful I might have spent so much energy that I was not able to ski for more than a minute or. It was undoubtedly the reducing mobility making water starts much more difficult. I could also ‘read’ the worry and huge empathy of my friend driving the boat because he knew how much this meant to me. I now use the annual first waterskiing attempt of the season as my own ‘Parkinson’s test’. The test is simple: will I be able to ’get out of the water’. During the summer of 2019 my ability to ski had deteriorated considerably and to such an extent that it got me down, having just a little hope that the 2020 season would be better. Lockdown delayed the start of the 2020 season to early August 2020 and I had by then been ‘in the trial’ for 8 months. On my first attempt I ‘popped’ out without any trouble or hesitation and skied a long time. I was elated, ‘over the moon’. A battle with PD won?! I knew I would be ok for another year’s waterskiing. But not only my physical ability had deteriorated, Parkinson’s also increasingly adversely affected my mental wellbeing and mood. Even though I ‘did lots of things’, I became more passive and even less communicative, particularly at home. I did not recognise my mental state and the impact of this on my partner and others close to me.

	This was before I started the FosL -0 FosC trial. I have already called the effect of the trial drug and its delivery to be transformational, physically, and mentally. Neuropsychology helps better communication and resolving thought processes which in combination of much reclaimed physical ability has greatly improved my quality of life. Whilst I still have fear of the unknown but nevertheless, overall I am more positive. I have no doubt that this 'in the round' improvement is substantially (85%) due to the continuous delivery of drugs by means of the pump. Since starting the trial more and more people said: 'you look really well'. Indeed I do. I further developed my business, took the EUPATI course. I became busy and enjoyed it. Looking back at the last 6 months prior to starting the trial on the 19th Dec 2019, (June 2019-Dec2019) I had deteriorated a lot and began to notice this in the response from people around me. I could not cut a steak when eating out, was very soft spoken, struggled at revolving doors, changes in surface materials, colour and texture. I needed a walking stick giving a little more security in case of freezing when walking. I felt down. The deterioration during 2019 followed by the dramatic improvement in my physical ability has really re-invigorated me. Foslovodopa-Foscarbidopa has given me back a stronger voice, given me more confidence including travelling on my own to the Netherlands staying in different places every night for six days including having to manage drug vials at max 7-8 degrees C. I have not needed a stick to walk, got better at waterskiing and really enjoyed life with family and friends and also my work.

	When I started, the drug delivery system seemed complex and was time consuming. But now I can probably do this blindfolded. Reclaimed and retained skills, fitness etc all help maintaining appositive outlook. I enjoy my work greatly and hope to continue working for some time. I had a huge and very positive experience when I received the Scottish Green Energy "Champion of Renewables" Award in December 2022. A huge honour and I was surprised how many people came up to me saying "*you look better than in 2019".* I think that too, but for me there is of course the awareness that despite fos evodopa-foscarbidopa PD is relentlessly progressing but I am and I feel much more capable of coping with that. I hope my own more positive outlook may also reduce worries by my family about my health.
10. If there are disadvantages of foslevodopa-foscarbidopa over current treatments on the NHS please describe these. For example, are there any risks with foslevodopa-foscarbidopa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	There are in my view no disadvantages over current treatments on the NHS. A minor issue is the requirement to keep the medication at a temperature between 6-8 because this may make travelling a bit more difficult. I am not aware of any side effects. My only worry would be a broken pump or empty battery.
11. Are there any groups of patients who might benefit more from foslevodopa-foscarbidopa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	I have no knowledge of this. I would say however that I think that the treatment is slightly easier when the recipient still has a good level of dexterity to self administer the drug and change the infusion set.

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering Parkinson's and foslevodopa-foscarbidopa? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Yes there are lots of equality issues related to gender, cultural background, ethnicity, nationality, wealth and many more. I am aware that currently more attention is paid to the differences between men and woman with PD because of the hormonal changes in woman which, as is becoming increasingly clear, have a major impact on progression in woman and on how woman experience PD. There are also huge disparities in understanding and treatment of people with PD in Africa when compared with the USA/Europe etc. There are also significant differences in PD treatments and their availability between England, Wales, Scotland and Northern Ireland. Therefore it is not inconceivable that inequalities in access to this highly effective treatment may vary within the UK.
13. Are there any other issues that you would like the committee to consider?	Yes: The cost benefit modelling is very difficult to follow, impenetrable even, but I am not qualified to comment on this. I do think however that the costs to the Health Service is just one piece of any cost benefit analysis. I say this based on my own personal experience. Prior to the start of the trial in December 2019, my mobility was low. I needed a walking stick to get about and to stop myself from falling. Posture was bad and I increasingly began to lose confidence especially when I had to negotiate public spaces such as a station concourse or revolving doors at an airport. Both my private and working worlds were shrinking and in combination with Covid effects I might have been forced to close the company if I had not been enrolled in the trial. The trial drug greatly improved my ability to continue working not least because I regained confidence. The main effect of the trial in economic terms was however not only that I, personally, could continue to work but also that I

	did not have to make other people who I employed redundant. In fact since early 2021 I have been able to grow the company and now employ 7 people (includes PT) including myself (total 4.80 FTE). I consider that a significant economic gain. Cost benefit analysis should take such factors into account. My business is growing because of my own determination and my reclaimed confidence which is recognised by my clients. This should also feature in the economic case. 7 people (4.8 FTE) are employed in a small community who through their local expenditure support other local jobs is undoubtedly relevant in making cost benefit appraisals.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Potential overestimation of treatment benefit for foslevodopa-foscarbidopa Report sections: 2.3.1, 3.2, and 3.3	Para 3.2: Given the length of time (in my case now 3 full years and 5 months, I don't understand why because the study is 'Open Label' it has a risk of bias. Para 3.2.2: Concern about unintentional unblinding due to treatment effect. Surely this proves efficacy rather than a flaw or weakness of the study. The efficacy of FosL-FosC is clearly so good that those participating in the 'double blind' trial who receive FosL-FosC 'know' this and those on a placebo 'know' they don't. This cannot reasonably lead to the conclusion that the benefits of FosL-FosC are overestimated. Para 3.2.3: Change from Cleo 90 to Neria guard was indeed an improvement, not because of the needle or insertion mechanism. It is because due to the design the 'sticky nature' of the FosL-FosC, which can be almost glue like, the removal of the tube from the cannula when using Cleo requires squeezing and lifting up whilst the Nerio connection requires an easier sideways move. The uplift when using Cleo is more likely to dislodge the canula or cause discomfort.

Patient expert statement

Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and Levodopa-carbidopa intestinal gel Report sections: 3.4 and 4.2.6.4	
Cost-effectiveness model OFF states 0-16 are inadequate at capturing the range of health effects of advanced Parkinson's, given the data available Report sections: 4.2.4.3, 4.2.6.4 and 4.2.10.1	
Patients are assumed to retain a lasting benefit from treatment following discontinuation	

Patient expert statement

Report sections:4.2.4.3	
The last observation carried forward (LOCF) assumption does not align with the trial data Report sections: 4.2.6.4	
Problems with the use of Palmer *et al.* 2002 in informing Best medical therapy effectiveness Report sections: 4.2.6.4	
The company did not use the trial M15-736 trial data on the comparator arm Report sections: 4.2.6.4	

Patient expert statement

The company uses efficacy data and discontinuation data from different sources Report sections: 4.2.7.1	
Troublesome dyskinesia appears to be a source of unaccounted for patient burden Report sections: 4.2.8.1	
The regression analysis used for health state cost by OFF time appear inappropriate Report sections: 4.2.4.3	
The quality of life utility values used in the company's base	

Patient expert statement

case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making Report sections: 4.2.4.3	
Are there any important issues that have been missed in EAR?	Yes, there is one such issue I will attempt to highlight at the very end of this section 'My experience with…. **My experience with FosL-FosC in my own journey with Parkinson's**. FosLevodopa-FosCarbidopa has been 'transformational' in every aspect of my life. To name a few: I had the first undisturbed 5.5 hour sleep in about 3 years on the first night of the trial. Having slept badly for many years, waking up to turn over very slowly in bed, I now sleep still sleep well. As a right-handed person, I had become increasingly left handed in the years prior to joining the trial. In fact I could not use a computer mouse with my right hand. Some three months into the trial I suddenly realised I had returned to being right handed including using the computer mouse. My confidence grew, my activity level went up and this resulted in regaining some of my fitness. Fitness training and activity is as we know very important and may slow down Parkinson's. The health improvement that I experienced was significant. My only worry about this has been fear of the withdrawal of the drug. I literally cannot bear the thought of having to go back to the pre FosL-FosC medication regime. I think I would find it very hard to have to come to terms with this. It took me at least 6 years following diagnosis to even begin to accept PD. The relentless progression may ultimately result in losing one's dignity and I would find this exceptionally hard to accept. We know to a large extent what lies in store and I most certainly know the substantial steps back I would

	be forced to take if I returned to the pre trial oral medication regime. It not only fills me with fear, it fills me with horror. I have always been a very active person and because of the huge benefit I have from the trial feel that I should try to actively pursue further opportunities for others to benefit. The new life, or rather the parts of my life that have been reclaimed due to FosL-FosC have encouraged and stimulated me to try and speak up for those who may not be able to. I was much more positive again and had energy for new challenges I enrolled as a student patient with a view to become a Fellow of the European Patient Academy for Therapeutic Innovation (EUPATI) . Fellows are frequently recruited to participate in patient Advisory Groups (PAG) Patient Engagement Councils (PEC), as speakers at conferences, as patient advocates, and many other organisations such as Patient Focussed Medicine Development (PFMD), or Patient Engagement Open Forum (PEOF). These roles are likely to mainly relate to in my case Parkinson's but PFMD, PEOF activities are relevant to all disease areas. I am a member of the Steering group of the Fair Patient Engagement Planner and will take part in the annual 2023 PEOF face to face meeting of patients, carers, patient organisations, researchers, regulators, clinicians and others. Since I was diagnosed I have been able to continue working full time. In 2014 I left the company I had joined in 1985 and established a new business MVGLA now in its 8th year. The business was successful from the start but during 2018, 2019 things became more difficult for me personally most notably traveling but as explained elsewhere the benefit I have from the FosL-FosC trial has returned some 80-85% of my life without PD. I mean here 'whole life' benefit and not just medical benefit. It is not just the management of Parkinson's symptoms but very importantly living a full life with family, friends and colleagues. Whole life benefits also mean to me retaining independence, being able to support others with PD, campaign for Parkinson's research funding, raising awareness of PD and importantly, maintaining an active professional role as a landscape architect advising the renewable energy industry in respect of effects on landscape and views of windfarms for example. I am first and foremost a landscape architect by choice

	and the trial made it possible to continue to work in the renewable energy sector culminating in receiving the Scottish Renewables Green Energy 'Champion of Renewables' Award 2023 (SGEA23). I wish and hope that becoming exclusively a 'professional Parkinsonian' will be kicked into the long grass for as long as possible because of FosL-FosC continuation. I hope that many others will have the opportunity to benefit from this treatment and would urge NICE to strongly endorse its use. I know any decision by NICE has no direct bearing on the decisions to be made in Scotland but NICE's support would certainly be helpful. . **What the EAR has missed.** Understandably perhaps the EAR is highly technical and, I have no doubt it will carefully consider all relevant evidence, but, the report does however not demonstrate much empathy with us People living with Parkinson's and that makes me sad. Perhaps the following quote taken from a short piece prepared for the website of the Dundee Research Interest Group by an undergraduate student, Caitlin Brown, from Yale University will illuminate what I mean. *"My previous experience has been that it is all too easy to get "lost" in the research, in such a way that I can fail to truly appreciate why the research I am conducting can have a meaningful and significant impact on the lives of real people.* https://www.ppu.mrc.ac.uk/news/visiting-student-yale-conversation-drig-members

	I hope this will not turn into: *My previous experience has been that it is all too easy to get "lost" in the* **numbers**, *in such a way that I can fail to truly appreciate why the* **drug's cost benefit assessment** will *have a significant impact on the lives of real people.*

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- My lived and personal experience of the FosL-FosC drug is that it has reclaimed substantial parts of my physical and mental quality of life which I had lost due to Parkinson's disease.
- The significant improvement in motor symptoms allowed me to re-engage in sporting activity and maintaining my fitness which, as is widely known, is vitally important and slows down progression. Physical exercises also help maintaining positive mood.
- My outlook on life changed positively and reinvigorated me to become an active campaigner promoting and supporting causes I believe in. The ability to maintain an active working life is very important in this.
- The assessment of cost and benefit or perhaps 'value for money' as considered in the EAR is impenetrable to me and I am not qualified to comment on the details within the EAR. However, the economic case is based on the financial effects of the drug on the ringfenced NHS budget. It appears to ignore 'whole lifetime or whole society' cost and benefits. It fails to recognise the growing economic costs of the ever increasing no people who develop Parkinson's. An economic time bomb.
- And finally: the EAR does not demonstrate an empathetic understanding of Parkinson's.

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 8 December**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Parkinson's UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose

Table 1 About you

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Potential overestimation of treatment benefit for foslevodopa-foscarbidopa Report sections: 2.3.1, 3.2, and 3.3	No	We support the Association of British Neurologists statement in their submission about this being an innovative therapy for people with Parkinson's, where there are currently limited treatment options available. We welcome the recommendation from the EAR that the committee should consider the population outlined suitable and the suggestion that further clinical advice should be sought to clarify the population.
Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG Report sections: 3.4 and 4.2.6.4	No	While we have no new data or evidence to clarify this point further, we would like to reiterate the impact of troublesome dyskinesia and OFF time and state that this is variable for each individual with Parkinson's.
OFF states 0-16 is inadequate at capturing the range of health effects of advanced Parkinson's, given the data available Report sections: 4.2.4.3, 4.2.6.4 and 4.2.10.1	No	We have no evidence or insights we can share on this point.

Patients are assumed to retain a lasting benefit from treatment following discontinuation Report sections:4.2.4.3	No	We have no evidence or insights we can share on this point.
The LOCF assumption does not align with the trial data Report sections: 4.2.6.4	No	While we don't have robust evidence to support this assumption, our initial response shared an insight from a person with Parkinson's about the impact the therapy has had on their OFF state and we would reiterate this. *"As my Foslevodopa starts to wear off I experience pain, however if I boost my dose the pain disappears."* People with Parkinson's and care partners also shared what their OFF state means for their daily lives: ● *"In my case 'off' means my right leg becomes heavy and weak, and from a sitting or lying position I struggle to raise it. Sometimes, but not always. I drag my right leg when walking. It also means my right arm becomes weak and my fingers stiffen and are difficult to move. If I am sat in a deep armchair it means I struggle to stand up. If I am in bed I struggle to turn over or get in/out of bed."* ● *"Apart from walking everything is in slow motion and my tremor gets much worse. Non-motor symptoms, like constipation, tend to be "off" almost the whole time."* ● *"Immoblie, stuck in a chair, but shaking uncontrollably,or not being able to get up from a chair, for hours. Being stuck in the bedroom not able to get dressed in the morning or walk downstairs, and the same at night. Being so frozen that everything has to be done for me."* ● *"The uncertainty of my fluctuations means that I can't risk going day fishing, as I used to."*
Problems with the use of Palmer *et al.* 2002 in informing BMT Report sections: 4.2.6.4	No	We have no evidence or insights we can share on this point.

The company did not use the trial M15-736 trial data on the comparator arm Report sections: 4.2.6.4	No	We have no evidence or insights we can share on this point.
The company uses efficacy data and discontinuation data from different sources Report sections: 4.2.7.1	No	We have no evidence or insights we can share on this point.
Troublesome dyskinesia appears to be a source of unaccounted for patient burden Report sections: 4.2.8.1	No	While we have no new data or evidence to clarify this point further we would like to reiterate the impact of troublesome dyskinesia and OFF time and state that this is variable for each individual with Parkinson's.
The regressions used for health state cost by OFF time appear inappropriate Report sections: 4.2.4.3	No	We have no evidence or insights we can share on this point. However, we believe that the additional evidence the EAR suggests is reasonable.
The utility values used in the company's base case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making	No	We have no new data or evidence to clarify this point. As stated above there are limited treatment options for people with Parkinson's where oral medication is

Report sections: 4.2.4.3		failing to control their symptoms or who are in the advanced stages of the condition. While we acknowledge the EAR's recommendation for an individual study to assess consistent utility values in the OFF state, we would be concerned if this further delayed use of the therapy by people who could benefit from it.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Nothing	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	N/A
Additional issue 2: Nothing	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	N/A

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

Technical engagement response

March 2023

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1 Introduction

This document provides the Evidence Assessment Group's (EAG's) critique of the company's response to technical engagement (TE) for the appraisal of foslevodopa-foscarbidopa for the management of Parkinson's disease (PD). Each of the issues outlined in the TE report are discussed in detail in Section 2. For a summary of the EAG's assessment on each issue, see Table 1. The company's updated base case analyses are outlined in Section 3 and the EAG's analyses are reported in Section 4.

Table 1. Issues for TE and current status regarding issue resolution

Key Issue		Status according to the EAG	Company approach	EAG approach
1	Potential overestimation of treatment benefit for foslevodopa-foscarbidopa	Unresolved	Additional clinical opinion provided	Additional trial evidence or analyses are unlikely to be available or possible
2	Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG	Unresolved	Observed means in updated NMA and inconsistent handling of missing data (LOCF used in 1 study)	LS mean data and consistent use of MMRM to account for missing data, but one trial omitted from analysis as data unavailable
3	'Off' states 0–16 is inadequate at capturing the range of health effects of advanced Parkinson's, given the data available	Unresolved (different opinions)	Maintains that chosen model structure is suitable for decision making	Maintains that the current model structure is flawed given the data available.
4	Patients are assumed to retain a lasting benefit from treatment following discontinuation (patients who discontinue do so into the OFF state they were last in and then follow the transition matrix of BMT)	Partly resolved (different opinions)	Revised approach. Patients who discontinue treatment are distributed across OFF states according to the baseline OFF state distribution.	Patients who discontinue treatment are assumed to have equal treatment outcomes to patients in the BMT arm.
5	The LOCF assumption does not align with the trial data	Resolved	Accepted EAG approach	Patients on treatment in the LOCF period are assumed to remain in their health state.

6	Problems with the use of Palmer *et al.* 2002 in informing BMT	Unresolved (data limitation considered unresolvable) (Data application issue was not addressed by the company)	Explored use of Palmer *et al.* 2000 data but found no valuable data. Currently uses 13 data points where each hourly level of OFF time is assumed to have the same time on treatment listed in the two states of Palmer *et al.* 2002. These 13 points are used to create a prediction curve that links OFF time to duration of levodopa therapy.	Use two datapoints to produce the prediction curve, taking the midpoint OFF time of the two states listed in Palmer *et al.* 2002.
7	The company did not use the trial M15-736 trial data on the comparator arm	Unresolved (different opinions)	Maintain that improvements in the BMT arm are a "trial effect" that would not be seen in clinical practice for BMT but would for LCIG and foslevodopa-foscarbidopa	Maintain that the company has not provided sufficient evidence that the "trial effect" would exist in clinical practice for foslevodopa-foscarbidopa.
8	The company uses efficacy data and discontinuation data from different sources	Unresolved (different opinions)	Maintain that cohort 2 of the M15-741 trial is the most appropriate source of discontinuation rates to reflect anticipated UK clinical practice.	Maintain that the source of efficacy data and discontinuation data should come from the same place if possible.
9	Troublesome dyskinesia appears to be a source of unaccounted for patient burden	Unresolved (different opinions)	Consider troublesome dyskinesia to be uncommon and well-managed and any implementation would rely on limited data.	Consider there to be an unaccounted-for patient burden from troublesome dyskinesia. Acknowledge difficulty in long-term modelling from data limitation.

10	The regressions used for health state cost by 'Off' time appear inappropriate	Unresolved (different opinions)	The company maintain that in the absence of more robust data, the full Adelphi dataset used in a regression is required to make a valid model, due to the limited sample size.	Due to the poor fit of regression analysis to the underlying cost data and the lack of company response on the issues brought forward the EAG maintains that the direct data should be used.
11	The utility values used in the company's base case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making	Unresolved (different opinions)	The combined dataset is used to inform the regression.	Only M15-736 is used to inform the regression.
+	The data source for discontinuations for LCIG appears to go on for 16 years but only 2 years of data was used	Unresolved (different opinions)	The company did not address this issue.	The EAG believes the company should investigate using all the data available from Norlin *et al.* 2021[1].
+	The source for the rate of dyskinesia in LCIG patients appears to relate to oral levodopa.	Resolved	0% rate of dyskinesia in patients receiving LCIG	0% rate of dyskinesia in patients receiving LCIG
+	Applying AEs only in the first cycle is inappropriate when most of these AEs would be expected to progress over time.	Partly resolved	Infusion site-related AEs, dizziness, and falls applied continuously over the model horizon, and removed injection-related AEs for BMT	The EAG also believes dyskinesia related AEs should be applied over the time horizon
+	LCIG recurring AEs continue occurring at the same rate regardless of the percentage of patients on treatment	Resolved	Recurring AEs for LCIG are applied based on the percentage of patients receiving treatment in the cohort	Recurring AEs for LCIG are applied based on the percentage of patients receiving treatment in the cohort
+	The Dirichlet distribution applied to the health state transition probabilities for the PSA appears to have been calculated erroneously	Resolved	Correction accepted	Corrected
+	LCIG administration and treatment management costs appear to be overestimated	Partly resolved?	LCIG administration costs: £2,929 LCIG management costs: £141.41	

			Two non-consultant led appointments for foslevodopa-foscarbidopa, one associated with titration, and another with monitoring	

Abbreviations: AEs, adverse events; BMT, best medical therapy; EAG, evidence assessment group; LCIG, levodopa carbidopa intestinal gel; LOCF, last observation carried forward; LS, least square; MMRM, mixed models for repeated measures; PSA, probabilistic sensitivity analysis

2 Issues for technical engagement

2.1 *Key Issue 1: Potential overestimation of treatment benefit for foslevodopa-foscarbidopa*

As discussed in the Evidence Assessment Group (EAG) report, the company submission (CS) focuses on a subpopulation of the population in the NICE final scope; adults with Parkinson's disease (PD) that is responsive to levodopa, but with symptoms not adequately controlled by their current medical therapy and for whom apomorphine or deep brain stimulation (DBS) are unsuitable or no longer providing adequate symptom control. In the company's response to technical engagement, the company reports that, "*there is expected to be limited impact on the clinical efficacy of foslevodopa-foscarbidopa based on whether patients have been previously treated with apomorphine or DBS*" and it is reported that the company's clinical experts consider that, "*prior use of apomorphine is not expected to affect efficacy of subsequent therapies*". However, the company does not provide any robust clinical evidence to support these opinions and so the EAG considers it still remains unclear to what extent the effectiveness of foslevodopa-foscarbidopa differs between the population specified in the scope, the patient population in the main trial (M15-736), and the narrower population the company is focusing on.

The EAG also considers it to remain unclear how the efficacy results of M15-736 are impacted by the substantial proportion of patients who were likely to be aware of their treatment allocation due to the clear differences in safety profile and the decrease in morning akinesia with foslevodopa-foscarbidopa compared with oral carbidopa/levodopa (CD/LD). The EAG agrees with the company that there is a risk in all double-blind randomised controlled trials (RCTs) that participants or outcome assessors may correctly guess the treatment allocation. However, the EAG is particularly

concerned that for M15-736 the key efficacy outcome, OFF time, was captured in patient reported PD diaries which are subjective, and at higher risk of bias than objective outcome assessments.

The EAG's clinical experts are in agreement with the company's clinical experts view that the use of patient diaries as an instrument to collect 'Off' time data is standard in PD trials. Additionally, the EAG agrees with the company and the company's clinical experts that M15-736 is a well conducted double blind RCT, which provides the best available evidence for the relative clinical effectiveness of foslevodopa-foscarbidopa compared with oral CD/LD. However, the EAG considers that it is likely that patients on foslevodopa-foscarbidopa may overestimate the efficacy of their treatment and that patients on BMT may underestimate the efficacy of treatment as a result of patients correctly deducing which treatment they were randomised to.

The stakeholder responses to this issue are collated in Table 2. The EAG notes that the stakeholder comments indicate that foslevodopa-foscarbidopa would be a welcome treatment option for PD patients, but the EAG does not consider the responses to provide any definitive answers to the key issues.

Table 2. Stakeholder responses to Key Issue 1: Potential overestimation of treatment benefit for foslevodopa-foscarbidopa

Stakeholder	Comment
Parkinsons UK	We support the Association of British Neurologists statement in their submission about this being an innovative therapy for people with Parkinson's, where there are currently limited treatment options available. We welcome the recommendation from the EAR that the committee should consider the population outlined suitable and the suggestion that further clinical advice should be sought to clarify the population.
Clinical expert University of Plymouth	The population addressed in the submission is a sub-population of the trial population, particularly those in 741, in which previous DBS was not an exclusion criterion. Patients who were experiencing significant fluctuations despite previous DBS were included. However, these patients were not included in 736. Although some ([redacted]) of 741 participants had previous apomorphine exposure, it is not known how many participants were unsuitable for apomorphine. The trial population was more representative of patients suitable for DBS and apomorphine than patients suitable for LCIG (those who have failed apomorphine and/or DBS or those in whom these therapies are contra-indicated). It is possible that this is particularly the case for those in whom the treatment was discontinued. There may have been an overestimation of the treatment benefit due to unblinding in the RCT. However, the findings are dramatic and consistent across several measures. Additionally, they are sustained and reproduced in the other studies reported.
Clinical expert	The scope of the patients in the trial is a narrower population than the NICE scope overall. This smaller population of patients may be older, more frail and possibly

South Tyneside and Sunderland Foundation Trust	with more cognitive issues rendering them unsuitable or intolerant of other treatments. Severe depression, cardiac disease, somnolence, autonomic dysfunction or significant impulse control disorders can all represent relative contraindications to other advanced therapies. Patients might have stopped apomorphine due to infusion site reactions or nodules or have problems with subcutaneous injections. Patients with gastric surgery may not be suitable for LCIG. The company might be able to provide more information on whether some patients in study M 15 736 had been on other advanced therapies, if so which therapy and the reason for discontinuation. Patient diaries are not a perfect way to record symptoms as they are necessarily somewhat subjective. It is not clear if there was a kinetograph or other wearable monitoring device as well in any of the patients; if so this might provide useful corroborative information to the available patient diaries. It is not clear to me whether patients were required to complete the diary daily and if not, there might be some recall bias or failure to recall symptoms. If patients find it difficult to write, a handwritten diary will pose its own issues and if they have apathy or cognitive issues this also compounds the difficulties with engagement with this process that can be burdensome. Patient diaries are however a commonly used source of useful direct patient information prospectively in other studies and can be very informative. Considerable efforts were made to have effective blinding between the study arms. The study M15 736 was a large multicentre study over 57 sites. Given the high proportion of side effects such as skin changes or nodules in the treatment group, and the effectiveness of the drug versus placebo at reducing morning akinesia, it is very likely that patients were effectively unblinded. Cellulitis and other infections were more common in the treatment group. There is often a tendency to overestimate treatment response in infusions so one can see a large placebo effect in many studies with infusions. It is difficult to estimate how large this overestimation effect would be. It is likely that it would be relatively greater for non motor symptoms such as quality of life, anxiety, mood rather than factors related to motor symptoms that are objectively easier to measure, such as falls. Perfectly blinded studies are often very difficult to achieve however good the blinding method due to obvious drug effects.
Patient expert	I believe that the treatment has delayed me having to access DBS operation by around 2 years. However, I also believe that if the treatment is stopped (i.e. the pump is stopped) for any time longer than half and hour I will experience an 'off' period which will take me a long time to get back 'on'.

Abbreviations: DBS, deep brain stimulation; EAR, Evidence Assessment Report; LCIG, levodopa-carbidopa intestinal gel; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial.

In summary, the EAG considers this issue to be unresolved and that additional trial evidence or analyses are unlikely to be available or possible to address this issue at this point in time.

2.2 *Key Issue 2: Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG*

The company has presented an updated network meta-analysis (NMA) in their response to technical engagement (TE) using observed means from all three trials included in the NMA for the outcome of OFF time (DYSCOVER[2], M15-736[3], Olanow 2014[4]). The EAG notes that the company reported that they have used observed means data as the resulting NMA, "may not run the risk of biased

parameter estimates associated with using least squares (LS) means data". However, the EAG is unclear what the company means by this statement and as mentioned in the EAG report, the EAG's preferred dataset is the least-squares means data. The EAG considers that there is likely to be bias in the observed mean data, for example, due to differences in baseline values and high levels of missing data from the high level of discontinuations. The EAG therefore considers that the inclusion of covariates, including baseline score, in the calculation of the LS mean values helps to address some of the bias that would be presented in the observed means data for the change from baseline to Week 12 in hours of average daily normalised OFF time. The EAG considers it unclear which covariates have been included in the LS mean analyses of the trials but nevertheless considers that the use of the LS mean data in the NMAs would be preferable to the use of observed mean data.

Unfortunately, the EAG does not have access to the LS mean with mixed model repeated measures (MMRM) data from Olanow 2014 to enable the EAG to re-run the NMA with the EAG preferred dataset. However, the EAG NMA presented in the EAG report (and reproduced below [Table 5]) includes the LS mean data from the two remaining study's which the EAG had access to. The results of the EAG NMA should be interpreted with caution as the NMA omits one of the trials of relevance, but it does include the consistent use of mixed model repeated measures (MMRM) results from both trials which was a further issue the EAG noted in the company's NMAs. The EAG considers it unclear whether the company's updated NMA includes a consistent use of MMRM results from all three trials or if the data from Olanow 2014 still comprise of imputation of missing data using last observation carried forward (LOCF). The EAG notes that the MMRM analysis in Olanow 2014 was reported to give similar results to the LOCF, but the MMRM data were not used in the NMAs presented in the company submission (CS).

The EAG was unable to validate the data for DYSCOVER and Olanow 2014 in the company's updated NMA as the observed mean changes are not reported in the publications. Additionally, the EAG notes that there is a discrepancy in the standard errors (SEs) for M15-736 in the Excel file provided by the company for the updated NMA in response to TE and the SEs used in the company NMA provided in response to clarification questions (or calculated using the standard deviations reported in the CS). The EAG is unclear of the reason for this discrepancy and is uncertain whether the correct standard errors for M15-736 have been used in the company updated NMA. The EAG also identified an error in the SEs used for M15-736 in the EAG NMA which the EAG has corrected, but it should be noted that it does not change the original conclusions.

The results of the company's updated NMA using only observed mean data are presented in Table 3 and the EAG notes that they are consistent with the earlier company NMA provided in response to clarification questions (Table 4). For [redacted] the difference in 'OFF' time between foslevodopa-foscarbidopa and levodopa-carbidopa intestinal gel (LCIG) was [redacted] but did [redacted] the FE or the RE models. In contrast, in the EAG NMA the difference in 'OFF' time between foslevodopa-foscarbidopa and LCIG was [redacted] but also did [redacted] the FE or the RE models (Table 5). The EAG considers it important to highlight that all of the NMA results suffer from the same uncertainty and risk of bias as the underlying M15-736 data. In addition, there is also likely to be some heterogeneity between the trials due to differences in BMT and the variation in patients' PD.

The EAG notes that the company has updated their base-case using the relative risks derived from the updated NMA in the model and the results are discussed in Section 3.

Table 3. Company response to TE updated NMA for difference in mean 'Off' time change from baseline (95% CrI) (Adapted from Company response to TE - EAG additional questions, Table 1)

Treatment	RE (DIC = [redacted])	FE (DIC= [redacted])
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]

Updated company analysis including observed mean data from DYSCOVER, M15-736, Olanow 2014

Abbreviations: BMT, best medical therapy; CrI, credible interval; DIC, deviance information criteria; FE, fixed effects; LCIG, levodopa-carbidopa intestinal gel; LS, least squares; RE, random effects.

Table 4. Company response to clarification questions NMA for difference in mean OFF time change from baseline (95% CrI) (Adapted from Company response to clarification questions Table 13 [Company's updated NMA results of limited network of trials])

Treatment	RE (DIC = [redacted])	FE (DIC= [redacted])
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]

Company analysis including LS mean data from DYSCOVER, observed mean data from M15-736 and data from Olanow 2014 unclear.

Abbreviations: BMT, best medical therapy; CrI, credible interval; DIC, deviance information criteria; FE, fixed effects; LCIG, levodopa-carbidopa intestinal gel; LS, least squares; RE, random effects.

Table 5. Updated EAG NMA results for difference in LS mean OFF time change from baseline (95% CrI)

Treatment	RE (DIC = [redacted])	FE (DIC= [redacted])
Foslevodopa-foscarbidopa vs BMT	[redacted]	[redacted]
LCIG vs BMT	[redacted]	[redacted]
Foslevodopa-foscarbidopa vs LCIG	[redacted]	[redacted]

EAG analysis including LS mean data from M15-736 and DYSCOVER.

Abbreviations: BMT, best medical therapy; CrI, credible interval; DIC, deviance information criteria; FE, fixed effects; LCIG, levodopa-carbidopa intestinal gel; LS, least squares; RE, random effects.

The EAG notes that the company disagrees with the EAG's preferred approach of assuming similar clinical efficacy between foslevodopa-foscarbidopa and LCIG in the economic model and that the company and its clinical experts consider there to be benefits of foslevodopa-foscarbidopa that suggest superior efficacy. However, the EAG considers the results of the EAG NMA support the EAG's assumption of similar clinical efficacy between foslevodopa-foscarbidopa and levodopa-carbidopa intestinal gel (LCIG). The EAG also notes that the stakeholder comments from one clinical expert appear to be supportive of the EAG view on the methods for the NMA, although there were limited comments from stakeholders on this key issue (Table 6).

Table 6. Stakeholder responses to Key Issue 2: Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG

Stakeholder	Comment
Parkinson's UK	While we have no new data or evidence to clarify this point further, we would like to reiterate the impact of troublesome dyskinesia and OFF time and state that this is variable for each individual with Parkinson's.
Clinical expert University of Plymouth	Nothing to add to this point.
Clinical expert South Tyneside and Sunderland Foundation Trust	There are no direct head-to-head comparator studies of foslevodopa-foscarbidopa and other treatments currently available for advanced Parkinson's disease. I am in broad agreement with EAG comments about the indirect treatment comparison methods chosen.
Patient expert	No comment.

Abbreviations: EAG, External Assessment Group.

In conclusion, the EAG maintains its view that the company should update the NMAs of OFF time and ON time without troublesome dyskinesia to include LS mean data and using MMRM to account for missing data for all three included trials: M15-736, Olanow 2014 and DYSCOVER. Additionally, the EAG considers it important to highlight that the results from both the EAG and the updated company NMA are associated with uncertainty and hence the EAG considers the assumption of similar efficacy for foslevodopa-foscarbidopa and LCIG in the EAG base case to be reasonable.

2.3 *Key Issue 3: 'Off' states 0–16 is inadequate at capturing the range of health effects of advanced Parkinson's, given the data available*

In the EAG report OFF time alone was identified as not adequately representing the heterogeneity of Parkinson's disease and the data available for informing efficacy, utility, and costs for 17 health states was considered insufficient. A previous model submitted to CADTH[5] was critiqued on the basis that OFF time alone does not accurately represent the diversity of health impacts and this was further verified by data from Norlin *et al.* 2021.[1] The predicted utility values from this paper are shown in Table 7 and demonstrate utility can vary significantly independent of reported OFF time.

Table 7. Predicted utility values

Off-category	H&Y I	H&Y II	H&Y III	H&Y IV	H&Y V
0%	0.733 (0.02)	0.649 (0.03)	0.521 (0.04)	0.333 (0.1)	− 0.081 (0.15)
0 to <25%	0.692 (0.02)	0.619 (0.02)	0.495 (0.02)	0.316 (0.04)	− 0.085 (0.05)
25 to <50%	0.659 (0.02)	0.595 (0.02)	0.475 (0.02)	0.303 (0.04)	− 0.089 (0.05)
50 to <75%	0.568 (0.03)	0.529 (0.03)	0.419 (0.03)	0.266 (0.06)	− 0.098 (0.09)
75-100%	0.486 (0.07)	0.469 (0.06)	0.368 (0.06)	0.233 (0.08)	− 0.106 (0.12)

Values presented as mean (SD).
Abbreviations: H&Y: Hoehn and Yahr scale; SD: standard deviation.
Source: Norlin 2021.13

The M15-736 trial contained 73 patients at baseline and the population at the end of month three is 47. Using this limited dataset to inform the baseline patient population and transition rates for 17 separate health states frequently results in a reliance on single patients to determine the trajectory of states over a three-year period. Furthermore, with discontinuation being applied uniformly and the high number of missing patients between baseline and three months, there is a reliance on assuming the few patients that remain are representative of the transitions for the missing patients. In one state, OFF 14, patient trajectories are assumed to remain static due to missing data.

Previous models Kalabina *et al.* 2019,[6] Walter and Odin 2015,[7] Chaundhuri *et al.* 2022,[8] Lowin *et al.* 2011[9] and Lowin *et al.* 2017[10] utilised health states driven by OFF time and H&Y state. The EAG advised the company to adopt a model that utilised a similar structure.

As the issue described here is related to the model structure, it contributes to several other key issues the EAG has raised. One source of unaccounted for health effect in the model was troublesome dyskinesia beyond what was recorded as a treatment related adverse event during the trial period, discussed further as part of key issue 9. The issues with the model having insufficient

data to inform the high number of health states results in inadequate data available to inform the cost and HRQoL by state, as laid out in key issues 10 and 11. The limited population data also resulted in some spurious assumptions using the last observation carried forward (LOCF) method in the model, but the company has since resolved this in their response to key issue 5.

In the company's TE response, they maintain that OFF time is the most representative outcome to model changes in symptom control and that incorporating H&Y would add complexity and increase uncertainty. Given how broad this issue is and the large number of arguments the company has presented for their case the company arguments and EAG responses to those arguments are compiled into Table 8.

Table 8. Company arguments relating to key issue 3 and EAG response

N	Company comment	EAG response
1	H&Y is not an appropriate proxy measure for PD disease progression, as it only captures one aspect of motor symptoms;	The EAG accepts that H&Y only captures one aspect of motor systems, a model that used only H&Y would be considered a simplification. Since the EAG is proposing using both H&Y and OFF time this criticism of H&Y is not relevant.
2	Patients are unlikely to achieve transitions between discrete H&Y states as identified by NICE as part of its published clinical guidelines for PD;[11]	NICE did not state that patients are unlikely to achieve transitions between discrete H&Y states, the exact comment made was, "Individuals unlikely to improve whole stages as a result of Interventions" which is what was reiterated by the company's experts.[12] This statement is distinct as Parkinson's is a progressive disease so one would expect patients to, over time, experience declines in H&Y. It is worth noting that this is a 30-year model with around [redacted] of patients surviving up to 12 years.
3	Including H&Y would significantly increase the complexity of the traces and there is insufficient time to conduct significant model changes over the technical engagement period;	The EAG accepts that the time during TE may be insufficient to change the model and that the introduction of H&Y increases the complexity of the model, though this complexity is needed to accurately model the disease progression.
4	Clinical experts noted that H&Y does not take into account QoL, and in clinical practice H&Y is not a relevant measure of a patient's experience of their disease;	Expert stakeholders appear to disagree with the company experts that H&Y is not a relevant measure. Furthermore, the company statement that, "clinical experts noted that H&Y does not take into account QoL" lacks face validity given both the Norlin *et al.* 2021[1] data shown in Table 7 and a look at the H&Y scoring (1 means Unilateral involvement only and 5 means Confinement to bed). There is

		clearly significant variation in patient QoL based on H&Y state, regardless of OFF time.
5	OFF time and H&Y state are intrinsically linked and unable to be appropriately modelled separately;	The EAG accepts that OFF time and H&Y are linked, to a degree, as there are unlikely to be any patients with 0 OFF hours and a H&Y score of 5 (maximum) nor 16 OFF hours and a H&Y score of 1 (minimum). However, it is unclear what issue this would cause. While multicollinearity in a regression analysis can undermine the statistical significance of an independent variable, a Markov model is not concerned with determining the power of specific variables, only the most suitable model for predictions of future costs and QALYs. It is notable that the CADTH submission did not consider this a significant issue[5]. Previous submissions such as TA757 for HIV have used the linked values of CD4 count and viral load. Furthermore, the Norlin *et al.* 2021[1] data in Table 7 clearly shows variation in QoL for H&Y state beyond that caused by its link to OFF time as in every state, except between H&Y1 and 2, the highest OFF time of the previous H&Y values results in higher QoL than the lowest OFF time with the subsequent H&Y value.
6	The models suggested to support inclusion of H&Y have significant limitations; -Lowin et al. 2011 is derived from an earlier model version based on a decision tree, and the rationale for such a jump from a simple decision tree to a 12-health state model is lacking. Kalabina et al. 2019, Lowin et al. 2017 and Chaudhuri et al. 2022 implemented the same model structure - data availability and robustness of data available to inform health state transitions as important limitations of these models -Walter and Odin, recommended structure from CADTH submission. This approach would likely improve the cost-effectiveness of LCIG and foslevodopa-foscarbidopa, although, it was unclear on how OFF time was derived for one of the comparators, as it was not a part of the RCT informing the paper.	- It is unclear what point the company is making with the “lack of rationale” argument for updating the decision tree model to a Markov, since the company agree that a multi-state Markov model is the best approach. -Data availability is an expected issue in this disease area. As there is so limited data, using as much of the data available for the patients that do exist to inform as few health states as possible seems the most appropriate approach to account for this issue. -The EAG suggested changes leading to improved CE is addressed in another bullet point. The company does not specify which comparator in the model they are referring to so the EAG cannot confirm this claim. In investigating this claim it appears all treatments have a source of OFF time.
7	1-hour increments in ‘Off’ time were chosen to account for the continuous administration of foslevodopa-foscarbidopa, and the more stable hour-to-hour symptom control associated with this method of	The EAG agrees that one-hour increments could be suitable and appropriate at modelling treatment benefit if the company had sufficient data to inform the model.

	administration, along with being the minimum clinically meaningful change;	
8	The company conducted a validation exercise comparing their OFF-state trajectories against Chaudhuri *et al*. 2022, showing that these are similar despite the difference in model structure;	The company's validation exercise only compares proportion of patients in OFF state 3 and 4 over time, OFF state 1 and 2 should also be shown. Nevertheless, it would not be expected that using less granular would result in dramatically different OFF time trajectories. The issue is whether there is sufficient population data available to produce reliable efficacy, utility, and cost estimates for so many health states. With this in mind, the EAG conducted an additional validation exercise, comparing the health state costs and utilities used in the Chaudhuri *et al.* 2022 model to the company's model, with results shown in Table 9 and Table 10 respectively. This demonstrates both major issues with the company's current structure, with that being significant variation in health related QoL and costs exists outside of OFF time and the granular nature of the analysis does not appear to produce valid results, particularly in the higher OFF states, due to the lack of available data.
9	The current approach is considered to be a conservative one;	The EAG accepts that the request to expand the health effects modelled would likely improve the cost-effectiveness of foslevodopa-foscarbidopa relative to BMT. However: - The company have used the additional unaccounted-for benefit to argue for a more favourable discontinuation assumption as part of key issue 4. -Higher discontinuations in foslevodopa-foscarbidopa means expanding the "on-treatment" benefit would likely decrease the cost-effectiveness versus LCIG. - The difference between higher and lower OFF hours is far lower in higher H&Y states as shown by the Norlin *et al.* data and so the EAG considers this could decrease the longer-term benefit associated with foslevodopa-foscarbidopa.
10	Introduction of H&Y would result in greater uncertainty.	The EAG does not agree that the introduction of H&Y would increase uncertainty. At present the reliance on OFF time to represent all QoL and costs for patients results in significant uncertainty as discussed further in key issue 10 and 11. The aim of the inclusion of H&Y would decrease uncertainty as there would likely be a smaller range of utility and costs

		represented by each health state (as defined by OFF time and H&Y). 0

Abbreviations: EAG, External Assessment Group;

Table 9. Total health state specific costs used in the company base case compared to Chaudhuri *et al.* 2022

Health state	Total yearly costs in company's base case	Total yearly costs in Chaudhuri *et al.* 2022 model by H&Y				
		0	I	II	III	IV
OFF 0	[redacted]	£909.78	2,939.26	7,745.39	16,323.16	28,527.88
OFF 1	[redacted]	£2,420.28	£6,698.20	£14,814.40	£26,512.23	£40,118.93
OFF2	[redacted]					
OFF 3	[redacted]					
OFF 4	[redacted]					
OFF 5	[redacted]	£5,749.84	£13,276.89	£24,642.43	£37,904.90	£50,812.43
OFF 6	[redacted]					
OFF 7	[redacted]					
OFF 8	[redacted]					
OFF 9	[redacted]	£11,761.99	£22,727.81	£35,955.50	£48,691.42	£59,622.99
OFF 10	[redacted]					
OFF 11	[redacted]					
OFF 12	[redacted]					
OFF 13	[redacted]	£20,665.47	£33,960.17	£46,962.11	£57,756.84	£66,690.17
OFF 14	[redacted]					
OFF 15	[redacted]					
OFF 16	[redacted]					

*taken from the previous OFF state with available observed data

Table 10. Utility values based on a linear mixed model regression used in the company base case compared to Chaudhuri *et al.* 2022

Health state	Company model utility value (SE*)	Chaudhuri *et al.* 2022 utility value by H&Y				
		0	I	II	III	IV
OFF 0	[redacted]	0.818	0.748	0.677	0.607	0.536
OFF 1	[redacted]	0.709	0.638	0.568	0.497	0.427
OFF2	[redacted]					

OFF 3	[redacted]					
OFF 4	[redacted]					
OFF 5	[redacted]	0.599	0.528	0.458	0.387	0.317
OFF 6	[redacted]					
OFF 7	[redacted]					
OFF 8	[redacted]					
OFF 9	[redacted]	0.489	0.419	0.348	0.278	0.207
OFF 10	[redacted]					
OFF 11	[redacted]					
OFF 12	[redacted]					
OFF 13	[redacted]	0.379	0.309	0.238	0.168	0.097
OFF 14	[redacted]					
OFF 15	[redacted]					
OFF 16	[redacted]					
Dead	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Stakeholder comments can be found in Table 11. The two clinical experts appeared to largely agree with the EAG statements on the advised use of H&Y in the model.

Table 11. Stakeholder responses to Key Issue 3: 'Off' states 0–16 is inadequate at capturing the range of health effects of advanced Parkinson's, given the data available

Stakeholder	Comment
Parkinson's UK	We have no evidence or insights we can share on this point.
Clinical expert University of Plymouth	Agree that H&Y can be easily derived from the MDS-UPDRS. There may be other contributors to OFF state-associated QoL, in addition to the duration of OFF time, such as the severity of the OFF state, predictability of the OFF state and timing of the OFF state, such as early morning OFF. There is heterogeneity in rate of disease progression, and this is related to factors such as age, sex and H&Y stage.
Clinical expert South Tyneside and Sunderland Foundation Trust	Broadly in agreement with EAG comments. The trial model is quite complex. A simpler model with broader categories for "off" states may be preferable. The complex model also has few data points for some of the health states.
Patient expert	No comment.

Abbreviations: EAG, External Assessment Group; H&Y, Hoehn and Yahr

The EAG maintains the position that the current model structure does not accurately reflect the diversity of health effects from this disease and the data available is insufficient to inform the high number of health states.

2.4 *Key Issue 4: Patients are assumed to retain a lasting benefit from treatment following discontinuation (patients who discontinue do so into the OFF state they were last in and then follow the transition matrix of BMT)*

In the EAG report it was noted that patients who discontinue treatment do so into the OFF states they were in while on treatment meaning they retain a long-term advantage from treatment. The EAG's clinical experts suggested OFF time declines would be seen immediately and were sceptical of long-term benefits of treatment once discontinued unless patients were switched to another advanced treatment. The EAG recommended patients who discontinue immediately revert to the efficacy of patients in the BMT arm, resulting in substantial decreases in the cost-effectiveness for foslevodopa-foscarbidopa versus both BMT and LCIG.

The company accepted that discontinuations in the base case model submitted did not align with current clinical practice and adapted their model so patients revert to the baseline OFF state distribution upon discontinuation.

The EAG acknowledges the company's comments and accepts that patients may retain health-related benefits from the duration they had improved OFF time. However, the company has chosen to model treatments using only OFF time. The EAG considers that this does not adequately represent the heterogeneity of Parkinson's disease. Within the confines of the current model structure, the company needs to justify that some benefit to OFF time would be retained. Furthermore, patient and clinical expert stakeholders' statements recorded in Table 12, appear to be sceptical of the companies claim that there would be a long-lasting benefit.

In addition, the EAG conducted an illustrative scenario to depict what would occur if discontinuation was 0% up to year 12 at which point it was 100% for foslevodopa-foscarbidopa, with the results shown in Figure 1. The purpose of this illustrative scenario was to demonstrate reversion to baseline OFF hours occurs regardless of timepoint in the model (note that the EAG does not believe this is a realistic scenario). This means patients discontinuing either LCIG or foslevodopa-foscarbidopa after approximately [redacted] cycles will experience an improvement in OFF time, with this improvement significantly increasing for patients who discontinue at later cycles, which the EAG considers to be clinically implausible.

Figure 1. EAG scenario to demonstrate issue with company's implementation of discontinuation assumption

Table 12. Stakeholder responses to Key Issue 4: Patients are assumed to retain a lasting benefit from treatment following discontinuation (patients who discontinue do so into the OFF state they were last in and then follow the transition matrix of BMT)

Stakeholder	Comment
Parkinson's UK	We have no evidence or insights we can share on this point.
Clinical expert University of Plymouth	From my experience, changes in OFF time for patients who discontinue treatment are seen within hours. However, it is plausible that patients may have some longer-term benefit from their treatment. While on treatment patients will have had better sleep and increased mobility, maintaining a better level of function, muscle strength and cardiovascular fitness than they would have had with progressively worsening and increasing duration OFF time. Some of these benefits might be sustained following treatment discontinuation.
Clinical expert South Tyneside and Sunderland Foundation Trust	Patients are, I think, unlikely to retain a lasting benefit from treatment with foslevodopa-foscarbidopa following its discontinuation. There is no current evidence of it having neuroprotective properties, indeed no therapeutic agent for Parkinson's disease has to date been convincingly proven to do so. There is normally a "washout period" before a drug that has been discontinued can be assumed to be completely out of the person's system. This may be longer for a subcutaneous than an oral preparation. The difficulty with Parkinson's disease trials is the lack of a clinical marker (or biochemical one) for slowing of disease progression as distinct from symptomatic benefit from the drug. UPDRS scales are not a perfect model to differentiate these. Parkinson's disease is a very heterogenous condition and the prognosis in each case can be variable. It may be that the company are commenting on the possible long term positive impact on patients who have had the foslevodopa-foscarbidopa therapy and during that time, benefitting from potentially greater mobility and less falls and more physical fitness than those not on the drug. Against this, patients with Parkinson's disease on the drug are perhaps more likely to have infections and skin site reactions which could be a cause of reduced physical fitness. Patients who have Parkinson's disease can require longer to recover from significant infections than the normal population.
Patient expert	In my opinion I would not experience a lasting benefit if I stopped the treatment and went onto the oral regime. The reason for this is because the medication doesn't

	last long in the body and therefore, I would experience a severe 'off' if I stopped the medication.

Abbreviations: EAG, External Assessment Group;

The EAG maintain that patients should revert to the contemporaneous natural disease health states upon discontinuation. Moreover, the company's implementation of their assumption is fundamentally flawed and requires correction.

2.5 *Key Issue 5: The LOCF assumption does not align with the trial data*

During the clarification stage it was identified that the majority of the reduction in mean OFF hours, for patients treated with foslevodopa-foscarbidopa, is achieved during the first month with OFF hours increasing slightly between month 2 and 3. The EAG argued that this contradicted the company's base case, that assumed that the patient transitions seen during the 3 month trial period would continue to be applied during the following 3 years, this was the last observation carried forward (LOCF) assumption.

The EAG suggested two alternative approaches, one which carries forward the transition observed between month 2 and month 3 in the model and one which assumes no patients on treatment remain in the same health states observed at the end of the M15-736 trial period. In response, the company cited the long-term continuous decline in OFF time observed in patients on foslevodopa-foscarbidopa in the M15-741 trial as evidence that assuming continuous improvement was valid. This was not considered sufficient justification by the EAG because:

- The M15-741 trial resulted in a [redacted] from baseline OFF time at 52 weeks than the M15-736 did at 3 months;
- The difference in OFF time from week 26 to later time points was not [redacted];
- The [redacted] still occurs in week 1 in the M15-741 trial, so extrapolating change from baseline to month 3 (W13 in the graph) would still be unjustified.

Therefore, the EAG maintained, in the report, that the LOCF assumption was inappropriate in the report and used the alternative approach that assumed patients remain in their health state for the duration of the LOCF period. The EAG also suggested additional data from the M15-736 trial extension or M20-098 would help resolve this issue and clarify the trajectory of patients during this period. Stakeholder comments are shown in Table 13, notably the clinical expert agreed that the LOCF assumption was not supported by the trial data.

Table 13. Stakeholder responses to Key Issue 5: The LOCF assumption does not align with the trial data

Stakeholder	Comment
Parkinson's UK	While we don't have robust evidence to support this assumption, our initial response shared an insight from a person with Parkinson's about the impact the therapy has had on their OFF state and we would reiterate this. "As my Foslevodopa-foscarbidopa starts to wear off I experience pain, however if I boost my dose the pain disappears." People with Parkinson's and care partners also shared what their OFF state means for their daily lives: ● "In my case 'off' means my right leg becomes heavy and weak, and from a sitting or lying position I struggle to raise it. Sometimes, but not always. I drag my right leg when walking. It also means my right arm becomes weak and my fingers stiffen and are difficult to move. If I am sat in a deep armchair it means I struggle to stand up. If I am in bed I struggle to turn over or get in/out of bed." ● "Apart from walking everything is in slow motion and my tremor gets much worse. Non-motor symptoms, like constipation, tend to be "off" almost the whole time." ● "Immobile, stuck in a chair, but shaking uncontrollably, or not being able to get up from a chair, for hours. Being stuck in the bedroom not able to get dressed in the morning or walk downstairs, and the same at night. Being so frozen that everything has to be done for me." ● "The uncertainty of my fluctuations means that I can't risk going day fishing, as I used to."
Clinical expert University of Plymouth	Nothing to add to this point. Agree the trial data do not support the LOCF assumption used in the model.
Clinical expert South Tyneside and Sunderland Foundation Trust	Not able to comment.
Patient expert	No comment.

Abbreviations: EAG, External Assessment Group;

In the company's TE response, they stated that data from the M15-736 extension and M20-098 are not yet available to inform the LOCF period transitions. However, they accept the EAG's recommended alternative approach to the LOCF period of assuming patients remain in their health states for this period (provided they do not discontinue treatment). An issue remains with the uncertainty about what patients' trajectory would be during this period, due to the lack of data, but the EAG believes this is no longer a key issue.

2.6 *Key Issue 6: Problems with the use of Palmer* et al. *2002 in informing BMT*

In the EAG report it was noted that the data used to inform the transitions of BMT and the transitions of patients on treatment after the LOCF period (3 years) was based on two data points sourced from Palmer *et al.* 2002.[13] This paper sourced its data from a cross-sectional survey, published in 2000, of 60 patients in the USA.[14] This is notable as a limited source of data for informing such a significant part of the model.

The EAG suggested exploring the original source of the paper to determine if there were more data available. At technical engagement the company stated that no appropriate data were available from this study and the EAG agreed that Palmer *et al.* 2002 appeared to be the only usable source to model long term transmission rates for patients treated with levodopa.

Furthermore, the EAG critiqued the company's current method of using the available data. The company graphed the two data points as shown in Figure 2, with the midpoint for every OFF-time state set to 5.53 years or 11.38 (based on the Palmer *et al*. 2002 data), depending on if they were more or less than 25% of the patient day. This effectively assumes all patients under 25% OFF and over 25% OFF time had the same time on treatment. An exponential curve, fitted to these data, was then used to estimate the relationship between time on treatment and OFF time, with the assumption being that patients in lower OFF states are more likely to transition than those in higher OFF states, contradicting the previous assumption used to generate the data. The EAG suggested, if the company were to use these data, the company should plot the two midpoints of under 25% and over 25% OFF time. This method is demonstrated in Figure 3.

Figure 2. Company base case exponential model fitted to the two datapoints taken from Palmer *et al.* 2002

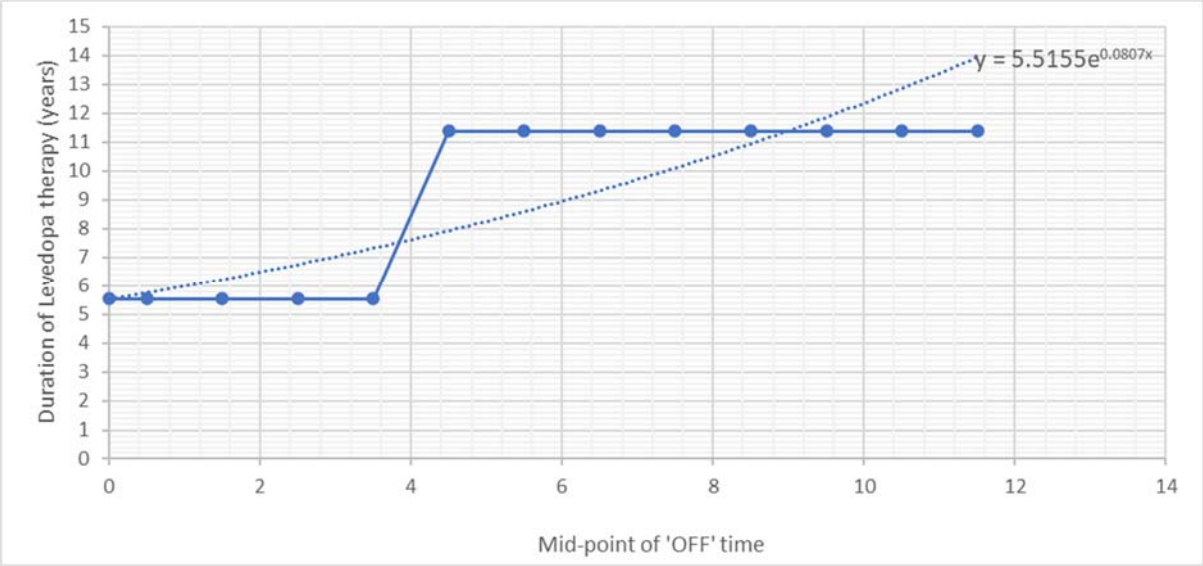
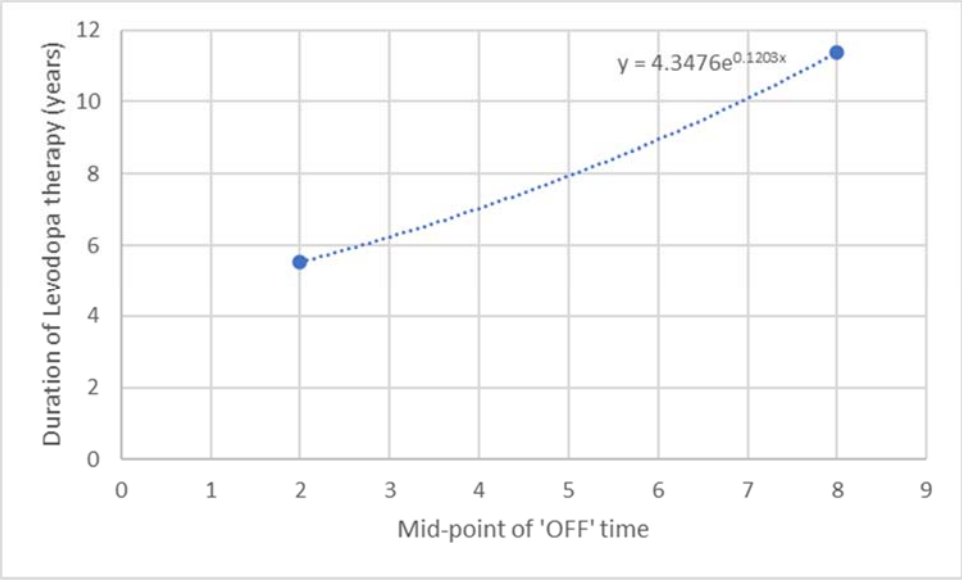


Figure 3. EAG alternative exponential model fitted to the two datapoints taken from Palmer *et al.* 2002



The only comment made by a stakeholder, notes that this issue links with key issue 7, in that the relative weakness of the Palmer *et al*. 2002 data provides a stronger case for using the trial data where possible. Stakeholders' comments can be seen in Table 14.

Table 14. Stakeholder responses to Key Issue 6: Problems with the use of Palmer *et al.* 2002 in informing BMT

Stakeholder	Comment
Parkinson's UK	We have no evidence or insights we can share on this point.

Clinical expert University of Plymouth	Nothing to add to this point.
Clinical expert South Tyneside and Sunderland Foundation Trust	See comment on issue 7
Patient expert	No comment.

Abbreviations: EAG, External Assessment Group;

Based on the EAG accepting the lack of other available data, the company considers in their TE response that this should no longer be considered to be a key issue. However, the company failed to address the criticism of their method for applying the Palmer *et al*. 2002 data, therefore the EAG consider this issue unresolved.

2.7 *Key Issue 7: The company did not use the trial M15-736 trial data on the comparator arm*

At the clarification stage, the EAG questioned why the M15-736 trial data was not used to inform the BMT arm and requested a scenario in which it was used and the LOCF assumption was applied for two cycles. The company declined to provide this scenario as the trial data showed improvement in BMT arm patients, which they speculate was due to it being in a trial setting with increased exposure to the healthcare system, efficacy and safety outcomes could be improved over outcomes in clinical practice. As the population is defined by patients with symptoms not adequately controlled by their current medical therapy.[15] While the EAG accepted that this "trial effect" is plausible, the EAG considers that this would equally apply to foslevodopa-foscarbidopa as well as BMT.

In the company's TE response, they make the case that LCIG and foslevodopa-foscarbidopa are associated with greater exposure to the healthcare system, as reflected by the higher modelled administration and management costs and which is more closely reflective of the healthcare interaction observed in the M15-736 trial. As the company considers the "trial effect" to be caused by interaction with the healthcare system, their position is that the trial-based interaction, seen in the foslevodopa-foscarbidopa arm, would be equivalent to clinical practice while this would not be the case in the BMT arm.

One clinical expert stakeholder agreed with the company's proposition and the other questioned the use of the use of such uncertain data as an alternative when high quality trial data are available. These stakeholder responses can be seen in Table 15.

Table 15. Stakeholder responses to Key Issue 7: The company did not use the trial M15-736 trial data on the comparator arm

Stakeholder	Comment
Parkinson's UK	We have no evidence or insights we can share on this point.
Clinical expert University of Plymouth	If the purpose of the model is to demonstrate the potential value of the therapy in the NHS setting, then I agree that the benefit of that treatment is a combination of the treatment effect and the placebo effect. The comparator of BMT in the NHS setting would not have exposure to an infusion and therefore experience neither placebo nor treatment benefit.
Clinical expert South Tyneside and Sunderland Foundation Trust	Not able to comment The company may be able to provide more information on why it has chosen Palmer et al data which is a rather old dataset (2000) rather than the trial data M15 736. Data from the M15 736 trial or a more recent data source would be useful to see and I think, important to have sight of, for the comparator arm
Patient expert	No comment.

Abbreviations: EAG, External Assessment Group;

The company points to higher modelled administration and management costs to show patients on advanced device-aided therapies (DATs) would have greater interaction with the healthcare system and thus get this "trial benefit" in clinical practice. Yet, the treatment management costs for foslevodopa-foscarbidopa and BMT are identical meaning the only greater interaction modelled is based purely on the higher administration cost, which is calculated as [redacted] titration and monitoring sessions. The "trial benefit" observed in BMT patients is 1 hour and represents over one third of the decline in OFF time observed in the foslevodopa-foscarbidopa arm as can be seen Figure 4. The company's position appears to therefore be that 1 hour of the OFF time decrease from foslevodopa-foscarbidopa, maintained for 3 years during the LOCF period, is due to greater interaction from [redacted] titration and monitoring sessions at administration. The EAG considers this to be clinically implausible.

Figure 4. Plot of mean change in average daily normalised OFF time from M15-736 trial

2.8 *Key Issue 8: The company uses efficacy data and discontinuation data from different sources*

During the clarification stage the EAG questioned the use of trial data from M15-736 to inform transitions while the same trial was not used to inform discontinuations. The company justified this by stating that sample 2 of the M15-741 trial used a new infusion set, now intended as the only commercial infusion set for foslevodopa-foscarbidopa and that it was more consistent to assume a constant source of discontinuation (M15-741) as opposed to switching from M15-736 for the first 3 cycle to M15-741. The company has reiterated both of these arguments in response to technical engagement.

It is the EAG's understanding that the new infusion set provided to cohort 2 in the M15-741 trial is also provided to all patients in the M15-736 trial, and so this is not considered a relevant argument for using one trial over the other. Furthermore, the argument that using different sources for discontinuation introduces heterogeneity into the data is true, but this is also the case in assuming a different source for efficacy and discontinuation. The EAG maintained in the EAG report that if the M15-736 data are used for efficacy it should be used to inform discontinuations. It was also suggested that data from M20-098 (open label extension to M15-736) could be used but the company have clarified in their TE response that these data will not be available within the current timeframe of this appraisal.

In the company's TE response, they reiterate their previous arguments and add the following:

- The M15-741 cohort 2 use of the new infusion set involved training provided on the correct use and application of the infusion set cannula including aseptic technique (the company do not note whether this was provided in the M15-736 trial).
- Clinical experts have advised that rates of discontinuation are expected to fall with continued use and training with foslevodopa-foscarbidopa in clinical practice.
- M15-736 discontinuation rates are likely inflated compared with rates expected in future clinical practice due to a number of discontinuations due to difficulty in administering foslevodopa-foscarbidopa, rather than discontinuations due to AEs or lack of efficacy. In M15-736, among the primary reasons for the 31 treatment discontinuations in all patients, five (16.1%) were due to difficulty with the drug delivery system and eight (25.8%) were due to "withdrawal of consent".

Overall, the justification the company gave for the use of M15-741 discontinuations was that these were more likely to be representative of clinical practice. In the stakeholder response, recorded in Table 16, one of the clinical experts agreed with the company's core case that it is more representative.

Table 16. Stakeholder responses to Key Issue 8: The company uses efficacy data and discontinuation data from different sources

Stakeholder	Comment
Parkinson's UK	We have no evidence or insights we can share on this point.
Clinical expert University of Plymouth	I don't think the participants in 741 and 736 are too dissimilar. The efficacy data are comparable. I think 741 cohort 2 data might be more reflective of the discontinuation rate were the therapy to be started within the NHS. The lessons learned from the earlier high discontinuation rate enabled practice to improve, in addition to utilising a new administration set. These learnings can be implemented in care services.
Clinical expert South Tyneside and Sunderland Foundation Trust	Not able to comment The company may be able to provide a more detailed rationale for why they have used efficacy and discontinuation data from different sources.
Patient expert	No comment.

Abbreviations: EAG, External Assessment Group;

The EAG acknowledges the company's comments but maintains that the efficacy data and discontinuations should come from the same source if possible. In response to the company's new arguments:

- The company are not clear on whether the nature of the infusion set provided in M15-736 and M15-741 differ. The company previously implied at clarification that patients in sample 2 of M15-741 were the only ones to receive the new infusion set that is intended to be the commercial infusion set but this now appears not to be the case.
- The EAG accepts that discontinuations may be likely to fall over time with continued use and training, but this does not justify using a different source for efficacy and baseline OFF state and discontinuation.
- Since the M15-741 CSR does not appear to separate reason for discontinuation by sample 1 and 2 the EAG cannot validate the company's claim that discontinuation rates in M15-736 are inflated due to difficulty administering.

The EAG position remains the same as the observed effectiveness from a trial is fundamentally linked with the discontinuation rate in that trial. Since the baseline patient data and first cycle efficacy data is based on M15-736 this should be the source of discontinuation for the first cycle. The transitions used in the model is based on a cohort of patients that may be different were the discontinuation rate the equivalent of M15-741. Either the M15-741 data should be used to inform baseline states and efficacy, or the M15-736 data should be used to inform discontinuation.

2.9 *Key Issue 9: Troublesome dyskinesia appears to be a source of unaccounted for patient burden*

Dyskinesia is currently represented as a one-time AE in the model. In the EAG report and during the clarification stage it was noted that troublesome dyskinesia would likely continue and progress throughout a patient's life and could represent a significant burden to patients that has not been incorporated into the model.

In the company's TE response, they note the following:

- In the M15-736 trial, in both arms, troublesome dyskinesia was rare being recorded as under 1 hour.

- 'On' time with troublesome dyskinesia at baseline was only 1.00 and 1.20 hours in the LCIG and control arms, respectively, in Olanow *et al.* 2014.[4]
- In the DYSCOVER trial,[2] treatment difference between LCIG and control in normalised 'On' time with troublesome dyskinesia did not reach statistical significance.
- Anti-dyskinetic treatment, such as amantadine, along with new methods of symptom management have significantly improved management of troublesome dyskinesia.
- Not including troublesome dyskinesia may be considered conservative as:
    - The point estimates from M15-736 suggest foslevodopa-foscarbidopa may provide better control of troublesome dyskinesia.
    - LCIG can result in biphasic dyskinesia.

Stakeholders' comments, shown in Table 17, appear to agree that the impact of dyskinesia is likely to develop over time. Although they also acknowledge that this issue only impacts a minority of patients.

Table 17. Stakeholder responses to Key Issue 9: Troublesome dyskinesia appears to be a source of unaccounted for patient burden

Stakeholder	Comment
Parkinson's UK	While we have no new data or evidence to clarify this point further we would like to reiterate the impact of troublesome dyskinesia and OFF time and state that this is variable for each individual with Parkinson's.
Clinical expert University of Plymouth	Agree dyskinesia can be troublesome. As well as physically limiting (for a minority), it can also be socially stigmatising and impact social confidence. There is some rationale for how long term (i.e. >3 months) continuous dopaminergic stimulation may result in reduced dyskinesia – via neuromodulatory mechanisms. This effect might not be so apparent in the shorter term – up to 3 months.
Clinical expert South Tyneside and Sunderland Foundation Trust	Troublesome dyskinesias are not included in the model. It is true that dyskinesias can develop over time but in general, oral medications are reduced or "pared down" over time to combat this problem. Dyskinesias are usually not troublesome to patients in my experience. Patients on the whole report a preference to be mobile and "on" with dyskinesias rather than immobile and off. They find the "off" state generally more disabling than the "on" state with dyskinesias. Dyskinesias can be socially embarrassing and are sometimes more noticeable to relatives and carers than to patients. A proportion of patients do get clinically troublesome and disabling dyskinesias and if the data is available, it would be helpful to see it. Any available kinetograph data may help corroborate patient's impression. Troublesome dyskinesia can in some patients be a burden and can lead to falls. It tends to be more embarrassing than

	disabling. In my experience, the proportion of patients with this problem is relatively small so it may not impact the analysis greatly. If the data for troublesome dyskinesias for trials in this drug and also in LCIG trials is available, it would be helpful to see it included in the model.
Patient expert	I do not suffer from dyskinesia as result of oral meds or use of the pump.

Abbreviations: EAG, External Assessment Group;

The EAG acknowledges the company's comments but is still of the opinion that this represents an unaccounted-for patient burden. There is likely difficulty in long term modelling due to a combination of lack of data and treatment management/Anti-dyskinetic treatment making projecting forward any current data unreliable. Nevertheless, as stakeholder experts have acknowledged, troublesome dyskinesia does appear to be a significant issue for a minority of patients. In addition, data from the M15-736 trial indicates [redacted].

The EAG maintains that this is an unaccounted-for area of treatment burden though acknowledges the difficulty in implementing this in the model long-term.

2.10 *Key Issue 10: The regressions used for health state cost by 'Off' time appear inappropriate*

In the EAG report 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.

The EAG investigated professional care, hospitalisation costs and respite care (the key drivers of health state costs) finding all three to be overestimated for every OFF state (with the exception of OFF 0 and OFF 1) when compared to the observed Adelphi data used to estimate the respective costs in the model, as shown in Table 18, Table 19, and Table 20. Furthermore, the EAG notes that the overestimation in costs for the last available OFF state (OFF 10) carries on until the OFF 16 state, for which there were no data available in the Adelphi study. For this reason, the EAG replaced the health state costs with the raw data from the Adelphi study as the illustrative base case. The EAG health state inputs compared to the regression are shown in Table 21.

Table 18. Professional care costs (observed vs estimated)

Health state	Total yearly costs in the model	Professional care (% of total cost)	Professional care cost estimated in the model	% patients* in the model	% patients* in Adelphi	Time^ in the model	Time^ in Adelphi	Total yearly costs in Adelphi	Difference
OFF 0	[redacted]	71.7%	£2,496	9%	[redacted]	41	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	75.8%	£4,765	16%	[redacted]	45	[redacted]	[redacted]	[redacted]
OFF 2	[redacted]	78.6%	£8,255	26%	[redacted]	49	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	80.3%	£13,057	37%	[redacted]	53	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	81.3%	£18,991	50%	[redacted]	57	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	81.8%	£25,608	64%	[redacted]	61	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	81.7%	£32,325	75%	[redacted]	65	[redacted]	[redacted]	[redacted]
OFF 7	[redacted]	81.2%	£38,599	84%	[redacted]	69	[redacted]	[redacted]	[redacted]
OFF 8	[redacted]	80.2%	£44,096	91%	-	73	-	-	-
OFF 9	[redacted]	79.0%	£48,731	95%	-	77	-	-	-
OFF 10	[redacted]	77.4%	£52,618	98%	[redacted]	81	[redacted]	[redacted]	[redacted]
OFF 11	[redacted]	75.8%	£53,428	99%	-	85	-	-	-
OFF 12	[redacted]	74.2%	£58,982	100%	-	90	-	-	-
OFF 13	[redacted]	72.6%	£61,818	100%	-	94	-	-	-
OFF 14	[redacted]	71.1%	£64,570	100%	-	98	-	-	-
OFF 15	[redacted]	69.8%	£67,286	100%	-	102	-	-	-
OFF 16	[redacted]	68.7%	£69,990	100%	-	106	-	-	-

*proportion of patients using professional care within each OFF state (in the model vs observed).
^time (hours per week) of used professional care (in the model vs observed)
Observed values were taken from Table 47 of the company response to clarification.

Table 19. Hospitalisation costs (observed vs estimated)

Health state	Total yearly costs in the model	Hospital (% of total cost)	Hospital costs estimated in the model	% patients * in the model	% patients * in Adelphi	Hospitalisations in the model	Hospitalisations in Adelphi	Total yearly costs in Adelphi	Difference
OFF 0	[redacted]	16.1%	£559	11%	[redacted]	1.6	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	14.4%	£907	18%	[redacted]	1.6	[redacted]	[redacted]	[redacted]
OFF 2	[redacted]	12.9%	£1,356	28%	[redacted]	1.5	[redacted]	[redacted]	[redacted]
OFF 3	[redacted]	11.6%	£1,878	39%	[redacted]	1.5	[redacted]	[redacted]	[redacted]
OFF 4	[redacted]	10.4%	£2,423	52%	[redacted]	1.5	[redacted]	[redacted]	[redacted]
OFF 5	[redacted]	9.4%	£2,932	64%	[redacted]	1.4	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	8.5%	£3,352	75%	[redacted]	1.4	[redacted]	[redacted]	[redacted]
OFF 7	[redacted]	7.7%	£3,654	84%	[redacted]	1.4	[redacted]	[redacted]	[redacted]
OFF 8	[redacted]	7.0%	£3,833	91%	-	1.3	-	-	-
OFF 9	[redacted]	6.3%	£3,907	95%	-	1.3	-	-	-

OFF 10	[redacted]	5.7%	£3,901	97%	[redacted]	1.3	[redacted]	[redacted]	[redacted]
OFF 11	[redacted]	5.2%	£3,669	99%	-	1.2	-	-	-
OFF 12	[redacted]	4.7%	£3,756	100%	-	1.2	-	-	-
OFF 13	[redacted]	4.3%	£3,654	100%	-	1.1	-	-	-
OFF 14	[redacted]	3.9%	£3,545	100%	-	1.1	-	-	-
OFF 15	[redacted]	3.6%	£3,433	100%	-	1.1	-	-	-
OFF 16	[redacted]	3.3%	£3,320	100%	-	1.0	-	-	-

*proportion of patients using professional care within each OFF state (in the model vs observed)
Observed values were taken from Table 41 of the company response to clarification.

Table 20. Respite costs (observed vs estimated)

Health state	Respite care costs estimated in the model	% patients* in the model	% patients* in Adelphi	Total yearly costs in Adelphi	Difference
OFF 0	£141.92	3%	[redacted]	[redacted]	[redacted]
OFF 1	£293.20	5%	[redacted]	[redacted]	[redacted]
OFF 2	£542.27	7%	[redacted]	[redacted]	[redacted]
OFF 3	£928.02	10%	[redacted]	[redacted]	[redacted]
OFF 4	£1,494.60	13%	[redacted]	[redacted]	[redacted]
OFF 5	£2,287.67	17%	[redacted]	[redacted]	[redacted]
OFF 6	£3,349.94	23%	[redacted]	[redacted]	[redacted]
OFF 7	£4,715.01	28%	[redacted]	[redacted]	[redacted]
OFF 8	£6,401.84	35%	-	-	-
OFF 9	£8,410.36	42%	-	-	-
OFF 10	£10,718.89	49%	[redacted]	[redacted]	[redacted]
OFF 11	£12,682.47	57%	-	-	-
OFF 12	£16,049.34	64%	-	-	-
OFF 13	£18,940.95	70%	-	-	-
OFF 14	£21,886.02	76%	-	-	-
OFF 15	£24,814.86	82%	-	-	-
OFF 16	£27,669.02	86%	-	-	-

Table 21: 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
OFF 0	[redacted]	£8,079
OFF 1	[redacted]	£8,072
OFF2	[redacted]	£4,112
OFF 3	[redacted]	£6,122
OFF 4	[redacted]	£17,288
OFF 5	[redacted]	£3,075

OFF 6	[redacted]	£2,863
OFF 7	[redacted]	£686
OFF 8	[redacted]	£686*
OFF 9	[redacted]	£686*
OFF 10	[redacted]	£2,797
OFF 11	[redacted]	£2,797*
OFF 12	[redacted]	£2,797*
OFF 13	[redacted]	£2,797*
OFF 14	[redacted]	£2,797*
OFF 15	[redacted]	£2,797*
OFF 16	[redacted]	£2,797*

*taken from the previous OFF state with available observed data

The reason a regression model was needed was due to a lack of data in many of the specific OFF states, an issue that would be alleviated by a different model structure with fewer OFF states as laid out in key issue 3. This lack of data also led the company to argue for including patients with early and intermediate PD, which the EAG considers a misrepresentation of the SmPC population.

In the company's TE response, they note the following:

- Using direct health state data leads to costs that lack face validity: OFF state 4 is modelled as incurring the highest cost, while OFF states 7–9 are now associated with the lowest cost. OFF state 0, associated with greatest symptom control, is assigned a health state cost three times greater than that of OFF state 16 in the EAG's analysis.
- The company reiterates the case made at clarification, that the full Adelphi dataset is required to make a valid model due to the limited sample size.

Stakeholder comments are found in Table 22. It is notable that one clinical expert suggests that the Adelphi advanced population may be less appropriate for use in costing than those in the study with intermediate PD as the definition may differ.

Table 22. Stakeholder responses to Key Issue 10: The regressions used for health state cost by 'Off' time appear inappropriate

Stakeholder	Comment
Parkinson's UK	We have no evidence or insights we can share on this point. However, we believe that the additional evidence the EAR suggests is reasonable.
Clinical expert University of Plymouth	Re: early and intermediate PD. I would be interested to know the definitions of these terms. One definition of 'advanced' is that it includes everyone with wearing

	off. If early and intermediate are defined according to other criteria – e.g. H&Y or disease duration, then these categories might well include patients with wearing off (and therefore be 'advanced' according to different criteria). However, these patients are likely to be those suitable for apomorphine and DBS, and therefore not within the scope presented (who have to be unsuitable or have failed apomorphine and DBS). From the report (section 4.2.4.3) it appears that advanced patients were more likely to be in a nursing home, for example, and therefore not represented by the trial participants. I suspect trial participants are more representative of intermediate severity patients. In summary – I suspect the Adelphi intermediate patients are most similar to the trial populations, and that Adelphi advanced are more advanced than the trial populations. The terms early, intermediate and advanced should be clearly defined. Are informal care costs/lost earnings (patient and carer) considered in the model?
Clinical expert South Tyneside and Sunderland Foundation Trust	Not qualified to comment See issue 11 relating to this report section.
Patient expert	No comment.
Abbreviations: EAG, External Assessment Group;	

The company has not presented any new evidence in support of their position and so the EAG's position remains the same. The fact that using the direct health state data leads to the implausible results identified by the company strengthens the case made in key issue 3 that the structure of the model is inadequate. While the regression analysis indicated a general correlation between OFF hours and health costs, the implausible individual OFF state costs indicates that:

- Using purely OFF hours to represent health related costs is flawed and there is likely to be an additional driving cause of health costs and/or;
- The health states are too granular, resulting in some patients with marginally higher OFF times having lower health costs than those with lower OFF times as the distinction between a few hours of OFF time does not make a significant difference to the patient.

The company has also not acknowledged or responded to the overestimation of the regression relative to the raw data. This issue would need to be resolved before the regression could be considered as an option.

2.11 *Key Issue 11: The utility values used in the company's base case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making*

The EAG disagreed, in the EAG report, 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 is shown in Table 30. This was considered strong supporting evidence for key issue 3, that OFF time alone is an insufficient measure of patient efficacy. Furthermore, the EAG consider it likely that the company did not attempt to account for age, sex, baseline OFF hours and treatment duration at baseline in their regression model. The EAG also requested the company use the data from the UK population with severe PD from the real-word Adelphi study to estimate utility values for those same 'Off' categories, in order to validate the estimates.

Table 23. Mean utility values at baseline in all studies used by the company

OFF hours	M15-736		M20-098		M15-741		M15-737	
	Frequency (n=[redacted])	Mean (SD)	Frequency (n=[redacted])	Mean (SD)	Frequency (n=[redacted])	Mean (SD)	Frequency (n=[redacted])	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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In the company's TE response:

- It is maintained that using OFF time alone is appropriate for decision making.

- The company added the requested variables to their utility regression. Sex had a significant impact on utility (p=[redacted]), the coefficient for NROFF remained similar to that of the analysis excluding these additional covariates ([redacted] versus [redacted], respectively). Inclusion of age and sex in the linear regression model is therefore unlikely to have a significant impact on health state utility values.

- The company validated the regression coefficient for OFF hours against Thach *et al.* 2021 which utilized 2017 and 2019 Adelphi Real World Disease Specific Programme for PD. Stakeholder comments are found in Table 24 and mostly reiterate the advice provided for key issue 3. The coefficient was found to be within a 95% CI of the value obtained in this paper.

- The company explored the impact of using single studies to inform utility values. They argued that the AIC and BIC showed the pooled results provide a superior fit and allow for all the data to be used.

- The company argued that in the UK dataset only [redacted] patients in the overall PD cohort, and [redacted] patients in the advanced PD cohort, have EQ-5D values reported and these are mostly concentrated in the OFF 0 state. Therefore, the requested validation exercise could not be done.

Stakeholder comments are found in Table 24 and mostly reiterate the advice guidance provided for key issue 3.

Table 24. Stakeholder responses to Key Issue 11: The utility values used in the company's base case analysis carry a high degree of uncertainty and are unlikely to be robust for decision making

Stakeholder	Comment
Parkinson's UK	We have no new data or evidence to clarify this point. As stated above there are limited treatment options for people with Parkinson's where oral medication is failing to control their symptoms or who are in the advanced stages of the condition. While we acknowledge the EAR's recommendation for an individual study to assess consistent utility values in the OFF state, we would be concerned if this further delayed use of the therapy by people who could benefit from it.
Clinical expert University of Plymouth	H&Y score can be easily derived from MDS-UPDRS part III. I have nothing further to add to this point.
Clinical expert	I am not expert in this field. I have reviewed and broadly agree with the comments made by EAG on this issue and their suggestions for resolution as follows:

South Tyneside and Sunderland Foundation Trust	There are a large number of "off" states in the model used, some of which have little accompanying data. A simpler model using broader categories for off states might be more optimal and also more in line with previous studies. The exclusion of H and Y scale from the analysis is noted and I agree with EAG comment that if a method could be found to estimate/convert to H and Y score from the available MDS UPDRS scores this may provide additional useful information.
Patient expert	No comment.

Abbreviations: EAG, External Assessment Group;

The EAG maintains that the data shows that an alternative modelling approach would be superior. Either the data available to inform so many OFF states is insufficient or OFF time alone is not an adequate representation of health-related quality of life. The company attempted including the additional requested variables in the regression but only shared limited details of their results. The company states that sex was [redacted] at a 5% threshold, providing the p value, but they do not provide this information for other values. The company's primary assertion is that including these additional variables has limited impact on the coefficient for NROFF (utility by extra OFF hour), changing it from [redacted] to [redacted], yet without the full regression results this cannot be confirmed. The fact that the pooled trial data was the best fitting would be expected given the higher number of observations and that all trials share an approximately inverse linear relation between OFF time and utility. This does not address the key issue with pooling this data across multiple trials. The values shown in Table 30 show a clear additional external factor influencing QoL in these trials. The EAG considers that if the company were to include "Trial" as a dummy variable in the regression, it would likely be statistically significant. As there is a clear external factor the EAG has used the M15-736 trial data only to inform utilities in the illustrative base case as this is the key trial that informs efficacy and baseline OFF state.

2.12 Additional issues

2.12.1 Additional issue 1: The data source for discontinuations for LCIG appears to go on for 16 years but only 2 years of data was used

In the EAG report the discontinuation source of Norlin *et al.* 2021[1] appears to have 16 years of data, yet only the first 2 years of data were used. In response to this issue the company simply defined how long-term discontinuation was calculated in the model. The EAG suggests the company review this issue.

2.12.2 Additional issue 2: The source for the rate of dyskinesia in LCIG patients appears to relate to oral levodopa.

In the EAG report it was identified that the source for the rate of dyskinesia in patients receiving LCIG, originally from Schrag and Quinn 2000, relates to patients receiving oral levodopa. The company agreed this source was inappropriate, and so LCIG is now assumed to have equivalent dyskinesia to foslevodopa-foscarbidopa. The EAG accepts this change and considers this issue resolved.

2.12.3 Additional issue 3: Applying AEs only in the first cycle is inappropriate when most of these AEs would be expected to progress over time.

In the EAG report it was noted as unjustified for TRAEs for infusion site nodule, infusion site erythema, infusion site pain, infusion site reaction, dizziness, falls and dyskinesia to be applied only in the first cycle, since experts suggest these would be expected to progress over time. The company still considers that not all of these AEs would progress, although they have taken the conservative assumption of assuming these AEs remain constant over the model time horizon. As such, the EAG considers this issue resolved.

2.12.4 Additional issue 4: LCIG recurring AEs continue occurring at the same rate regardless of the percentage of patients on treatment

In the EAG report it was identified that the recurring AEs were applied to LCIG patients regardless of how many patients had discontinued treatment. The company have corrected this issue, so costs are only applied to patients on treatment. The EAG accepts this change and considers this issue resolved.

2.12.5 Additional issue 5: The Dirichlet distribution applied to the health state transition probabilities for the PSA appears to have been calculated erroneously

In the EAG report the Dirichlet distribution used to calculate probabilistic variation in health state transitions was incorrectly calculated. The company have accepted the EAGs correction, and this issue can be considered resolved.

2.12.6 Additional issue 6: LCIG administration and treatment management costs appear to be overestimated

In the EAG report, the administration costs of LCIG and foslevodopa-foscarbidopa appeared to have been erroneously overestimated. This was based on the £727 value used as the cost of titration and monitoring which was applied [redacted] times for foslevodopa-foscarbidopa and [redacted] for LCIG. It was unclear to the EAG how the £727 cost was estimated given that it was taken from Chaudhuri *et al.*, where no cost code was specified, and where the cost was categorised as the daily cost in the total of 5 days of "titration and monitoring".[8] Given that clinical expert opinion provided to the EAG was that LCIG patients require a day case to insert the PEG tube, followed by 5 days in-hospital for monitoring of dopamine levels, the EAG assumes that the £727 cost from Chaudhuri *et al.*, reflects a daily cost of inpatient stay, as opposed to hospital visits as stated by the company.

The administration costs for LCIG were likely to be overestimated as the company costed five days at £727 per day, in addition to the inpatient stay cost of inserting a PEG tube (£1,116, cost code FE12A), which reflects a short hospital stay, leading to a total cost of £4,789. Furthermore, the company added the cost of a NG tube insertion (£1,464) which the EAG's clinical experts advised no longer occurs in the UK.

The EAG preference, was therefore, to use the cost associated with administering LCIG included in the 2016 NICE guideline for PD (NG71), updated to 2021 costs, amounting to a total of £2,929.[16] The EAG also recommended using the costs of one gastroenterology non-consultant led outpatient appointment to model the cost of PEG tube removal. The EAG also advised a change of the treatment management cost for removal of PEG tube which was costed the same as for inserting a PEG tube, though there exists a lower cost code that is explicitly for removal of PEG tube (NG71).

Given the lack of clarity around the hospital day cost of £727, and the company's explanation that foslevodopa-foscarbidopa is intended to be initiated in hospital with four following hospital visits, the EAG notes that it is possible that treatment administration costs associated with foslevodopa-foscarbidopa are overestimated in the model. The EAG's clinical experts advised that treatment with foslevodopa-foscarbidopa was expected to require one outpatient visit.

The company accepted this approach, and the model has also been updated in relation to the treatment management costs of LCIG and foslevodopa-foscarbidopa. In addition to accepting the EAGs recommended costs the company has now based foslevodopa-foscarbidopa administration on

two non-consultant led appointments, with the cost based on one hour of non-consultant doctor time in the latest PSSRU costs (£120).

This issue is considered resolve, although the EAG notes that the now reduced interaction with the healthcare system for patients treated with foslevodopa-foscarbidopa may contradict the company's argument for the existence of a "trial benefit" in clinical practice for these patients presented in key issue 7.

3 Company's revised cost-effectiveness results

3.1 Company revisions as a result of technical engagement

In response to the TE report, the company presented updated base case analyses. The updates are listed in Table 25 and the impact of changes in the model results are listed in Table 26.

Table 25. Changes to the company's cost-effectiveness model (copy of table 4 from the TE response)

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Changes outside of EAG key issues			
Foslevodopa-foscarbidopa dosing	Patients received 10 mL foslevodopa-foscarbidopa	As per the M15-736 trial, the EAG updated the foslevodopa-foscarbidopa dose to 10.4 mL for the first month, followed by 10.2 mL. This has been updated and corrected to patients receiving 10.4 mL for exactly 28 days	See Table 26 below
Source for utilities adjustments	Janssen *et al.* 2019 used to adjust utility values by age and sex	During clarification questions this source was requested to be changed to Ara and Brazier 2010	See Table 26 below
Key issues			
Key Issue 2: Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG	Use of relative risks derived from the NMA using a mix of observed and LS means for foslevodopa-foscarbidopa and LCIG efficacy	Use of relative risks derived from the NMA using only observed means	See Table 26 below
Key Issue 4: Patients are assumed to retain a lasting benefit from treatment following discontinuation	Patients discontinuing active treatments in the model remained in the health states which they occupied at the point of discontinuation, at which point transition probabilities for the BMT arm were applied	Patients discontinuing active treatments in the model are redistributed to the BMT arm based on baseline distribution	See Table 26 below
Key Issue 5: The LOCF assumption does not align with the trial data	For the LOCF period (Months 3–36), the transition probabilities calculated for the trial period (Month 0–3) were applied	Patients remain in their health states for the LOCF period	See Table 26 below
Additional issues			
Additional issue 2: The source for the rate of dyskinesia in	7.0% rate of dyskinesia in patients receiving LCIG	0% rate of dyskinesia in patients receiving LCIG	See Table 26 below

LCIG patients appears to relate to oral levodopa.			
Additional issue 3: Applying AEs only in the first cycle is inappropriate when most of these AEs would be expected to progress over time.	AEs applied only in the first cycle, and injection-related AEs were applied for BMT based on M15-736	Infusion site-related AEs, dizziness, and falls applied continuously over the model horizon, and removed injection-related AEs for BMT	See Table 26 below
Additional issue 4: LCIG recurring AEs continue occurring at the same rate regardless of the percentage of patients on treatment	The rate of recurring AEs for LCIG occurred at the same rate regardless of the percentage of patients receiving treatment in the cohort	Recurring AEs for LCIG are applied based on the percentage of patients receiving treatment in the cohort	See Table 26 below
Additional issue 6: LCIG administration and treatment management costs appear to be overestimated	LCIG administration costs: £4,789 LCIG management costs: £718 Four outpatient visits for titration and monitoring purposes for foslevodopa-foscarbidopa	LCIG administration costs: £2,929 LCIG management costs: £141.41 Two non-consultant led appointments for foslevodopa-foscarbidopa, one associated with titration, and another with monitoring	See Table 26 below
Abbreviations: AE: adverse event; BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; LOCF: last observation carried forward; LS: least squares; NMA: network meta-analysis.			

Table 26. Updated base case results, with-PAS (reproduced from table 5 from the TE response)

	BMT			LCIG		
	Incremental QALYs	Incremental costs	ICER (change from clarification questions ICER)	Incremental QALYs	Incremental costs	ICER (change from clarification questions 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]

	BMT			LCIG		
	Incremental QALYs	Incremental costs	ICER (change from clarification questions ICER)	Incremental QALYs	Incremental costs	ICER (change from clarification questions ICER)
Updates to the base case not relating to EAG issues (applied individually, deterministic)						
Foslevodopa-foscarbidopa dosing	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]
Source for utilities adjustments	0.79	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]
Updates to the base case relating to EAG issues (applied individually, deterministic)						
Key Issue 2: Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.09	[redacted]	[redacted]
Key Issue 4: Patients are assumed to retain a lasting benefit from treatment following discontinuation	0.60	[redacted]	Foslevodopa-foscarbidopa dominant	−0.21	[redacted]	Foslevodopa-foscarbidopa dominated
Key Issue 5: The LOCF assumption does not align with the trial data	0.63	[redacted]	Foslevodopa-foscarbidopa dominant	−0.03	[redacted]	[redacted]
Additional issue 2: The source for the rate of dyskinesia in LCIG patients appears to relate to oral levodopa	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]
Additional issue 3: Applying AEs only in the first cycle is inappropriate when most of these AEs	0.78	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]

	BMT			LCIG		
	Incremental QALYs	Incremental costs	ICER (change from clarification questions ICER)	Incremental QALYs	Incremental costs	ICER (change from clarification questions ICER)
would be expected to progress over time.						
Additional issue 4: LCIG recurring AEs continue occurring at the same rate regardless of the percentage of patients on treatment	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.11	[redacted]	[redacted]
Additional issue 6: LCIG administration and treatment management costs appear to be overestimated	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]
Company's revised base case (deterministic)	0.46	[redacted]	Foslevodopa-foscarbidopa dominant	−0.11	[redacted]	[redacted]
Company's revised base case (probabilistic)	0.46	[redacted]	Foslevodopa-foscarbidopa dominant	−0.12	[redacted]	[redacted]

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

Abbreviations: AE: adverse event; BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; LOCF: last observation carried forward; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

3.2 *Company's updated base case*

The company's updated base case results are given in Table 27 for the probabilistic and Table 28 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 south-west quadrant incremental cost-effectiveness ratio (ICER) of

[redacted] and [redacted] costs saved per QALY forgone, for the probabilistic and deterministic results respectively. Best medical therapy (BMT) is dominated by foslevodopa-foscarbidopa.

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 27. Company's probabilistic base case results

Interventions	Total Costs (£)	Total LYG*	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	-	4.91	-	-	-	-
LCIG	[redacted]	-	5.03	[redacted]	-	-0.12	[redacted]
BMT	[redacted]	-	4.45	[redacted]	-	0.46	Dominant

*LY 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 28. Company's deterministic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	9.072	4.91	-	-	-	-
LCIG	[redacted]	9.072	5.03	[redacted]	0	-0.11	[redacted]
BMT	[redacted]	9.072	4.45	[redacted]	0	0.46	Dominant

[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.

4 EAG's cost-effectiveness results

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

- Assumed equal efficacy between LCIG and foslevodopa-foscarbidopa (key issue 2);
- Patients who discontinue have equivalent outcomes to natural disease progression arm (key issue 4);
- Alternate implementation of Palmer *et al.* 2002 data using only the available data from the paper (key issue 6);
- Use M15-736 for discontinuations to match efficacy during trial period, then M15-741 cohort 2 and M15-737 (key issue 8);
- Use direct data to inform resource use for health state cost (key issue 10);
- Use only the M15-741 trial to inform utilities;
- Use only the M15-736 trial to inform utilities.

The EAG did not have the time to add a scenario using the M15-736 BMT arm trial data though this scenario is needed to fully explore plausible cost-effectiveness outcomes. Results of the EAG's scenarios are given in Table 29. Scenarios show significant variation in cost-effectiveness depending on the assumptions used.

Table 29. Results of EAG scenarios (deterministic)

	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	4.91	4.45	5.03	0.46	-0.11
	ICER (£/QALY)	-	-	-	Dominant	[redacted]
1	Assumed equal efficacy LCIG and foslevodopa-foscarbidopa					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.91	4.45	5.08	0.46	-0.17
	ICER (£/QALY)	-	-	-	Dominant	Dominated
2	Patients who discontinue have equivalent outcomes to natural disease progression arm					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.80	4.45	4.88	0.35	-0.09
	ICER (£/QALY)	-	-	-	Dominant	[redacted]
3	Alternate implementation of Palmer *et al.* 2002 data using only the available data from the paper					

	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.04	4.65	5.13	0.39	-0.09
	ICER (£/QALY)	-	-	-	Dominant	[redacted]
4	Use 736 discontinuations, 741 cohort 2 and 737					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.83	4.45	5.03	0.38	-0.20
	ICER (£/QALY)	-	-	-	Dominant	Dominated
5	Use direct data to inform resource use for health state cost					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.91	4.45	5.03	0.46	-0.11
	ICER (£/QALY)	-	-	-	£238,957	[redacted]
6	Use only the M15-741 trial to inform utilities					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.73	4.32	4.82	0.40	-0.09
	ICER (£/QALY)	-	-	-	Dominant	[redacted]
7	Use only the M15-736 trial to inform utilities					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.84	5.64	5.88	0.19	-0.04
	ICER (£/QALY)	-	-	-	Dominant	[redacted]

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

In this section of the report, the EAG also presents its illustrative base case ICER. The EAG does not have a base case due to key issue 7 being unresolved. The key differences between the company's base case ICER and EAG's illustrative base case ICER are given in Table 30.

Table 30. 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	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
3	Implementation of Palmer *et al.* 2002, how to extrapolate the two data points	Implementation of Palmer *et al.* 2002 data using 13 data points	Alternate implementation of Palmer *et al.* 2002 data using 2 data points
4	Which set of trials to inform discontinuation	Use 741 cohort 2 and 737	Use 736 discontinuations, 741 cohort 2 and 737

5	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
6	Use combined or single trials to inform utility	Use combined trial data	Use only the M15-736 trial to inform utilities

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

Table 31 shows the cumulative impact of each assumption for the EAG illustrative base case (deterministic results). In the EAG's illustrative base case, foslevodopa-foscarbidopa has an ICER higher than would be considered cost-effective using the standard ICER range of £20,000 to £30,000, with a south-west quadrant cost-effective position versus LCIG. The EAG does not have a preferred base case as key issue 7 has not been resolved. The trial benefit observed in the BMT arm should be taken into account, given how little interaction the company considers foslevodopa-foscarbidopa patients have with the healthcare system, the company's argument that a "trial effect" benefit should only be considered for foslevodopa-foscarbidopa based on additional contact with the healthcare system appears implausible.

Table 31. EAG's illustrative 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	4.91	4.45	5.03	0.46	-0.11
	ICER (£/QALY)	-	-	-	Dominant	[redacted]
1	Assumed equal efficacy LCIG and foslevodopa-foscarbidopa					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.91	4.45	5.08	0.46	-0.17
	ICER (£/QALY)	-	-	-	Dominant	Dominated
2	Patients who discontinue have equivalent outcomes to natural disease progression arm					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.80	4.45	4.94	0.35	-0.14
	ICER (£/QALY)	-	-	-	Dominant	Dominated
3	Alternate implementation of Palmer et al. 2002 data using only the available data from the paper					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.95	4.65	5.07	0.30	-0.12
	ICER (£/QALY)	-	-	-	Dominant	[redacted]
4	Use 736 discontinuations, 741 cohort 2 and 737					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.90	4.65	5.07	0.25	-0.18

	ICER (£/QALY)	-	-	-	Dominant	[redacted]
5	Use direct data to inform resource use for health state cost					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	4.90	4.65	5.07	0.25	-0.18
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]
6	Use only the M15-736 trial to inform utilities					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.82	5.70	5.91	0.12	-0.09
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]

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

Table 32. EAG's probabilistic illustrative base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	-	5.82	-	-	-	-
LCIG	[redacted]	-	5.90	[redacted]	-	-0.08	[redacted]
BMT	[redacted]	-	5.70	[redacted]	-	0.12	[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 33. EAG's deterministic illustrative base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	9.072	5.82	-	-	-	-
LCIG	[redacted]	9.072	5.91	[redacted]	£0	-0.09	[redacted]
BMT	[redacted]	9.072	5.70	[redacted]	£0	0.12	[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

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