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

Part 1 slides for public – fully redacted

Technology appraisal committee C [9 May 2023]

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Company: AbbVie

Background on Parkinson’s (1/2)

Parkinson's requires highly personalised management

Overview

- Chronic, progressive, neurodegenerative condition that affects dopamine regulation in the brain

Epidemiology

- ~145,000 people in UK live with Parkinson’s, of these ~34% have complex or advanced disease

Symptoms

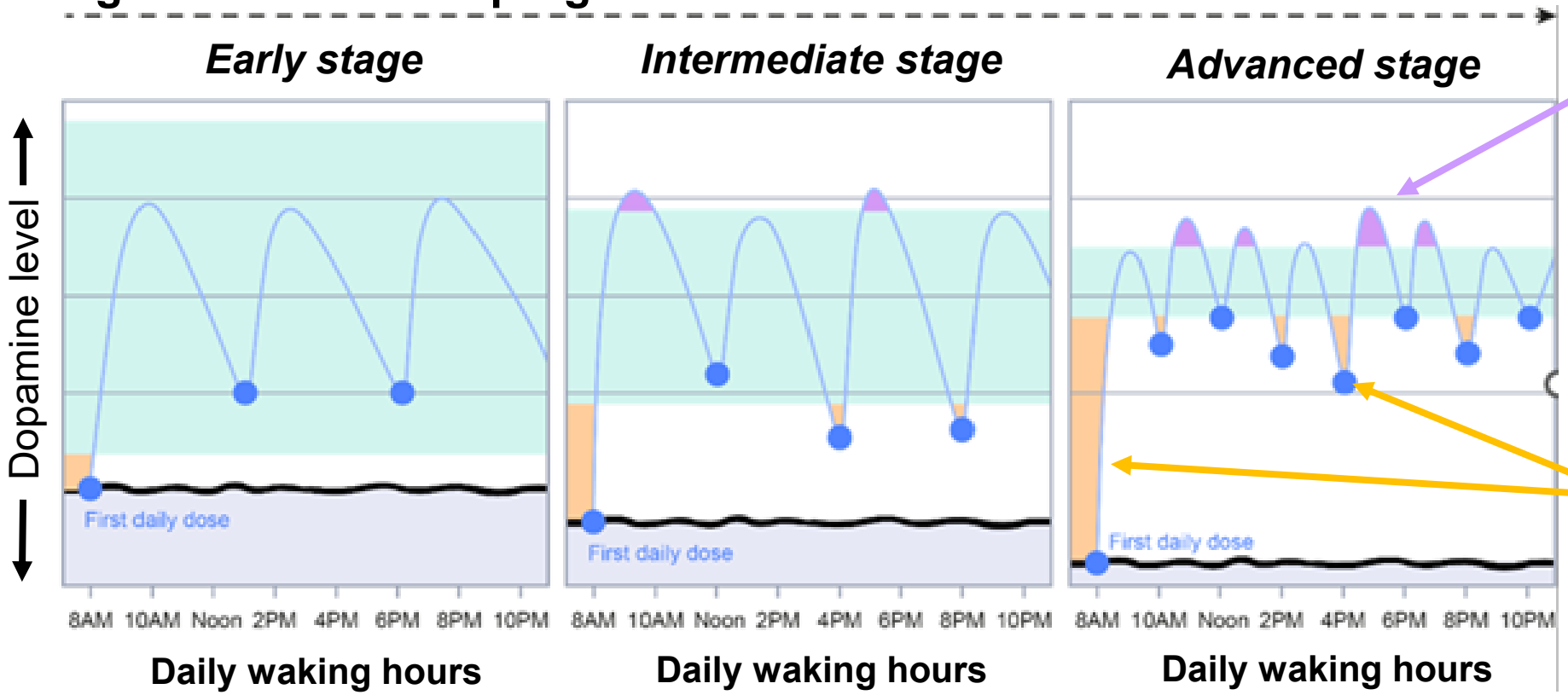
- People with Parkinson's typically present with motor symptoms, including slowness or absence of movement, tremors and rigidity
- Also associated with many non-motor symptoms, some may precede the motor dysfunction by 10 years. These can include psychological and physical symptoms (e.g. loss of sense of smell and constipation)
- Symptoms vary between people so Parkinson’s requires highly personalised management

Background on Parkinson's (2/2)

Advanced disease leads to motor fluctuations

- Levodopa is gold standard therapy to for controlling motor symptoms: this is the aim of treatment
- ON time = Parkinson's well controlled, OFF time = Parkinson's returns
- Reducing 'OFF' time a key goal of treatment for clinical management of Parkinson's

Figure: Parkinson's progression over time



In advanced Parkinson's:

Involuntary movement or 'dyskinesia' during 'ON' time can occur with *over medication*

Therapeutic window of levodopa narrows as Parkinson's progresses leading to motor fluctuations

'OFF' time symptoms of Parkinson's can occur with *under medication*

Natural dopamine levels fall as Parkinson's progresses

Levodopa dose given Medicated dopamine level

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Treatment pathway

Company focuses on a subset of advanced Parkinson's – people responsive to levodopa but for whom apomorphine or DBS are unsuitable or no longer providing adequate symptom control

Initial therapy: oral levodopa with carbidopa, adjunct therapies†, amantadine. Non-oral advanced therapies (DBS, LCIG) used as Parkinson's progresses

Advanced Parkinson's: levodopa-responsive with severe motor fluctuations and hyperkinesia or dyskinesia

Foslevodopa-foscarbidopa (fos-fos)

Technology being appraised

LCIG (levodopa-carbidopa intestinal gel, continuously delivered into small intestine via pump)*

Suitability criteria:
- Apomorphine or DBS unsuitable
- ≥50% OFF periods

BMT (amantadine and levodopa plus adjunct therapies†)

Used when LCIG, apomorphine or DBS are unsuitable

Comparators in company model

Apomorphine (+/- BMT)

DBS

Suitable for some people with advanced Parkinson's but not included as comparators in company modelling

*LCIG has NHS Commissioning Policy. †Adjunct therapies: dopamine agonists, MAO-B inhibitors, COMPT inhibitors

Clinical expert comments on LCIG

- Little experience with LCIG – long wait times and strict criteria
- May use when people very frail with more cognitive than motor difficulties

What are appropriate comparators for fos-fos? How is advanced disease defined?

Abbreviations: BMT, best medical therapy; COMT, catechol-o-methyl transferase; DBS, deep brain stimulation; fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel; MAO-B, monoamine oxidase-B

Perspectives on living with Parkinson's

People with Parkinson's and carers value improvements to predictability

Submissions from Parkinson's UK and people who live with Parkinson's

Carers find the condition troubling particularly:

- stress of supporting and enabling their partner
- unpredictability of advanced Parkinson's can mean leaving the house isn't possible
- sleep deprivation from around the clock care and often face financial distress

On using fos-fos pump following oral therapies:

- reduced number of peaks and troughs in motor complications (ON/OFF time, dyskinesia and dystonia)
- allows greater confidence and freedom in daily living such as ability to drive
- means medication adherence and side-effects are no longer issues
- less chance of carer burnout with more predictable disease including bladder, cognitive and psychosis symptoms

"Living with Parkinson's has become increasingly challenging… I feel a burden on my family"

"Using fos-fos now means I can eat dinner with my wife, which means a lot to us""

"With fos-fos, fluctuations in ON and OFF periods are greatly reduced"

"Life sentence in a small cell that gets smaller and smaller"

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Abbreviations: fos-fos, foslevodopa-foscarbidopa

Clinical perspectives

Achieving good dopamine control has many benefits for people with Parkinson's

Submissions from clinical experts and a professional clinical body

"Great need for more effective and well tolerated treatments for advanced Parkinson's"

"Fos-fos is a game changer, I would prescribe it for people who have been diagnosed with Parkinson's disease for between 3-5 years to help with their motor function"

- No disease modifying therapies for Parkinson's – unmet needs remain
- Existing therapy options often unsuitable (DBS and apomorphine)
  - administration of fos-fos more discreet and easier than levodopa-carbidopa intestinal gel (LCIG)
  - avoiding brain surgery (with DBS) easier and safer
  - key benefit of fos-fos is its overnight control of dopamine
- Reduced hospital admissions, length of stay, and admission related morbidity
- Social benefits associated with fos-fos: positive impact for carers and family
- Good dopamine control with fos-fos for a number of years can mean ageing similar to that of a healthy person. Poor dopamine control can drive faster neurological and physical degeneration
- Concerns about pump and managing skin tolerability

Abbreviations: DBS, deep brain stimulation; fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel

Equality

Technology could be more widely available than some other treatments for advanced Parkinson's

Potential equality considerations

- Company raised no equalities issues
- Parkinson's UK comments:
  - Treatment availability: ease of use should make it more available than some treatments that are only offered in specialist centres but, need to store drug in fridge and accessory items take up space
  - Visual and cognitive impairments: pump adjustment relies on good visual function. Also people with cognitive impairment may find the device harder to use than oral therapy
  - Age: 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
- Clinical expert comment: Pump-based therapies might be less acceptable in some cultural or ethnic groups

NICE comments:

If the technology is recommended, a clinician would need to determine if it is suitable.

Issues related to differences in prevalence or incidence of a disease between different age groups cannot be addressed in a technology appraisal.

Parkinson's can be classed as a disability under Equality Act

Foslevodopa-foscarbidopa (Produodopa, AbbVie)

Technology details

Marketing authorisation	• Treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results
Mechanism of action	• A prodrug combination of levodopa and carbidopa • Levodopa is metabolised to dopamine once it has reached the brain, improving nerve conduction and reducing the physical symptoms associated with Parkinson's • Carbidopa prevents metabolism of levodopa until it has crossed the blood-brain barrier
Administration and dosing	• By continuous subcutaneous infusion via a pump (24 hours a day) • Dose adjusted to reach clinical response: maximal functional 'ON' time and minimal number and duration of OFF episodes and ON episodes with troublesome dyskinesia • Maximum recommended daily dose is 6000 mg (25 ml fos-fos per day, equivalent to approximately 4260 mg of levodopa per day) • People with Parkinson's or carers can independently administer an extra dose to manage acute OFF symptoms experienced during continuous infusion
List price	• **Fos-fos ~£31,000 per year**: £592.90 per week or £84.70 per 10 ml vial (per day [max. recommended 25 ml per day]) • Confidential simple patient access scheme (PAS) discount

How many people on fos-fos start with a higher loading dose to achieve a clinical response?
How many likely to self-administer an extra dose to manage acute OFF symptoms (if permitted)?

Abbreviations: max. maximum; MHRA, Medicines and Healthcare products Regulatory Agency; ml, millilitre

Decision problem

Company submission on narrower population may be reasonable

	Final scope	Company submission	EAG comments
Population	Adults with Parkinson's that is responsive to levodopa, with motor symptoms uncontrolled by standard therapy	Final scope population (on BMT) + "for whom apomorphine or DBS unsuitable or no longer providing adequate symptom control"	Narrower population reasonable – has high unmet need, but clinical evidence presented for broader population
Intervention	Fos-fos	Same as final scope	N/A
Comparators	• BMT • DBS • LCIG • Apomorphine +/- standard oral medication	• LCIG • BMT	Agree, based on the narrower population
Outcomes	• ON/OFF time • dyskinesia • motor complications • cognitive function • mortality • AEs • HRQoL	Same as final scope minus cognitive function	No issue, the technology's primary target is motor symptoms of Parkinson's
Subgroups	Subject to available evidence: • Proportion time spent in OFF state • Apomorphine unsuitable • DBS unsuitable	None considered	No issues, but notes population is narrower than trial population (and scope)

To what extent might the effectiveness of fos-fos differ between the population specified in the scope and the narrower population the company is focusing on?

Abbreviations: AE, adverse event; BMT, best medical therapy; DBS, deep brain stimulation; HRQoL, health related quality of life; LCIG, levodopa-carbidopa intestinal gel

Key issues

ICER impact key: Large  Small  Unknown  Quadrant change 

Key issue	Resolved?	ICER impact	
		BMT	LCIG
Uncertainty with potential overestimation of treatment benefit for fos-fos	No		
Uncertainty in indirect comparisons of fos-fos and LCIG	No	NA	
BMT comparator data: (a) M15-736 trial data not used; and (b) limitations of method using data from Palmer	No		
Modelling: (a) OFF state approach inadequate for capturing range of health effects in advanced Parkinson's and (b) high number of OFF states	No		
Uncertain benefit after treatment discontinuation	Partially		
Sources differ for efficacy and discontinuation data	No		
Unaccounted burden of 'troublesome dyskinesia'	No		
Robustness of utility values used	No		
Regression used for health state cost by OFF time	No		

Abbreviations: BMT, best medical therapy; ICER, incremental cost-effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel

Clinical evidence

NICE National Institute for Health and Care Excellence

Key studies and outcomes

	Company base case – efficacy inputs	Company base case – discontinuations
	M15-736	**M15-741**
Design	Phase III, randomised, double-blind, double-dummy, active-controlled, parallel group study	Phase III open-label, single-arm study
Population	Advanced, levodopa-responsive PD with motor fluctuations inadequately controlled by current therapy, ≥2 hours OFF time per day. No prior DBS	Levodopa-responsive PD with motor fluctuations inadequately controlled by oral medications
Intervention	Fos-fos by 24-hour continuous subcutaneous infusion + oral placebo	Fos-fos by 24-hour continuous subcutaneous infusion
Comparator	Oral carbidopa/levodopa (immediate release) + 24-hour placebo continuous subcutaneous infusion	None
Duration	12 weeks double-blind treatment	52-weeks open-label treatment
Primary outcome	ON time without troublesome dyskinesia (hours, assessed by PD diary for 16-hour waking day)	Safety and tolerability
Key secondary outcomes	OFF time (hours, PD diary), MDS-UPDRS score, morning akinesia, dyskinesia & bradykinesia, sleep, HRQoL	ON time without troublesome dyskinesia, OFF time (PD diary), MDS-UPDRS symptoms score, sleep, HRQoL
Locations	65 centres in US and Australia (not UK/European)	60 centres globally including UK (n=[redacted])

Abbreviations: DBS, Deep brain stimulation; HRQoL, health related quality of life; MDS-UPDRS; Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease

Can continue treatment in **M20-098 open label extension study** (ongoing in Oct 2022)

Can continue treatment in **M15-737 open label extension study** (ongoing in Dec 2022)

M15-736 results

Key: Fos-fos / Oral CD/LD

Fos-fos increased ON hours without troublesome dyskinesia and reduced OFF hours, both statistically significantly and by >1 hour (clinically significant), vs oral CD/LD

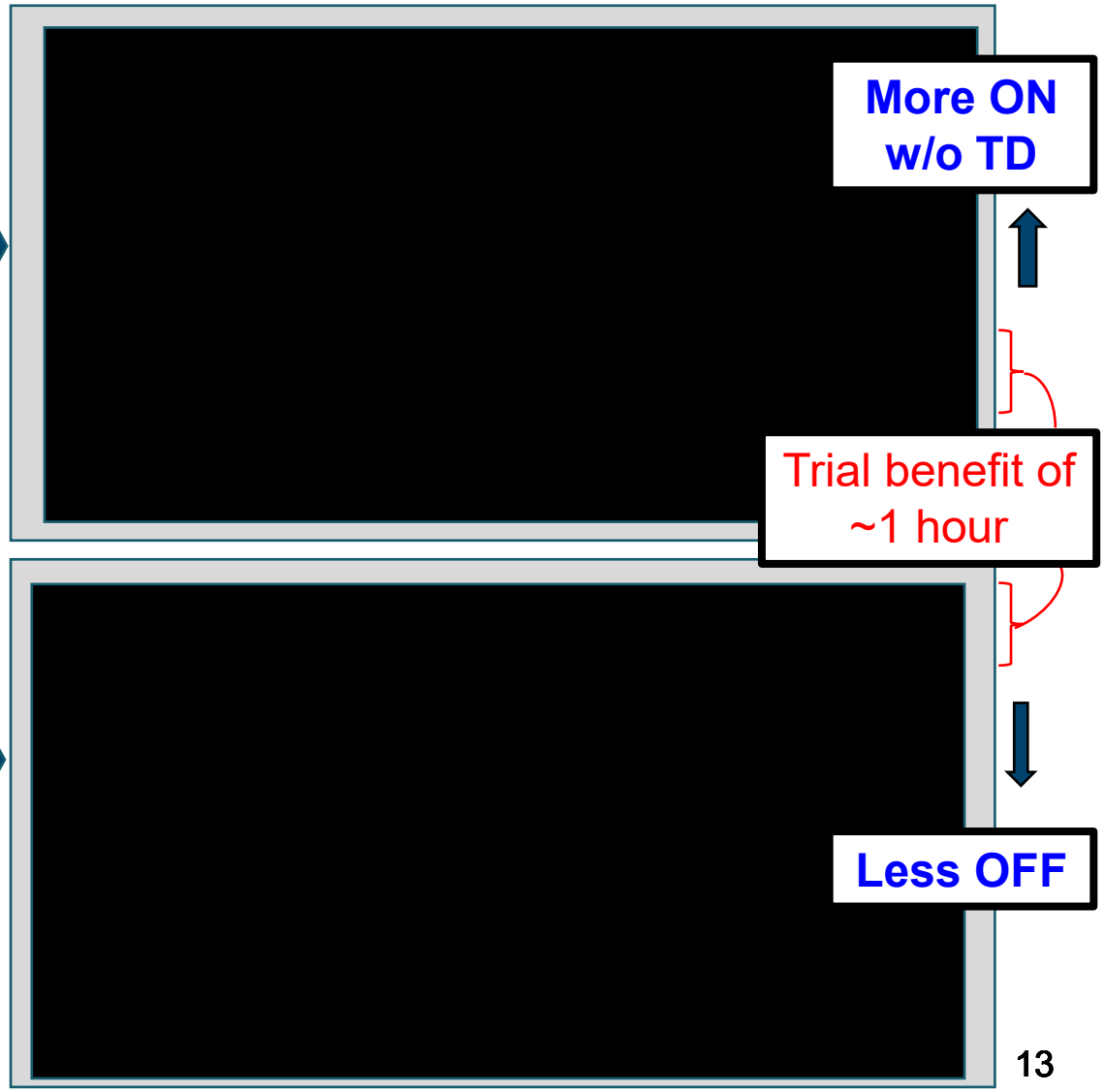
Table: ON hours without troublesome dyskinesia*: change from baseline to Week 12 (primary outcome)

Characteristic	Fos-fos	Oral CD/LD
Number of people at baseline	73	67
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	<0.01	

*Includes 'ON' time without dyskinesia and 'ON' time with non-troublesome dyskinesia

Table: OFF hours: change from baseline to Week 12

Characteristic	Fos-fos	Oral CD/LD
Number of people at baseline	73	67
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	<0.01	



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Abbreviations: CD/LD: carbidopa/levodopa; fos-fos; fos-fos; LS: least square; SD: standard deviation; TS, troublesome dyskinesia; w/o, without

Key issue: Uncertainty with potential overestimation of treatment benefit for fos-fos (1/2)

Company narrows population and people in trial may guess treatment

EAG comments – fos-fos effectiveness may be overestimated

- Company's submission is for narrower population than scope or trial population – not clear if fos-fos effectiveness differs in these populations
  - in M15-736 trial, prior DBS therapy not allowed, but prior apomorphine therapy permitted
- High risk of unblinding due to large difference in morning akinesia between fos-fos and oral CD/LD
- Outcomes captured in patient diary – subjective with risk of bias

Company TE response – M15-736 a robustly conducted RCT

- Likely limited impact on clinical efficacy of fos-fos based on whether people have previously had apomorphine or DBS
- People could correctly "guess" their treatment allocation, but this should not be considered a source of uncertainty in the cost-effectiveness analysis
- Additional clinical opinion provided through interviews with 3 clinicians who:
  - agreed with company's trial design – no better alternatives could have been used
  - considered use of patient diaries to collect OFF time as gold standard in Parkinson's trials
  - stated prior use of apomorphine is not expected to impact efficacy of subsequent therapies

Abbreviations: CD/LD, carbidopa/levodopa; DBS, deep brain stimulation; EAG, evidence assessment group; fos-fos, fos-fos; RCT, randomised controlled trial; TE, technical engagement

Key issue: Uncertainty with potential overestimation of treatment benefit for fos-fos (2/2)

Company narrows population and people in trial may guess treatment

BMT	LCIG
?	?

Company TE response *continued*

- Company notes: people who had prior apomorphine or DBS in M15-741 were similarly matched to full trial populations who were enrolled in M15-736 and M15-741 studies, so outcomes for these people not expected to be different from broader trial populations

EAG critique of TE response

- EAG's clinical experts agree with company experts' views
- EAG maintains it is likely that people on fos-fos may overestimate treatment efficacy and people having BMT may underestimate treatment efficacy, as a result of correctly deducing which treatment they are on so fos-fos ICERs likely to be **underestimated** (magnitude unclear)

Stakeholder comments at TE

- Trial populations more representative of people suitable for DBS (M15-741) and apomorphine (M15-736) than those suitable for LCIG
- In company's narrower population, people may be older, more frail and possibly with more cognitive issues
- Patient diaries can provide useful direct patient information but not without drawbacks

Is the trial design likely to significantly impact the interpretation of the results?

Abbreviations: BMT, best medical therapy; DBS, deep brain stimulation; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; ICER, incremental cost-effectiveness ration; LCIG, levodopa-carbidopa intestinal gel; RCT, randomised controlled trial; TE, technical engagement

Summary of evidence to inform company's comparisons

Fos-fos: indirect comparison with LCIG and naïve comparison with BMT

Fos-fos M15-736 trial data used in…

Indirect comparison with LCIG:

- No direct evidence comparing fos-fos with LCIG
- Used to estimate comparative efficacy for ON time (hours) without troubling dyskinesia and OFF time (hours):

Network of 3 randomised controlled trials

M15-736 trial: fos-fos vs oral CD/LD

Olanow 2014, DISCOVER: BMT vs LCIG

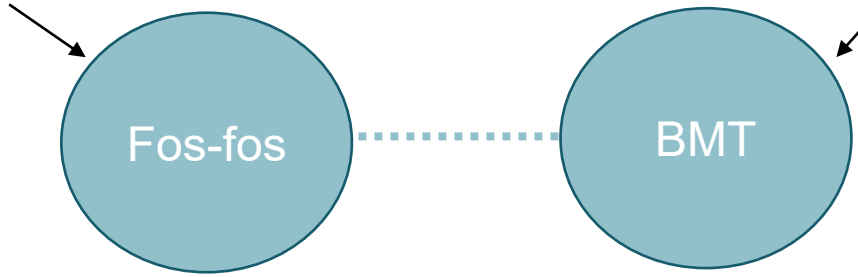
Naive comparison with BMT :

- BMT assumed to give no clinical benefit, representing people whose symptoms are not controlled by standard therapy:

Indirect comparison of 2 studies

M15-736 trial: fos-fos arm only; oral CD/LD arm not used

Palmer et al (2002): BMT is 'natural disease progression'



Abbreviations: BMT, best medical therapy; CD/LD: carbidopa/levodopa; fos-fos; foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel

Key issue: Uncertainty in indirect treatment comparisons of fos-fos and LCIG (1/2)

Inconsistent in use of observed and least squares (LS) means data in NMAs

Stakeholder comments: No head-to-head studies of fos-fos and other treatments for advanced Parkinson's

Background

- EAG generally agrees with company's methods of indirect comparison
  - NMA results have same uncertainty and high risk of bias as underlying M15-736 data
  - Heterogeneity between the trials likely due to differences in BMT and variation in people's Parkinson's
- EAG prefers to assume equal efficacy for fos-fos and LCIG as [redacted] in NMAs

EAG: Company inconsistent in use of observed and least squares (LS) means data in NMAs – EAG prefers LS means, which adjust for issues in baseline characteristics that are not matched

Company TE response

- Updated NMA for OFF time outcome using observed means from all 3 trials (not LS means data)
  - Suggests observed means may not run risk of biased parameter estimates associated with LS means
- **OFF time (hours per day):** There was a [redacted] with fos-fos compared with LCIG, but this did [redacted]. Improvement was greater with LCIG than fos-fos for **ON time** [redacted] (≥1 hour difference) but [redacted]

Table: Company's updated NMA after TE for **OFF time change from baseline** in *hours* (observed means)

Indirect comparison	RE: mean difference (95% CrI)	FE: mean difference (95% CrI)
Fos-fos vs LCIG	[redacted]	[redacted]

Abbreviations: BMT, best medical therapy; CD/LD: carbidopa/levodopa; CrI, credible interval; FE, fixed-effects; fos-fos; foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel; LS, least squares; NMA, network meta-analysis; RE, Random effects; TE, technical engagement

BMT	LCIG
NA	

Key issue: Uncertainty in indirect treatment comparisons of fos-fos and LCIG (1/2)

EAG prefers to assume equal efficacy between fos-fos and LCIG

EAG critique of TE response *continued*

- Notes likely bias in observed mean data, e.g. due to differences in baseline values and high levels of missing data from high level of discontinuations so prefers LS means
- Re-runs NMA using LS means data but omitting Olanow 2014 study as it did not have access to LS mean with mixed model repeated measures (MMRM) data so results should be viewed with caution
  - Not using Olanow 2014 means consistent use of MMRM results from both trials – another issue
- LCIG led to [redacted] in OFF time (<1 hour) compared with fos-fos that [redacted], in company approach there was a small reduction in OFF time (<1 hour)

Table: EAG's NMA re-run for **OFF time change from baseline** in *hours* (LS means data based on 2 trials only: M15-736, DISCOVER')

Indirect comparison	RE: mean difference (95% CrI)	FE: mean difference (95% CrI)
Fos-fos vs LCIG	[redacted]	[redacted]

- Comparing cost-effectiveness of assuming equal efficacy to the NMA results:
  - **decreases cost-effectiveness** of fos-fos vs LCIG using company's original NMA results
  - **improves cost-effectiveness** of fos-fos vs LCIG using results of EAG's updated analysis

What conclusions can be made around the relative effectiveness of fos-fos compared with LCIG? Is it reasonable to assume equal efficacy between fos-fos and LCIG?

Abbreviations: CrI, credible interval; EAG, evidence assessment group; FE, fixed-effects; fos-fos; foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel; LS, least squares; NMA, network meta-analysis; RE, Random effects; TE, technical engagement

BMT	LCIG
?	?

Key issue: BMT comparator data (a) M15-736 trial data not used

Company did not use BMT comparator data from foslevodopa-foscarbidopa trial

Background

- Fos-fos positioned in Parkinson's that is inadequately controlled by standard therapy, so company assumed BMT gave no benefit and resulted in natural disease progression

Company

- Trial data on BMT available from M15-736 for Parkinson's stabilised on oral LC/CD was not used in model, to remove impact of BMT being delivered in a trial setting with increased exposure to healthcare system
  - Notes treatment benefit (placebo effect) with BMT evident in trial
  - Declined to show scenario where M15-736 BMT trial data used to inform transition probabilities
- Compared with BMT, LCIG and fos-fos involve greater exposure to healthcare system – more like a trial

EAG comments

- BMT arm showed a benefit in M15-736 trial, where OFF time was reduced by almost 1 hour from baseline (>1/3 of the reduction in OFF time seen with fos-fos) – placebo effect equally likely with fos-fos
- Fos-fos has similar exposure to healthcare system to BMT, only difference is due to [redacted] titration and monitoring sessions
- Using M15-736 BMT data would make fos-fos more cost-effective vs LCIG and less cost-effective vs BMT
- Note: in response to an *Additional issue* company reduced burden of fos-fos administration appointments in model (leading to less cost of these) – so now less like a trial setting

Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; LC/CD, levodopa/carbidopa; LCIG, levodopa-carbidopa intestinal gel

Key issue: BMT comparator data (b) limitations of Palmer et al. (1/2)

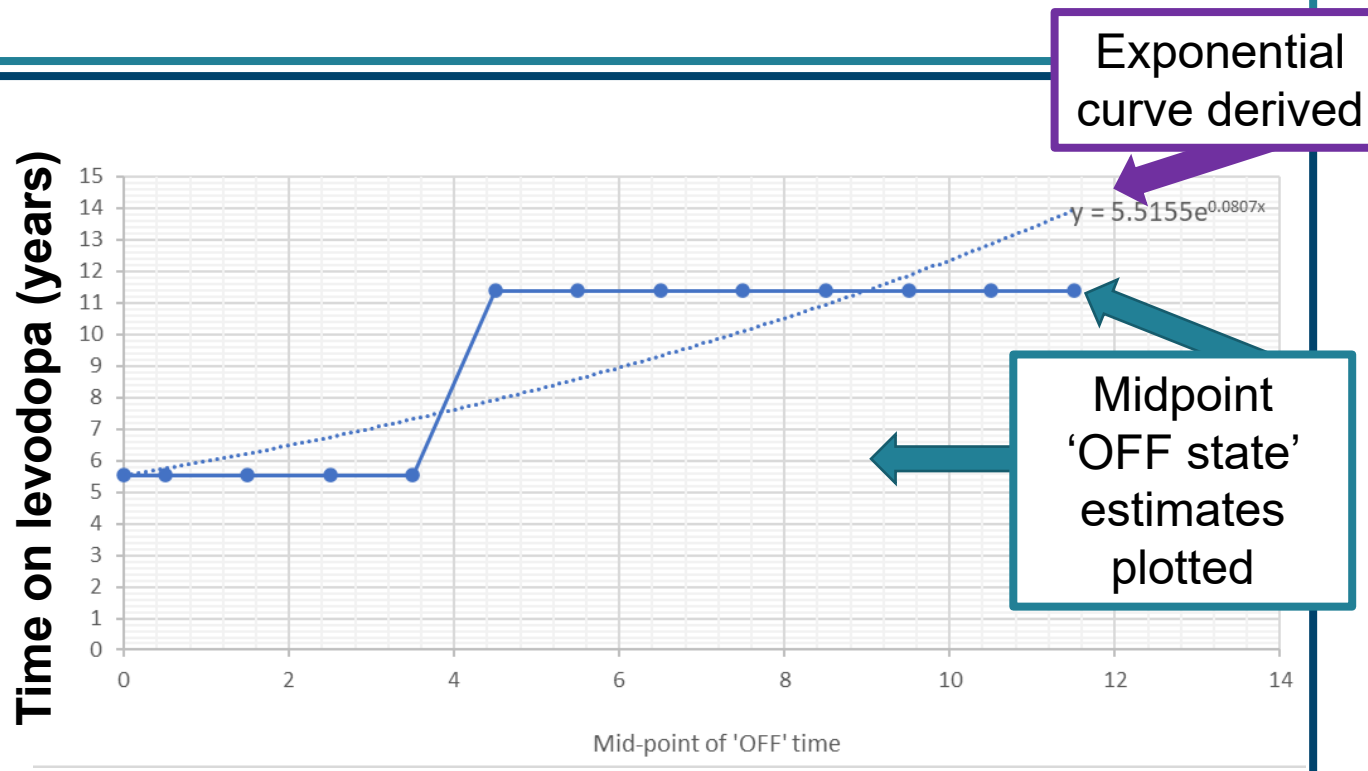
Transitions on BMT informed by limited data, with disagreement in how data used

Background

- For natural disease progression, Palmer et al. data used to inform transitions between OFF states on BMT and those on treatment after LOCF period (3 years)
- But Palmer et al. has only 2 data points: **(1) ≤25% OFF time per day and (2) >25% OFF time per day**
- EAG noted Palmer is a limited source but agrees it appears to be only usable source to model long term transmission rates for people having levodopa

Company

- Plotted midpoint for every OFF time state against 2 values for duration of levodopa treatment (5.5 or 11.4 years; Palmer et al.)
- Exponential curve was then fitted to data and used to calculate transition probabilities between OFF states
- Curve used to link OFF time to duration of levodopa treatment, because it is expected that people in higher OFF states are less likely to move to the next worse OFF state than people in the lower OFF states



Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; LOCF, last observation carried forward

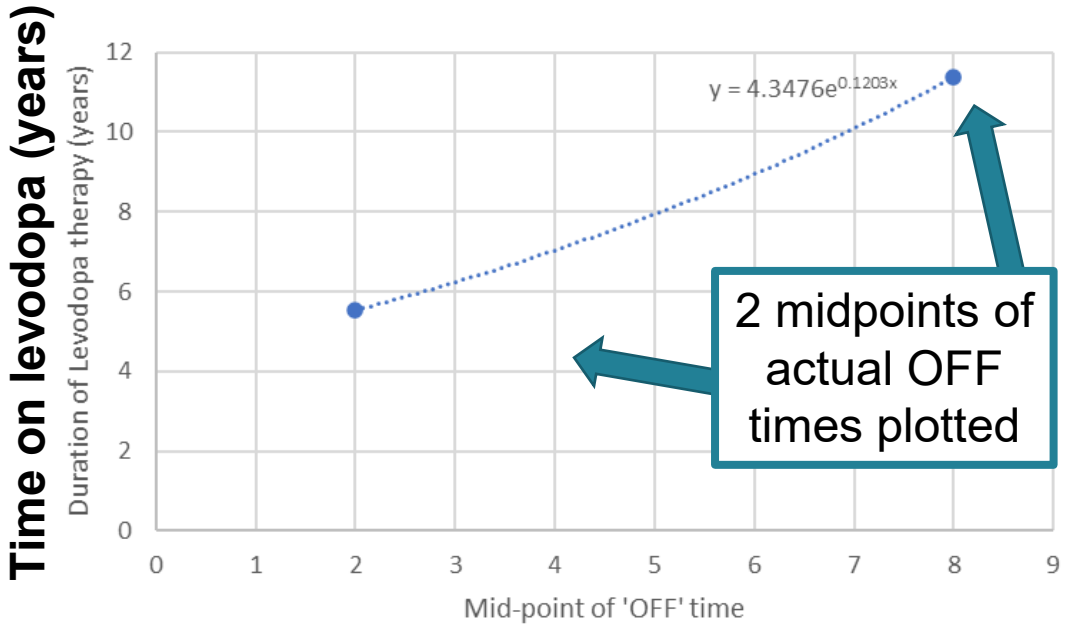
Key issue: BMT comparator data (b) limitations of Palmer et al. (2/2)

BMT | LCIG

Transitions on BMT informed by limited data, with disagreement in how data used

EAG comments

- Company has not provided any justification for the midpoints they created to produce their exponential curve
- EAG approach: all patients OFF for ≤25% or 0 to 4 hours per day have same levodopa treatment duration. Likewise for all patients OFF for >25% or 5 to 12 hours per day
- Effect of EAG midpoint OFF time approach, leading to a steeper curve with higher mean predicted OFF time, would make fos-fos more cost-effective vs LCIG and less cost-effective vs BMT



Stakeholder combined comments on BMT comparator issues (a) and (b)

- Agrees with potential trial effect for BMT – if used in an NHS setting, people would not have exposure to a placebo infusion and would have no placebo or treatment benefit
- Data on BMT from M15-736 trial or a more recent data source would be useful to see

What is the committee's view on the company's approach to modelling BMT?

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Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel

Cost effectiveness

NICE National Institute for Health and Care Excellence

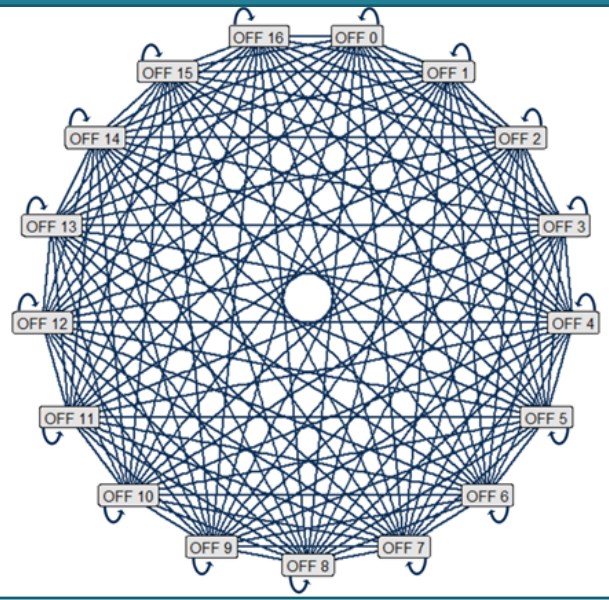
Company's model overview (1/2)

Model structure determined by possible hours of OFF time when awake

Markov state transition model

- 17 health states for 0 to 16 waking hours of OFF time + absorbing death state. No other outcome used:

Trial and LOCF period



Transitions possible between all health states (any number of OFF hours, from 0 to 16)

From all states → Dead

After trial period and LOCF period

Number of OFF hours (0 to 16) can stay the same or worsen

From all states → Dead

Cycle length

- 1st and 2nd model cycle: 3 months
- Beyond 2nd cycle: 6 months
- Half-cycle correction applies

Time horizon: lifetime (20 years)

Perspective: UK Personal Social Services

- Perspective on outcomes was that of patients
- Non-professional carer disutility investigated as part of a scenario analysis as company noted advanced Parkinson's imposes a burden upon the patient's caregiver

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Abbreviations: BMT, best medical therapy; LCIG, levodopa-carbidopa intestinal gel; LOCF, last observation carried forward

Company's model overview (2/2)

Number of OFF hours affects costs and QALYs

Technology affects costs by:	Technology affects QALYs by:
• Initiation & administration costs • Number of OFF hours • Treatment costs • Treatment costs • Adverse event costs	• Number of daily OFF hours • Adverse events

Assumptions with greatest **ICER** effect:

- Transition rates between OFF time health states
- Source of BMT effectiveness
- Discontinuation source and assumptions used
- Health state costs and quality of life values

Abbreviations: AE, adverse event; BMT, best medical therapy; ICER, incremental cost-effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel; QALYs, quality-adjusted life years

Company's modelled OFF time

Modelled average OFF time (hours) similar for fos-fos and LCIG

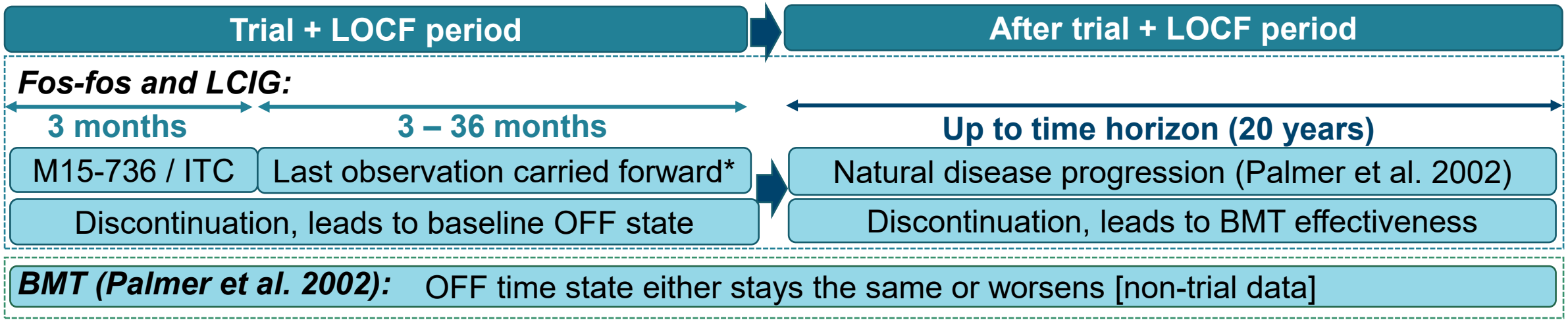

Figure: Average OFF time (hours) distribution across cycles, by treatment, showing that:

[redacted]

- With BMT, average OFF time increases gradually then levels out
- With fos-fos and LCIG, average OFF time falls then gradually increases to converge with BMT

*LOCF applied between months 3 - 36 because GLORIA trial data demonstrates LCIG is effective at 2 years. Abbreviations: BMT, best medical therapy; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LCIG, levodopa-carbidopa intestinal gel; LOCF, last observation carried forward

How company incorporated evidence into model

Several fos-fos trials used as sources of evidence

Input	Assumption and evidence source
Baseline characteristics	Age, sex, health state distribution from M15-736 trial
OFF time: fos-fos vs. LCIG	**Fos-fos** vs. **LCIG** estimated through an indirect comparison including M15-736 trial
OFF time: fos-fos vs. BMT	**Fos-fos** estimated from M15-736 trial evidence **BMT** estimated as natural history progression using Palmer et al. 2002 (not M15-736 trial control arm)
Treatment discontinuation	**Fos-fos**: cohort 2 of the M15-741 trial; **LCIG**: Nyholm et al. 2012 **BMT**: people do not discontinue. This remains the final option for treatment
Adverse events	**Fos-fos**: M15-736 trial; **LCIG**: published sources; **BMT:** M15-736 trial (control arm)
Utilities	M15-736, M20-098, M15-741, and M15-737 EQ-5D-5L data mapped to EQ-5D-3L AEs and carer disutilities* are all in EQ-5D form from various sources
BMT resource use	Dosing and proportion of each therapy sourced from Adelphi RWE study
Disease management resource use	Including hospitalisations, appointments, scans, respite and professional care sourced from Adelphi RWE study
Costs†	Acquisition, administration and health state costs, sourced from BNF, eMIT, published studies and clinical assumptions (fos-fos & LCIG); NHS reference costs

*As advanced Parkinson's imposes a significant burden on carers (non-professional) a carer disutility (utility loss) is included to take account of this. †Informal care costs and lost earnings excluded from model.

Abbreviations: BMT, best medical therapy; BNF, British National Formulary; eMIT, electronic market information tool; EQ-5D(-3L), EuroQol-5 dimensions(3-L version); fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel; RWE, real-world evidence

Key issue: (a) OFF state approach inadequate for capturing range of health effects in advanced Parkinson's and (b) high number of OFF states (1/2)

No previous NICE appraisals in PD, company modelled duration of OFF time

Background: No previous NICE appraisals in PD, but published models exist (e.g. Chaudhuri model for LCIG)

Stakeholder comments: As well as OFF state duration, other factors may contribute to OFF state-associated quality of life such as severity, predictability and timing (e.g. early morning) of the OFF state

Company	EAG
Approach: OFF time most appropriate outcome to model, as it best captures the progression and predictability of symptom control, outcomes which are of high importance to people with Parkinson's	**Insufficient data to inform 17 OFF time health states**: [redacted]
Approach: Modelling validation exercise conducted for OFF states 3 and 4 to assess how OFF time evolves over time in company's and Chaudhuri models show consistency for both BMT and LCIG	
Number of states: Clinical experts agree 1 hour is a clinically meaningful change in OFF time	

Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; H&Y, Hoehn and Yahr; HRQoL, health-related quality of life; LCIG, levodopa-carbidopa intestinal gel; PD, Parkinson's disease

Key issue: (a) OFF state approach inadequate for capturing range of health effects in advanced Parkinson's and (b) high number of OFF states (2/2)

BMT	LCIG
?	?

Not enough data on OFF states & OFF time may not be sufficient to model PD

Company response – approach is conservative:

- **Approach:** models that include H&Y scale have limitations, add complexity and increase uncertainty
- **Approach: c**linical experts noted that H&Y does not consider QoL, and in clinical practice H&Y is not a relevant measure of a patient's experience of their disease

EAG comments – not enough data on OFF states & OFF time insufficient to model PD:

- **Number of states & approach:** company does not have sufficient data to inform number of OFF states so should combine 5 OFF states and 5 H&Y states, as per previous LCIG model. Data collected from Parkinson's symptoms scale MDS-UPRS could be converted or used directly in place of H&Y
- **Approach:** EAG conducted additional validation exercise comparing health state costs and utilities inputs in Chaudhuri model to those in company's model, which showed major issues with structure → significant variation in HRQoL and costs invalid results in higher OFF states, due to lack of data
- **Approach:** Also, using OFF state alone may not sufficiently reflect diversity of health effects of Parkinson's and data informing efficacy, utility and costs → complexity needed to accurately model disease progression
  - Incorporating H&Y may **reduce cost-effectiveness** of fos-fos vs LCIG

Does the committee consider the model structure to be adequate or suitable for decision making?

Abbreviations: EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; H&Y, Hoehn and Yahr; MDS-UPDRS; Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; QoL, quality of life

Key issue: Uncertain benefit after treatment discontinuation (1/2)

Overall improvement in health and functioning may lead to some retained benefits

Stakeholder comments

- Changes in OFF time (hours) for people who discontinue treatment are seen within hours, but it is plausible that some longer-term benefits from treatment such as those related to having better sleep, increased mobility, improved functioning and fitness while on treatment might be sustained following treatment discontinuation – ageing may have a more normal trajectory
- People unlikely to retain a lasting benefit following discontinuation – no evidence of neuroprotective properties, although "washout period" may be longer for a subcutaneous than an oral preparation

Company

- People may retain health-related benefits from the duration they had improved OFF time
- In the model, people who discontinue treatment are distributed across OFF states according to baseline OFF state distribution to end of 3 year LOCF period (then natural disease progression)

Abbreviations: BMT, best medical therapy; EAG evidence assessment group; fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel; LOCF, last observation carried froward; TE, technical engagement

BMT LCIG

Key issue: Uncertain benefit after treatment discontinuation (2/2)

EAG's considers company's approach clinically implausible

EAG comments

- Prefers to assume people who discontinue treatment should revert to most recent natural disease health states – equal treatment outcomes to BMT arm
- Recalls issue with modelling approach: company models treatments using only OFF time which may not adequately reflect heterogeneity of Parkinson's, so should justify that some benefit to OFF time would be retained
- Company's approach flawed because people discontinuing either LCIG or fos-fos after approximately [redacted] experience an improvement in OFF time, with this improvement significantly increasing for people who discontinue at [redacted] – clinically implausible

What does committee consider to be the most appropriate approach to modelling treatment outcomes after discontinuation – baseline OFF time distribution or same as BMT? Are people likely to retain any benefit of treatment after discontinuation?

Abbreviations: BMT, best medical therapy; EAG evidence assessment group; LCIG, levodopa-carbidopa intestinal gel; TE, technical engagement

Key issue: Sources differ for efficacy and discontinuation data (1/2)

Company approach may not make best use of available fos-fos data

Background

- Discontinuation data for fos-fos taken from longer term M15-741 trial, not M15-736 where rates were higher

Company

- Discontinuation rates high across both pivotal clinical trials due to administration-related adverse events
- Discontinuation rates for fos-fos in model derived from cohort 2 of M15-741 trial, following steps taken to mitigate premature discontinuations in this trial with an updated protocol and new infusion set that are intended for clinical use
- Better to use single source (not combined with M15-736) to avoid introducing heterogeneity

EAG comments

- Best predictor for discontinuation for people with efficacy and baseline OFF time of M15-736 trial would be the discontinuations from that trial – using M15-741 also introduces heterogeneity
- Appears improved administration used in M15-741 cohort 2 also used by all patients in M15-736 trial
- Best available data from each period would be:
  - 0 to 3 months M15-736 trial period, 3 to 12 months cohort 2 of M15-741 and 12 to 24 months M15-737
  - Beyond this, due to lack of data, discontinuation should be assumed to be equal to LCIG
- EAG preferred scenario increases discontinuation rate for fos-fos making it less cost-effective vs BMT and LCIG → key driver of cost-effectiveness

Footnote – LCIG discontinuations data based on Nyholm et al. 2012 to 2 years, then standard rate assumed

Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel

Key issue: Sources differ for efficacy and discontinuation data (2/2)

BMT | LCIG

Lessons learned using fos-fos can be implemented in NHS practice

EAG comments *continued*

Table: Fos-fos discontinuation rates used in company base case and EAG preference (vs efficacy data source):

Time, months	Company (M15-741 cohort 2)	EAG preference (M15-736, M15-741 cohort 2, M15-737)	Source of fos-fos efficacy data (company and EAG)
0 to 3	[redacted]	[redacted] (M15-736)	M15-736 data
3 to 6	[redacted]	[redacted] (M15-741 cohort 2)	M15-736 LOCF
6 to 12	[redacted]	[redacted] (M15-741 cohort 2)	M15-736 LOCF
12 to 18	[redacted] (standard rate)	[redacted] (M15-737)	M15-736 LOCF
18 to 24	[redacted] (standard rate)	[redacted] (M15-737)	M15-736 LOCF
Beyond 24 mo.	[redacted] (standard rate)	[redacted] (standard rate)	M15-736 LOCF to 3 years

Stakeholder comments

- Participants and efficacy results of M15-736 and M15-741 trials seem similar
- Cohort 2 M15-741 data possibly more reflective of discontinuation rate if therapy to be started within NHS – lessons learned from earlier high discontinuation rates can be implemented in care services

What is the committee's view on the company's approach to modelling discontinuations?

Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; LCIG, levodopa-carbidopa intestinal gel; LOCF, last observation carried forward; mo., months

Key issue: Unaccounted burden of 'troublesome dyskinesia' (1/2)

Dyskinesia modelled as adverse event but not as symptom in recorded in Parkinson's diary

Background

- Dyskinesia (involuntary moment) can be an important symptom of Parkinson's that generally worsens over time. People may record dyskinesia in Parkinson's diary ('troublesome' or 'non-troublesome')
- Dyskinesia can be a result of being overmedicated in ON time

Company

- Dyskinesia included in model *only* as an adverse event, with assumed duration of 28 days
- In M15-736 trial, in both arms, 'troublesome dyskinesia' (recorded in Parkinson's diary) was rare and <1 hour

Table: Rate of adverse event 'dyskinesia' used in modelling:

Fos-fos	BMT	LCIG
[redacted]	[redacted]	[redacted]

- Published data show baseline ON time with troublesome dyskinesia may be 1 to 1.2 hours
- Dyskinesia management has been significantly improved with new treatments and better management
- Not including 'troublesome dyskinesia' separately as a symptom in model could be considered conservative
  - Point estimates from M15-736 trial suggest fos-fos may provide better control of troublesome dyskinesia than BMT
- Assuming [redacted] rate for adverse event 'dyskinesia' with LCIG is conservative
- LCIG can lead to biphasic dyskinesia on starting or ending a dose – having obvious symptoms impacts QoL

NICE

Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel; QoL, quality of life

BMT	LCIG
?	?

Key issue: Unaccounted burden of 'troublesome dyskinesia' (2/2)

Troublesome dyskinesia could be a source of unaccounted patient burden

EAG comments

- Troublesome dyskinesia could be a source of unaccounted patient burden in company's model
- M15-736 trial indicates based on Parkinson's diary that [redacted]
  - Change from baseline in average daily ON time with troublesome dyskinesia: [redacted] with fos-fos vs [redacted] with oral CD/LD
- Short term trial data on troublesome dyskinesia available but EAG recognises difficulty in long term modelling due to a lack of data and improved dyskinesia management
- Potential impact on cost-effectiveness unclear

Stakeholder comments

- Impact of troublesome dyskinesia and OFF time (hours) is variable for each person with Parkinson's
- Dyskinesia can be troublesome. As well as physically limiting (for a minority), it can also be socially stigmatising and impact social confidence (fear of falling over)
- People generally prefer to be mobile and ON with dyskinesias, than immobile and OFF
- Proportion of people with this problem is relatively small so it may not impact the analysis greatly
- If data for troublesome dyskinesias (as symptoms) available from trials of fos-fos and LCIG, it would be helpful to see it included in model

Does the committee consider troublesome dyskinesia to be an important unaccounted burden?

NICE

Abbreviations: CD/LD, carbidopa-levodopa; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel

Key issue: Robustness of utility values used (1/2)

EAG disagrees with company using combined data from 4 studies

- **Company base case** used linear mixed model to estimate utility for each OFF state. Used combined dataset of fos-fos arms in M15-736, M15-737, M15-741 and M20-098 for mapping EQ-5D values to inform utility values – increases sample size for higher OFF time Parkinson's health states, improving precision of estimates and uses most comprehensive and robust sources of QoL
- **EAG prefers** to use M15-736 data only to inform utilities as key trial informing efficacy & baseline OFF state

EAG comments

- Unclear why age, sex, baseline OFF hours and treatment duration not tested as variables in regressions used to estimate utilities – some may correlate with QoL
- Reported utility values did not decrease smoothly with OFF time
- Utility values for OFF states ≥10 based on [redacted] people so may be very uncertain
- EAG's clinical expert suggested QoL likely to be impacted by how predictable patterns of OFF hours are
  - Could also explain lack of trend in mean utility values at baseline as OFF hours increase and higher utility in OFF state in follow-up studies – predictability of OFF hours more important
- Company's approach where QoL only depends on total OFF hours at odds with data used in analysis – should have used data from both arms where possible

Company response to TE

- Regression: age and sex unlikely to have a significant impact on health state utility values
- Assumption of linearity supported by literature and clinical opinion
- Existing model structure is appropriate so did not test incorporating MDS-UPDRS data (EAG suggestion)

Abbreviations: EAG, evidence assessment group; EQ-5D, EuroQol-5 dimensions; MDS-UPDRS, movement disorder society-unified Parkinson's disease rating scale; QoL, quality of life

BMT | LCIG

Key issue: Robustness of utility values used (2/2)

Additional external factor is influencing quality of life not accounted for

EAG – maintains that data with an alternative modelling approach would be superior

- Aggregating changes in OFF hours (0-25%, 26-50%, 51-75% and 76-100%) gives larger sample sizes
  - Either 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
  - Baseline mean utility values not comparable for same OFF states in 2 main studies M15-736 and M15-741
  - Provides strong evidence for earlier key issue: *(a) OFF state approach inadequate for capturing range of health effects in advanced Parkinson's and (b) high number of OFF states*

OFF state 5 baseline utility value	
M15-736	M15-741
[redacted]	[redacted]

- Company did not adequately respond about variables not tested in linear regression model: clear evidence of additional external factor influencing quality of life across 4 trials
- Approach did not provide additional data for more states with higher OFF time at baseline, compared to using M15-736 study alone (except for OFF state 10)

Stakeholder comments

- Simpler model with broader OFF state categories might be better and more in line with previous studies
- Converting MDS-UPDRS to H&Y score would be useful and could easily be done

What is the committee's view on the approach taken by the company? Is the source of utility values suitable for use in decision making?

Abbreviations: EAG, evidence assessment group; H&Y, Hoehn and Yahr; MDS-UPDRS; Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; TE, technical engagement

Key issue: Regression used for health state cost by OFF time (1/2)

Regression overestimates health state costs and is based on all Parkinson's severities

Company – estimated a cost associated with each OFF state in model

- Used a regression model (instead of direct data) as many OFF states lacked data
- Regression model was fitted to resource use data from a RWE study of patients with early, intermediate and advanced stage Parkinson's ([redacted]), due to small sample size of 'patients with advanced Parkinson's'

EAG comments

- Use advanced Parkinson's subset ([redacted] n=[redacted]), by including early and intermediate Parkinson's, fos-fos marketing authorisation misrepresented
- Regressions used for health state costs appear flawed, leading to company's overestimated costs (see bar chart):
  - Largely driven by professional costs and OFF states with most data
- EAG preferred to replace health state costs with direct data from study – **large impact on ICER, particularly for BMT comparison**
- But notes EAG exploratory analysis based on full dataset as company did not provide advanced Parkinson's subset data, which is expected to have higher costs

Abbreviations: RWE, real world evidence

BMT LCIG

Key issue: Regression used for health state cost by OFF time (2/2)

Difficulties in using direct data relate to earlier key issue on limitations of model

EAG comments *continued*

- Due to poor fit of regression analysis to underlying cost data, direct data should be used
- But lack of direct data in many OFF states relevant to earlier key issue: *(a) OFF state approach inadequate for capturing range of health effects in advanced Parkinson's and (b) high number of OFF states*
  - Also why direct health state data leads to implausible results – strengthens EAG's case made in earlier key issue that structure of the model is inadequate
- Company did not acknowledge or respond to EAG's comments on overestimation of the regression relative to the raw data – issue needs to be resolved before regression could be considered as an option

Company TE response

- Using direct health state data, as in EAG approach, leads to costs lacking face validity (see bar chart)

Stakeholder comments

- Terms such as 'intermediate' and 'advanced' Parkinson's need to be clearly defined. Adelphi dataset 'intermediate' patients may be most similar to trial populations, and 'advanced' more advanced than trial populations as more likely to be in a nursing home

What is the committee's view on the approach taken by the company? Is the regression approach suitable for use in decision making?

Abbreviations: EAG, evidence assessment group; MA, marketing authorisation

Cost-effectiveness results

All ICERs are reported in PART 2 slides
because they include confidential discounts for:

- pramipexole (Commercial Medicines Unit prices)
- fos-fos and LCIG (PAS discount)

Results accounting for all these discounts:

- **fos-fos vs LCIG:** fos-fos is less costly and less effective (cost-effective in south-west quadrant) in company base case and applying EAG's preferred assumptions
- **fos-fos vs BMT:** fos-fos is less costly and more effective (dominates) in company base case and is more costly and more effective (not cost-effective) applying EAG's preferred assumptions

Note: No EAG preferred base case due to concerns with modelling approach and because issue on use of M15-736 trial comparator data for BMT unresolved. EAG's preferred assumptions used to provide an EAG illustrative base case

NICE Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel; PAS, patient access scheme

ICER impact key: Large Small Unknown Quadrant change

Summary of company base case and EAG's preferred assumptions

Key cost-effectiveness drivers include health state cost data and discontinuations

Table: Company base case assumptions and EAG's preferred scenarios with impact on fos-fos cost-effectiveness

Assumption	Company base case	EAG's preferred scenario	Impact on fos-fos cost-effectiveness
Efficacy of LCIG and fos-fos in ITC	NMA results: some improvement in ON time without TD and OFF time with fos-fos vs LCIG	Assumes equal efficacy due to uncertainty and risk of bias in NMA	**No longer cost-effective vs LCIG** No impact on BMT
Outcome on discontinuation	Patients distributed across OFF states by baseline OFF state distribution	Patients revert to most recent natural disease health state	Improved vs LCIG Overall unchanged vs BMT
Use of Palmer et al. data on natural disease progression on BMT	Derives 13 data points to create a prediction curve that links OFF time to duration of levodopa therapy	Uses midpoints related to 2 known data points to produce curve	Improved vs LCIG Overall unchanged vs BMT
Source of discontinuation data	Cohort 2 of M15-741 trial	Combination of M15-736, M15-741 cohort 2, M15-737	**No longer cost-effective vs LCIG** Overall unchanged vs BMT
Data to inform utilities	Uses combined dataset to inform regression	Only M15-736 is used to inform the regression	Improved vs LCIG Overall unchanged vs BMT
Data to inform resource use for health state cost	Full Adelphi dataset used in a regression	Direct data should be used	Improved vs LCIG **Worsened vs BMT**

Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; ITC, indirect treatment comparison; LCIG, levodopa-carbidopa intestinal gel; NMA, network meta-analysis; TD, troublesome dyskinesia

Other considerations (1/2)

Disease factors, modelling approach and lack of precedence contribute to uncertainty

Uncertainty – summary of overall assessment by company

- Some factors inherent to advanced Parkinson's have needed assumptions to be made, which introduce uncertainty
- Advanced Parkinson's is highly heterogenous, leading to difficulties modelling a clearly defined patient population, and choosing appropriate outcomes to model treatment effect and disease progression
- Cost-effectiveness analysis was limited by availability of literature in the condition – few data sources for exploring uncertainty
- Complexity of model and lack of previously accepted models (and previous NICE appraisal in Parkinson's) should be taken into account
    - Current model is a de-novo design that attempts to explain and capture the relevant components of the condition, using assumptions and decisions that have been validated by clinical experts and have been tested by scenario analyses in order to reduce uncertainty

Innovation: Step change in management of Parkinson's, could be given at local centres

Other considerations (2/2)

Use of a severity modifier not considered applicable

Severity

- **Company:** Use of a severity modifier is not applicable for fos-fos
    - Aspects of Parkinson's most relevant to people may not be adequately captured in the modelling, so true severity of the disease may not be captured in the QALY shortfall calculations:
        - EQ-5D simplistic measure of HRQoL for Parkinson's so improvements in control of symptoms may not be reflected in the QALYs
        - Including improved sleep symptoms and improved impact on early morning OFF time compared with BMT

EAG comments

- Agrees: based on a QALY shortfall analysis, applied both to company base case and using EAG's preferred assumptions, no severity modifier should be applied in the model

Abbreviations: BMT, best medical therapy; EQ-5D, EuroQol-5 dimensions; HRQoL, health related quality of life; QALY, quality-adjusted life years

Key issues

ICER impact key: Large  Small  Unknown  Quadrant change 

Key issue	Resolved?	ICER impact	
		BMT	LCIG
Uncertainty with potential overestimation of treatment benefit for fos-fos	No		
Uncertainty in indirect comparisons of fos-fos and LCIG	No	NA	
BMT comparator data: (a) M15-736 trial data not used; and (b) limitations of method using data from Palmer	No		
Modelling: (a) OFF state approach inadequate for capturing range of health effects in advanced Parkinson's and (b) high number of OFF states	No		
Uncertain benefit after treatment discontinuation	Partially		
Sources differ for efficacy and discontinuation data	No		
Unaccounted burden of 'troublesome dyskinesia'	No		
Robustness of utility values used	No		
Regression used for health state cost by OFF time	No		

Abbreviations: BMT, best medical therapy; ICER, incremental cost-effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel

NICE National Institute for Health and Care Excellence

Thank you.