Cost-effectiveness of extended-pulsed fidaxomicin versus vancomycin in older patients with *Clostridium difficile* infection in England

EP0706

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INTRODUCTION

- *Clostridium difficile* infection (CDI) is a major health concern, associated with significant clinical impact (high morbidity, mortality and recurrence) and a substantial economic burden.[1,2]
- Fidaxomicin is a narrow spectrum macrocyclic antibiotic that has demonstrated non-inferiority in terms of clinical cure of CDI, but significantly lower rates of recurrence compared with vancomycin in randomised phase III trials,[3,4] with subsequent cost-effectiveness benefits.[5]
- Recent evidence from a validated *in vitro* human gut model simulating CDI, suggests that extended-pulsed fidaxomicin (EPFX), which extends the standard 20-dose regimen over a longer time-frame after an initial daily dosing period of five days, may further increase the effectiveness of fidaxomicin for the treatment of CDI.[6] As the same number of tablets are administered between EPFX and standard fidaxomicin regimens, clinical benefits of EPFX are derived with no increase in drug acquisition costs.
- The results of a recent phase IIIb/IV, randomised controlled, open-label, parallel group study conducted in patients with CDI (EXTEND; ClinicalTrials.gov: NCT02254967) demonstrated superiority in sustained clinical cure for EPFX (200 mg administered twice-daily for 5 days and then 200 mg once-daily every second day from days 6–25) versus vancomycin (125 mg four times-daily for 10 days) at 30 days after the end of each treatment (primary endpoint), and significant reductions in recurrence rates at days 40, 55 and 90 (see ePoster EP0363).

OBJECTIVE

- To estimate the incremental cost-effectiveness of first-line treatment with EPFX versus vancomycin from an English National Health Service (NHS) and Personal Social Services perspective, in patients ≥60 years of age with CDI, including clinical data from the EXTEND study.

METHODS

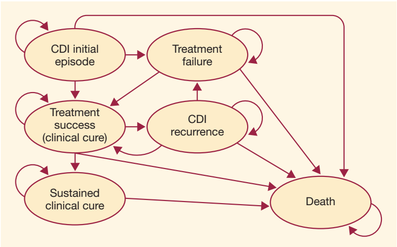
Model design

- Cohort-based semi-Markov model developed in Microsoft Excel® 2010, comprising six health states (Figure 1), reflecting the treatment pathway for CDI in the real-world setting.
- The cohort are allowed a maximum of three lines of therapy per CDI episode and up to two recurrent CDI episodes. First-line therapy is EPFX or vancomycin, and standard of care (vancomycin) is used as second-line therapy, with both user-changeable to allow additional scenario analyses; rescue treatment (assumed to have 100% clinical cure and 0% risk of recurrence) is applied as third-line therapy.
- The time horizon is 365 days and the cycle length is five days (based on this being the common denominator for EPFX and vancomycin treatment durations).

Model structure and transitions (Figure 1)

- The cohort enters the model in the CDI (initial episode) health state and receives EPFX or vancomycin. At the end of treatment, they transition to either the treatment success (clinical cure) health state, the treatment failure health state, or the death state.
- The cohort occupying the treatment success health state either remain in this state, transition to the death state, or transition to the CDI recurrence health state (up to a maximum of 90 days from treatment initiation).
- Those who transition to the CDI recurrence health state receive subsequent treatment and either transition to the treatment success (clinical cure) health state, the treatment failure health state, or the death state.
- The cohort that occupy the treatment failure health state can subsequently remain within this health state, or transition to the treatment success (clinical cure) or death states in successive cycles.
- The proportion of the cohort that have no recurrent CDI episodes within 90 days of treatment initiation, transition to the sustained clinical cure health state and subsequently remain within this health state, or transition to the death state.

Figure 1. Model structure and transitions



CDI, *Clostridium difficile* infection

Model inputs

- Model inputs were sourced from the EXTEND clinical study, English healthcare organisations and the literature (Tables 1 and 2).
- Quality of life inputs included health state utilities and adverse event disutility values, sourced from the literature.[7–11] It was assumed that the utilities reflected the utility values that would be observed in a patient population with CDI.

Model outputs

- Base-case analyses
  - Total costs per patient, total quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER) associated with using first-line EPFX in place of vancomycin.
- Explanation of terminology/methodology used in the base-case analyses
  - A QALY is a measure of the state of health of a person or group in which the benefits in terms of length of life, are adjusted to reflect the quality of life.
  - An incremental QALY gain demonstrates the health benefit of one drug versus another (e.g., EPFX versus vancomycin) in terms of length of life, adjusted to reflect the quality of life.
  - The ICER was calculated by dividing the Δcosts/ΔQALYs (where Δcosts is the total costs for a cohort receiving EPFX minus the total costs for a cohort receiving vancomycin and ΔQALYs is the total QALYS for a cohort receiving EPFX minus the total QALYs for a cohort receiving vancomycin). A threshold range of £20–30,000 is generally considered to be cost-effective and therefore acceptable to the payer.[12]

Table 1. Summary of clinical inputs, including mortality

Parameter	Values		Source
Clinical cure, %*	EPFX (n=177)	Vancomycin (n=179)	All data sourced from EXTEND study (see ePoster EP0363)
Clinical cure 2 days after EOT, %	78.0	82.1	
Risk of recurrence, %*	EPFX (n=138)	Vancomycin (n=147)	
Recurrence at Day 40	1.4	19.7	
Recurrence at Day 55	4.3	21.1	
Recurrence at Day 90*	7.2	22.4	
Incidence of adverse events, %†	EPFX (n=181)	Vancomycin (n=181)	
Anaemia	2.8	5.5	
Cardiac failure	2.2	5.5	
Constipation	5.5	2.8	
Diarrhoea	5.5	6.6	
Pyrexia	3.9	6.6	
Clostridial infection	3.9	13.3	
Pneumonia	2.8	5.5	
Sepsis	0.6	5.0	
Urinary tract infection	3.3	6.6	
Mortality, %‡	EPFX (n=183)	Vancomycin (n=181)	
Day 0–10	1.4		
Day 11–15	1.3		
Day 16–25	1.2		
Day 26–30	1.0		
Day 31–90	0.9		
Day 91 onwards§	0		

Analyses performed in *modified full analysis set; †safety analysis set; and ‡in all randomised patients in the EXTEND study; for risk of recurrence, data from the subgroup who experienced clinical cure 2 days after EOT were included; §values used for base-case analysis. Mortality rates were assumed to be the same for each treatment based on CDI-related mortality being disease-specific; §value was 0 based on no data being available from EXTEND after the 90-day follow-up period. CDI, *Clostridium difficile* infection; EOT, end of treatment; EPFX, extended-pulsed fidaxomicin

Table 2. Cost inputs

Parameter	Costs, GBP		Source
	EPFX	Vancomycin	
Drug acquisition costs†			
Total cost of treatment course	1350.00	189.24	BNF 2016[13]
Hospitalisation costs			
Total costs per 10-day admittance	8,214.00		DoH 2012[14] ONS 2016[15]
Cost of treating AEs			
Anaemia	46.35		ONS 2016[15] PSSRU 2015[16]
Cardiac failure	7,305.97		ONS 2016[15] Shyangdan 2014[9]
Constipation	1,414.96		
Diarrhoea	1,414.96		DoH 2015[17] ONS 2016[15]
Pyrexia	1,026.66		
Clostridial infection§	0		–
Pneumonia	1,992.84		DoH 2015[17] ONS 2016[15]
Sepsis	2,215.78		
Urinary tract infection§	0		–

†The drug acquisition cost for each dose was applied in the model. Costs were based on 20 doses of EPFX and 40 doses of vancomycin. The dosing schedules of EPFX and vancomycin were the same as those used in the EXTEND study. §It was assumed that hospitalisation costs already accounted for treating these AEs. AEs, adverse events; BNF, British National Formulary; DoH, Department of Health; EPFX, extended-pulsed fidaxomicin; GBP, British pound; ONS, Office for National Statistics; PSSRU, Personal Social Services Research Unit.

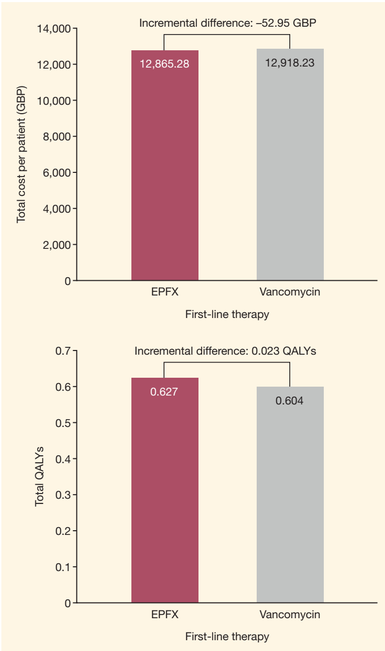
- Sensitivity analyses
  - Deterministic sensitivity analysis (DSA) was performed to determine the key drivers of the model, by adjusting each variable (except for the drug acquisition cost) individually, to observe the proportional effect on the ICER derived in the base-case analyses. A standard 20% variation was applied for the key input parameters.

RESULTS

Base-case analyses

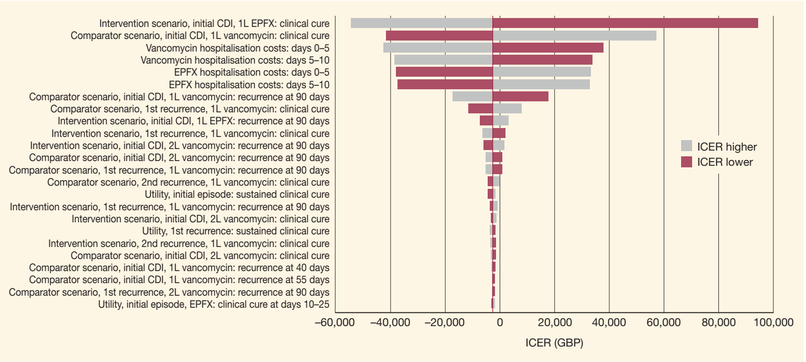
- First-line treatment of CDI with EPFX was associated with an incremental cost saving of £52.95 per patient compared with vancomycin and an incremental QALY gain of 0.023 (Figure 2), suggesting that economic and quality of life benefits are associated with EPFX versus vancomycin.
  - The incremental cost saving was attributed to lower respective costs for EPFX versus vancomycin, associated with hospitalisation (£10,815.45 versus £11,458.76) and AEs (£693.52 versus £1,199.00). These offset higher drug acquisition costs for EPFX versus vancomycin (£1,356.31 versus £260.47, respectively).
- First-line EPFX was cost saving and more effective versus vancomycin, based on an ICER of –£2,313.64

Figure 2. Total costs and QALYs associated with first-line EPFX or vancomycin in patients with CDI, based on results from the model



CDI, *Clostridium difficile* infection; EPFX, extended-pulsed fidaxomicin; GBP, British Pound; QALYs, quality-adjusted life years

Figure 3. Tornado diagram to show the results of the DSA



Parameters considered to have a minimal impact on the ICER were excluded from the Tornado diagram. CDI, *Clostridium difficile* infection; DSA, deterministic sensitivity analysis; EPFX, extended-pulsed fidaxomicin; ICER, incremental cost-effectiveness ratio; L, line of therapy

Sensitivity analyses

- In the DSA, the parameter that had the greatest impact on the ICER was the probability of clinical cure for first-line EPFX in the CDI (initial episode) health state (Figure 3).
  - Other key drivers included: the probabilities of clinical cure and recurrence for first-line vancomycin, and hospitalisation costs for patients receiving EPFX and vancomycin.

CONCLUSIONS

- The EXTEND study demonstrated significantly improved sustained clinical cure for EPFX versus vancomycin, in a high-risk patient population with CDI.
- Results from the model suggest that first-line EPFX is cost-saving and more effective versus vancomycin for the treatment of patients with CDI, from the perspective of the English healthcare system. The ICER of –£2,313.64 observed for EPFX is below the NICE threshold for cost-effectiveness[12] suggesting that the use of first-line EPFX versus vancomycin is acceptable to the payer.
- Reductions in CDI recurrence, costs of hospitalisation and management of adverse events, and increased quality of life in patients receiving first-line EPFX versus vancomycin are likely to offset the higher drug acquisition costs associated with EPFX.
- Strengths of the study were that the results of the analyses are based on clinical data derived from a relevant patient population and that the model permits the disease pathway beyond initial treatment to be captured, allowing the long-term economic impact of EPFX to be established. Limitations were that a number of assumptions were made, which require validation and updating once the data become available.
- Together with the clinical outcomes from the EXTEND study, these results demonstrate the potential utility of first-line EPFX for treatment of CDI in patients ≥60 years of age.

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DISCLOSURES

Maureen Watt is an employee of Astellas Pharma Inc. Charles McCrea is an employee of PAREXEL Access Consulting, who received a consultancy fee from Astellas Pharma Inc., to support the analyses.

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