Randomised, controlled, open-label study comparing the efficacy of extended-pulsed fidaxomicin (EPFX) with vancomycin therapy for sustained clinical cure of *Clostridium difficile* infection in an older population: the EXTEND study

EP0363

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INTRODUCTION

- *Clostridium difficile* infection (CDI) recurrence is estimated to occur in up to 25% of patients within 30 days of previous treatment; its successful prevention is a key unmet medical need[1]
- Recurrence may occur due to delayed recovery of disrupted intestinal microbiota following previous CDI treatment[2]
- Fidaxomicin, a narrow-spectrum macrocyclic antibiotic, is associated with greater conservation of the gut microbiota[3] and a significantly lower rate of CDI recurrence than vancomycin[4–6]
- A validated *in vitro* human gut model suggests that an extended-pulsed fidaxomicin (EPFX) regimen may allow more prolonged persistence of fidaxomicin at above inhibitory concentrations than standard-dosing regimens, thus suppressing CDI while simultaneously supporting microbiota recovery[7]
- EPFX is hypothesised to reduce recurrence rates beyond the extent documented for standard fidaxomicin treatment and therefore improve the rate of sustained clinical cure (SCC)

OBJECTIVE

- EXTEND (ClinicalTrials.gov identifier NCT02254967) is the first randomised multicentre study to evaluate the comparative efficacy of EPFX and standard vancomycin therapy in patients aged ≥60 years
- The primary endpoint was the rate of SCC of CDI at 30 days after end of treatment

METHODS

Study design and patients

- Open-label, randomised, active-comparator controlled, parallel-group, phase IIIb/IV study conducted at 86 centres in 21 countries
- Patients aged ≥60 years with clinically confirmed CDI
  - >3 unformed bowel movements (UBMs) or ≥200 mL unformed stool (for patients with rectal collection devices) within 24 hours, and
  - *C. difficile* toxin A or B confirmed in stool within 48 hours prior of randomisation (according to local laboratory CDI diagnostic test)

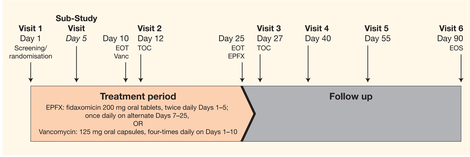
Treatment

- A flow chart of the study design is given in **Figure 1**
- Patients were randomised (1:1) to receive:
  - EPFX: fidaxomicin 200 mg oral tablets, twice daily on Days 1–5, then once daily on alternate days from Days 7–25, or
  - Vancomycin: 125 mg oral capsules, four-times daily on Days 1–10

Outcomes

- SCC of CDI (clinical response at test of cure (TOC) with no subsequent CDI recurrence) was assessed on Days 40, 55 and 90
  - The primary endpoint was SCC 30 days after end of treatment (EPFX: Day 55; vancomycin: Day 40)
- TOC assessments were made on Day 12 (vancomycin and EPFX) and Day 27 (EPFX) and comprised presence of CDI; CDI severity score; clinical response (ESCMID criteria)[8]
- Recurrence was defined as re-establishment of diarrhoea after TOC (more frequent UBMs than on Day 10 (vancomycin) or Day 25 (EPFX), confirmed by a CDI test positive for toxin A/B and requiring further CDI therapy)
- Adverse events (AEs, based on MedDRA v14.1) were recorded throughout the study period

Figure 1. Study design flow chart



EOT, end of treatment; EOS, end of study; EPFX, extended-pulsed fidaxomicin arm; TOC, test of cure; Vanc, vancomycin

Statistical methods

- The primary analysis set for efficacy evaluation was the modified Full Analysis Set (mFAS), comprising all randomised patients who met the inclusion criteria and received ≥1 dose of study medication
- The safety analysis included all randomised patients who received ≥1 dose of study medication
- Between-treatment comparisons were made using two-sided tests at the 0.05 significance level, along with the corresponding 95% confidence intervals (CIs)

RESULTS

Patients

- Of 403 screened patients, 364 were enrolled and randomised
  - 362 patients were included in the safety analysis (EPFX, n=181; vancomycin, n=181)
  - 356 patients were eligible for efficacy assessment (mFAS; EPFX, n=177; vancomycin, n=179)
- **Table 1** shows the demographics and baseline characteristics of the mFAS

Table 1. Demographics and baseline characteristics, mFAS

Characteristic	EPFX (n=177)	Vancomycin (n=179)	Total (N=356)
Sex, n (%)			
Female	107 (61)	100 (56)	207 (58)
Race, n (%)*			
White	149 (84)	153 (85)	302 (85)
Missing	28 (16)	26 (15)	54 (15)
Median (range) age, years	75 (60–94)	75 (60–95)	75 (60–95)
UBMs per day, n			
Mean (SD)	6.8 (4.7)	6.4 (3.4)	6.6 (4.1)
Median	5.0	5.0	5.0
Severe CDI (ESCMID score), n (%)	78 (44)	84 (47)	162 (46)
Recurrences in past 3 months, n (%)			
0	141 (79.7)	140 (78.2)	281 (78.9)
1	26 (14.7)	29 (16.2)	55 (15.4)
2	10 (5.6)	10 (5.6)	20 (5.6)
Cancer present, n (%)#	38 (22)	37 (21)	75 (21)
Use of antibiotics for condition other than CDI, n (%)			
Yes	128 (72)	129 (72)	257 (72)
No	49 (28)	50 (28)	99 (28)
Residential setting, n (%)			
Own residence	102 (58)	103 (58)	205 (58)
Family residence	66 (38)	59 (33)	125 (35)
Nursing home	4 (2)	6 (3)	10 (3)
Long-term care facility	1 (1)	4 (2)	4 (1)
Other	2 (1)	7 (4)	9 (3)
Missing	2	0	2

EPFX, extended-pulsed fidaxomicin; SD, standard deviation; UBMs, unformed bowel movements
*Not all study sites were permitted to report the race of patients; this information was reported as 'missing'.
#Provided by Interactive Web Response System at randomisation

Efficacy

Primary endpoint: SCC 30 days after end of treatment

- At 30 days after treatment end, significantly more EPFX patients (124/177 (70.1%; 95% CI 63.3–76.8)) achieved SCC than those receiving vancomycin (106/179 (59.2%; 95% CI 52.0–66.4); p=0.030) (**Figure 2**)

CDI clinical response at TOC

- The clinical responses were not significantly different between treatment groups either at Day 12 (p=0.721) or at 2 days after end of treatment (vancomycin: Day 12; EPFX: Day 27 (p=0.399)) (**Figure 2**)
  - Multivariate analysis indicated that patients with severe CDI at baseline were significantly less likely to achieve clinical response at Day 12 and at 2 days after end of treatment (**Table 2**)

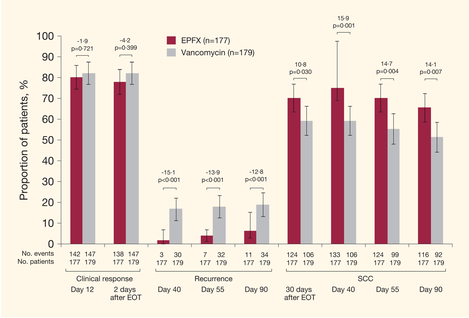
CDI recurrence at Days 40, 55 and 90

- Significantly fewer patients on EPFX than on vancomycin had CDI recurrence at Day 40 (1.7% vs 16.8%, respectively), Day 55 (4.0% vs 17.9%, respectively) and Day 90 (6.2% vs 19.0%, respectively) (p<0.001 at each time point; **Figure 2**)

SCC at Days 40, 55 and 90

- Significantly more patients on EPFX achieved SCC at Day 40 (p=0.001), Day 55 (p=0.004) and Day 90 (p=0.007) compared with those receiving vancomycin (**Figure 2**)
  - Multivariate analysis of the primary endpoint showed that patients with severe CDI were significantly less likely to achieve SCC than those with non-severe CDI (odds ratio 0.57, 95% CI 0.36–0.91; p=0.019)

Figure 2. Clinical response at Day 12 and 2 days after end of treatment, CDI recurrence and sustained clinical cure of CDI at 30 days after end of treatment (primary endpoint), and Days 40, 55 and 90 (mFAS)



Bars show 95% CI. EOT, end of treatment; EPFX, extended-pulsed fidaxomicin; mFAS, modified Full Analysis Set; SCC, sustained clinical cure of CDI

Adverse events

- The overall safety profiles of EPFX and vancomycin were generally similar
  - Overall, a similar proportion of EPFX patients (66.9%) and vancomycin patients (70.7%) reported ≥1 treatment-emergent AE (TEAE) (**Table 3**)
  - The most common TEAEs reported in EPFX patients were constipation (5.5%), diarrhoea (5.5%), pyrexia (3.9%) and *Clostridium* spp. infection (3.9%), and in vancomycin patients, *Clostridium* spp. infection (13.3%), diarrhoea (6.6%), pyrexia (6.6%) and urinary tract infection (6.6%) (**Table 4**)

Table 2. Multivariate analysis of clinical outcomes (mFAS)

Outcome	EPFX (n=177)	Vancomycin (n=179)
SCC 30 days after end of treatment, n (%)	124 (70.1)	106 (59.2)
Odds ratio (95% CI)	1.62 (1.04–2.53); p=0.035	
Odds ratio (95% CI) by baseline stratification		
CDI severe vs non-severe	0.57 (0.36–0.91); p=0.019	
Presence vs absence of cancer	0.59 (0.35–1.01); p=0.053	
Age group ≥75 vs <75 years	0.83 (0.53–1.30); p=0.414	
No. previous recurrences (2 vs 0)	0.69 (0.26–1.80); p=0.444	
No. previous recurrences (1 vs 0)	0.61 (0.33–1.11); p=0.105	
Clinical response at Day 12,* n (%)	142 (80.2)	147 (82.1)
Odds ratio (95% CI)	0.91 (0.54–1.54); p=0.047	
Odds ratio (95% CI) by baseline stratification		
CDI severe vs non-severe	0.42 (0.24–0.72); p=0.002	
Presence vs absence of cancer	0.72 (0.39–1.35); p=0.311	
Age group ≥75 vs <75 years	1.13 (0.65–1.96); p=0.660	
No. previous recurrences (2 vs 0)	1.09 (0.30–3.96); p=0.898	
No. previous recurrences (1 vs 0)	0.88 (0.42–1.84); p=0.733	
Clinical response 2 days after end of treatment (Day 12 or 27),* n (%)	138 (78.0)	147 (82.1)
Odds ratio (95% CI)	0.81 (0.48–1.35); p=0.007	
Odds ratio (95% CI) by baseline stratification		
CDI severe vs non-severe	0.54 (0.31–0.92); p=0.025	
Presence vs absence of cancer	0.49 (0.27–0.88); p=0.016	
Age group ≥75 vs <75 years	0.94 (0.55–1.62); p=0.825	
No. previous recurrences (2 vs 0)	1.27 (0.35–4.65); p=0.715	
No. previous recurrences (1 vs 0)	0.83 (0.41–1.72); p=0.624	
Median time to resolution of diarrhoea, h (95% CI)	34.0 (28.0–59.0)	22.0 (11.0–32.0)
	Difference p=0.068	
Patients with UBMs, n (%)		
At Day 5	**EPFX (n=160)**	**Vancomycin (n=170)**
0 UBM	64 (40.0)	69 (40.6)
1–2 UBMs	51 (31.9)	67 (39.4)
≥3 UBMs	45 (28.1)	34 (20.0)
At Day 13	**EPFX (n=146)**	**Vancomycin (n=32)#**
0 UBM	112 (76.7)	21 (65.6)
1–2 UBMs	22 (15.0)	6 (18.7)
≥3 UBMs	12 (8.2)	5 (15.6)
At Day 25†	**EPFX (n=135)**	**–**
0 UBM	115 (85.2)	–
1–2 UBMs	15 (11.1)	–
≥3 UBMs	5 (3.7)	–

SCC, sustained clinical cure; UBMs, unformed bowel movements per day
*Difference between rates (EPFX–vancomycin): Day 12, −1.9% (95% CI −10.0–6.2%), p=0.721, and 2 days after end of treatment, −4.2% (95% CI −12.5–4.1%), p=0.399; #147 patients reported as 'missing'; †For the vancomycin arm, UBM records were collected only up to Day 12 (±2)

Table 3. TEAEs during the study (safety population)

Event, n (%)	EPFX (n=181)	Vancomycin (n=181)
Any TEAE	121 (66.9)	128 (70.7)
Any severe TEAE*	44 (24.3)	56 (30.9)
Any TEAE related to study drug†	14 (7.7)	9 (5.0)
Any serious TEAE‡	68 (37.6)	78 (43.1)
Serious drug-related TEAE	3 (1.7)	6 (3.3)
Any TEAE leading to discontinuation of study drug	14 (7.7)	5 (2.8)
Drug-related AE leading to discontinuation of study drug	2 (1.1)	1 (0.6)
Deaths	29 (15.8)	36 (19.9)
TEAE-related deaths	3 (1.7)	3 (1.7)

TEAE, treatment-emergent adverse event
*Defined as adverse events causing inability to perform daily activities. †Possibly or probably related to study drug, as assessed by the investigator, or records where relationship was missing. ‡Defined as adverse events resulting in death, or considered to be life-threatening, requiring hospitalisation, or resulting in persistent or significant disability or incapacity, congenital anomaly, or other medically important events.

- Serious TEAEs occurred in 37.6% EPFX- and 43.1% vancomycin-treated patients; three (1.7%) and six (3.3%) patients, respectively, experienced drug-related serious AEs (**Table 3**)
- 65 patients (17.9%) died: 29 (15.8%) in the EPFX arm and 36 (19.9%) in the vancomycin arm
  - In the respective EPFX and vancomycin arms, 8 (4.4%) and 4 (2.2%) deaths occurred between Days 1 and 12; 8 (4.4%) and 5 (2.8%) between Days 13 and 27; and 13 (7.1%) and 27 (14.9%) after Day 27

Table 4. Most common treatment-emergent* and serious treatment-emergent† AEs during the study (safety population)

Any event,* n (%)	EPFX (n=181)	Vancomycin (n=181)
Anaemia	5 (2.8)	10 (5.5)
Cardiac failure	4 (2.2)	10 (5.5)
Constipation	10 (5.5)	5 (2.8)
Diarrhoea	10 (5.5)	12 (6.6)
Pyrexia	7 (3.9)	12 (6.6)
Clostridium spp. infection	7 (3.9)	24 (13.3)
Pneumonia	5 (2.8)	10 (5.5)
Sepsis	1 (0.6)	9 (5.0)
Urinary tract infection	6 (3.3)	12 (6.6)
Serious event,† n (%)		
Cardiac failure	3 (1.7)	8 (4.4)
Clostridium spp. infection	5 (2.8)	18 (9.9)
Pneumonia	2 (1.1)	7 (3.9)
Sepsis	1 (0.6)	9 (5.0)
Urinary tract infection	1 (0.6)	4 (2.2)
Respiratory failure	2 (1.1)	4 (2.2)

*Reported in ≥5% of patients in any treatment group. †Reported in ≥2% of patients in any treatment group

CONCLUSIONS

- Extended-pulsed fidaxomicin demonstrated superior sustained clinical cure of CDI and significantly reduced the recurrence rate at all study time points (from Day 40 to Day 90) versus standard vancomycin treatment
  - Both regimens displayed similar safety profiles
- Clinical response to CDI was similar among patients treated with EPFX and vancomycin, and the EPFX recurrence rate of 4% at 30 days after end of treatment is the lowest yet shown in such a randomised clinical trial
- As the EPFX regimen administers the same number of fidaxomicin tablets as the standard licensed regimen, the observed clinical benefits appear to be achieved with no increase in treatment costs

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