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Pharmacokinetics and safety of fidaxomicin in patients with inflammatory bowel disease and *Clostridium difficile* infection: an open-label Phase IIIb/IV study (PROFILE)

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Objectives: Inflammatory bowel disease (IBD) poses an increased risk for *Clostridium difficile* infection (CDI). Fidaxomicin has demonstrated non-inferiority to vancomycin for initial clinical cure of CDI in patients without IBD; however, lack of data has caused concerns regarding potential systemic absorption of fidaxomicin in patients with IBD.

Methods: The plasma pharmacokinetics (PK) of fidaxomicin and its primary metabolite OP-1118 were evaluated in a multicentre, open-label, single-arm, Phase IIIb/IV study enrolling patients with active IBD and CDI. Patients received fidaxomicin, 200 mg twice daily for 10 days. The primary and secondary endpoints were, respectively, plasma and stool PK of fidaxomicin and OP-1118 on Days 1, 5 and 10 of treatment. Other secondary endpoints included safety of fidaxomicin treatment (assessed until Day 180). ClinicalTrials.gov identifier: NCT02437591.

Results: Median T_{max} of fidaxomicin and OP-1118 for the PK analysis set (PKAS; 24 patients) was 1–2 h across Days 1, 5 and 10. C_{max} ranges were 1.2–154 ng/mL for fidaxomicin and 4.7–555 ng/mL for OP-1118 across Days 1, 5 and 10 (PKAS). The ranges of concentrations in stool were 17.8–2170 μg/g for fidaxomicin and 0–1940 μg/g for OP-1118. Sixty percent (15/25) of patients experienced treatment-emergent adverse events (TEAEs), none of which led to treatment discontinuation or death.

Conclusions: Maximum fidaxomicin and OP-1118 plasma concentrations observed in this study population suggest no increase in absorption, compared with patients without IBD. Incidence of TEAEs was similar to previous Phase III trials, suggesting that fidaxomicin is comparatively well tolerated in patients with IBD.

Introduction

Clostridium difficile infection (CDI) causes a substantial healthcare burden in developed countries.[1] Patients with inflammatory bowel disease (IBD) are at particular risk of developing CDI.[2] Following the onset of CDI, patients with IBD have a greater length of hospital stay, are at greater risk for CDI recurrence and have a higher mortality rate, compared with patients without IBD.[2–4] Notably, rates of CDI are higher among patients with ulcerative colitis (UC) and Crohn's disease (CD) with colonic involvement.[5,6]

Fidaxomicin, a narrow-spectrum macrocyclic antibiotic, has been shown in two Phase III trials to be non-inferior to standard vancomycin for the initial clinical cure of CDI.[7,8] Furthermore, fidaxomicin achieved significantly lower rates of CDI recurrence and higher rates of sustained clinical cure, compared with vancomycin.[7,8] However, patients with IBD were excluded from these studies. Consequently, only limited data are available on the use of fidaxomicin in patients with both IBD and CDI.[9] It is currently recommended that fidaxomicin is used with caution in patients with IBD and CDI,[10] owing to uncertainty whether absorption of

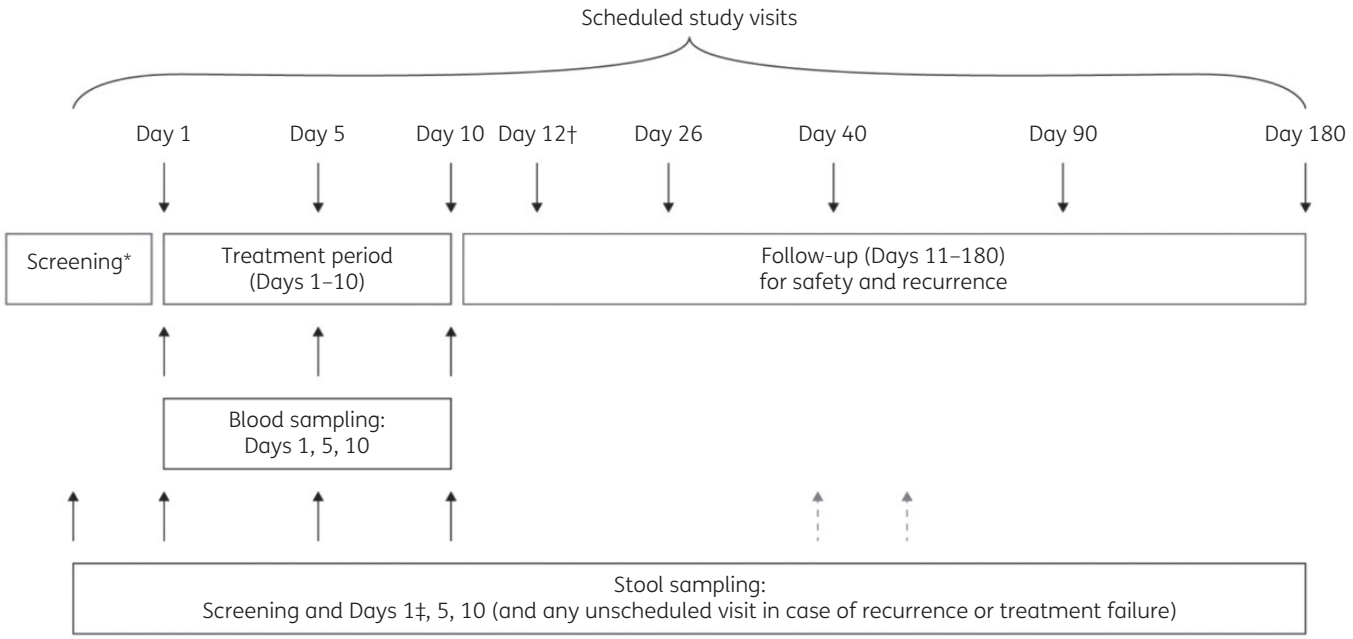

Figure 1. Study procedures. *Within 48 h of enrolment. Baseline visit (screening and Day 1) could have been completed on the same day. †Assessment via telephone. ‡Day 1 stool samples taken no earlier than 12 h after the first dose of fidaxomicin.

fidaxomicin is increased in the presence of the colonic and small bowel inflammation associated with IBD.

The PROFILE study was designed to evaluate the plasma pharmacokinetics (PK) of fidaxomicin and its primary metabolite OP-1118 in patients with IBD and CDI, and explore the safety of fidaxomicin treatment in these patients.

Patients and methods

Ethics

The study protocol and all amendments were reviewed and approved by independent Ethics Committees or Institutional Review Boards for each centre (Table S1, available as Supplementary data at *JAC* Online). The study was conducted in accordance with the International Council for Harmonisation guidelines and the Declaration of Helsinki, and all patients provided written informed consent.

Study design

This was an open-label, single-arm, Phase IIIb/IV study in patients with IBD and CDI from 28 sites in nine European countries, conducted between August 2015 and October 2016. The study duration was 180 days for all patients and comprised eight visits: three visits during the treatment period (Days 1–10 inclusive) and five visits during follow-up (Days 11–180 inclusive) (Figure 1). PROFILE is registered with ClinicalTrials.gov, number NCT02437591.

Participants

Patients aged ≥18 years with active IBD and CDI were included in the study. The main inclusion criteria were as follows: confirmed diagnosis of IBD for

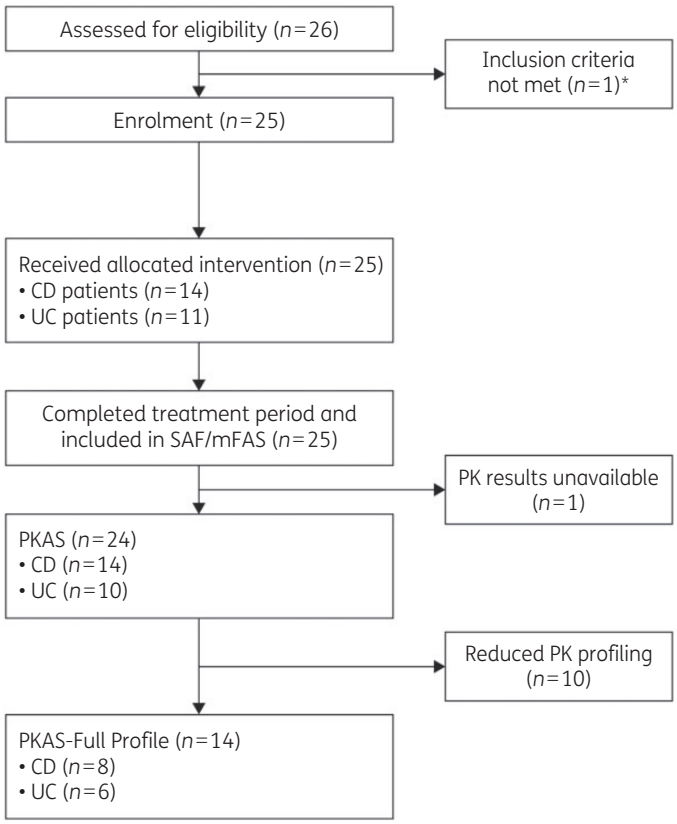

Figure 2. Patient flow diagram. *CDI not confirmed by local testing.

Table 1. Patient baseline characteristics (SAF)

Characteristic	CD ($n = 14$)	UC ($n = 11$)	Total ($n = 25$)
Female, *n* (%)	6 (43)	6 (55)	12 (48)
Race, *n* (%)			
white	13 (100)	9 (90)	22 (96)
Asian	0	1 (10)	1 (4)
missing	1	1	2
Age, years, median (range)	34.5 (19–55)	32.0 (21–81)	32.0 (19–81)
C-reactive protein, mg/L, median (range)	6.80 (0.0–96.3)	8.30 (0.3–89.4)	7.10 (0.0–96.3)
Time since IBD diagnosis, years, median (range)	1.2 (0–28)	6.2 (1–10)	2.9 (0–28)
CD location[a]			
ileal (L1)	7 (50)	NA	NA
colonic (L2)	1 (7)	NA	NA
ileocolonic (L3)	6 (43)	NA	NA
isolated upper GI	1 (7)	NA	NA
HBI total score categories, *n* (%)			
5–7 (mild disease)	6 (43)	NA	NA
8–16 (moderate disease)	6 (43)	NA	NA
>16 (severe disease)	2 (14)	NA	NA
UC extent			
proctitis (E1)	NA	1 (9)	NA
left-sided extending to splenic flexure (E2)	NA	1 (9)	NA
extensive disease (E3)	NA	9 (82)	NA
Partial Mayo Score total categories, *n* (%)			
2–6 (mild–moderate disease) or a score of 1 due to rectal bleeding	NA	9 (82)	NA
≥7 (severe disease)	NA	2 (18)	NA
IBD symptoms, *n* (%)			
abdominal cramps/pain	13 (93)	10 (91)	23 (92)
diarrhoea	14 (100)	9 (82)	23 (92)
blood in stool	6 (43)	9 (82)	15 (60)
defaecation urgency	7 (50)	9 (82)	16 (64)
weight loss	9 (64)	8 (73)	17 (68)
loss of appetite	9 (64)	6 (55)	15 (60)
fever	3 (21)	1 (9)	4 (16)
fatigue	9 (64)	8 (73)	17 (68)
joint pain	7 (50)	2 (18)	9 (36)
Severe CDI by ESCMID score, *n* (%)	2 (14)	5 (46)	7 (28)
Marked leucocytosis[b], *n* (%)	2 (14)	2 (18)	4 (16)
Pseudomembranous colitis, *n* (%)	0	2 (18)	2 (8)
Prior CDI[c], *n* (%)	2 (14)	3 (27)	5 (20)
No. of UBMs per day[d], mean (SD)	6.2 (3.7)	6.6 (3.5)	6.4 (3.5)
Antibiotic use within 90 days prior to enrolment, *n* (%)	4 (29)	8 (73)	12 (48)
for CDI	1 (7)	4 (36)	5 (20)
for conditions other than CDI	3 (21)	7 (64)	10 (40)
Antibiotic use for CDI within 90 days prior to enrolment by preferred WHO name, *n* (%)			
metronidazole	1 (7)	2 (18)	3 (12)
rifaximin	0	1 (9)	1 (4)
vancomycin	0	3 (27)	3 (12)

NA, not applicable; UBM, unformed bowel movement; SAF, all patients who received at least one dose of study drug.
[a]Two CD patients (ileal L1 and ileocolonic L3 locations) also had perianal disease. One CD patient had isolated upper GI disease in addition to ileocolonic disease.
[b]Leucocyte count $>15\times10^9$/L.
[c]In the 90 days prior to enrolment. No patient had >1 episode of CDI during this period.
[d]In the 24 h prior to enrolment.

Table 2. Relevant prior and concurrent medications during fidaxomicin treatment by IBD type (SAF)

Medication intake period Therapeutic subgroup (ATC level 2) chemical subgroup (ATC level 4)[a] preferred WHO name	CD ($n = 14$)	UC ($n = 11$)	Total ($n = 25$)
Prior medications within 90 days of enrolment			
Antidiarrhoeals and intestinal anti-inflammatory/anti-infective agents	13 (93)	11 (100)	24 (96)
aminosalicylic acid and similar agents	11 (79)	11 (100)	22 (88)
mesalazine	10 (71)	11 (100)	21 (84)
sulfasalazine	2 (14)	0	2 (8)
antibiotics	1 (7)	4 (36)	5 (20)
nystatin	0	1 (9)	1 (4)
rifaximin	1 (7)	2 (18)	3 (12)
vancomycin	1 (7)	4 (36)	5 (20)
antidiarrhoeal microorganisms	2 (14)	0	2 (8)
Lactobacillus acidophilus	1 (7)	0	1 (4)
Lactobacillus plantarum	1 (7)	0	1 (4)
VSL #3	1 (7)	0	1 (4)
Antibacterials for systemic use	4 (29)	7 (64)	11 (44)
meropenem	1 (7)	0	1 (4)
sulperazon	1 (7)	0	1 (4)
amoxi-clavulanico	0	1 (9)	1 (4)
bactrim	0	1 (9)	1 (4)
ciprofloxacin	3 (21)	3 (27)	6 (24)
moxifloxacin	0	1 (9)	1 (4)
vancomycin	1 (7)	4 (36)	5 (20)
metronidazole	4 (29)	5 (46)	9 (36)
Antimycobacterials	0	1 (9)	1 (4)
rifampicin	0	1 (9)	1 (4)
isoniazid	0	1 (9)	1 (4)
Antimycotics for systemic use	0	1 (9)	1 (4)
nystatin	0	1 (9)	1 (4)
fluconazole	0	1 (9)	1 (4)
Corticosteroids for systemic use	8 (57)	7 (64)	15 (60)
budesonide	3 (21)	1 (9)	4 (16)
dexamethasone	1 (7)	0	1 (4)
hydrocortisone	0	4 (36)	4 (16)
methylprednisolone	1 (7)	4 (36)	5 (20)
prednisolone	5 (36)	1 (9)	6 (24)
prednisone	1 (7)	2 (18)	3 (12)
Immunosuppressants	11 (79)	5 (46)	16 (64)
calcineurin inhibitors	0	2 (18)	2 (8)
ciclosporin	0	2 (18)	2 (8)
other immunosuppressants	8 (57)	4 (36)	12 (48)
azathioprine	7 (50)	4 (36)	11 (44)
methotrexate	2 (14)	0	2 (8)
TNF-α inhibitors	5 (36)	2 (18)	7 (28)
adalimumab	1 (7)	0	1 (4)
golimumab	0	1 (9)	1 (4)
infliximab	4 (29)	2 (18)	6 (24)
Concurrent medications during fidaxomicin treatment[b]			
Antidiarrhoeals and intestinal anti-inflammatory/anti-infective agents	12 (86)	11 (100)	23 (92)
aminosalicylic acid and similar agents	10 (71)	11 (100)	21 (84)
mesalazine	9 (64)	11 (100)	20 (80)
sulfasalazine	1 (7)	0	1 (4)

Continued

Table 2. *Continued*

Medication intake period Therapeutic subgroup (ATC level 2) chemical subgroup (ATC level 4)[a] preferred WHO name	CD ($n = 14$)	UC ($n = 11$)	Total ($n = 25$)
Antibacterials for systemic use	0	1 (9)	1 (4)
moxifloxacin	0	1 (9)	1 (4)
Corticosteroids for systemic use	6 (43)	8 (73)	14 (56)
budesonide	2 (14)	1 (9)	3 (12)
hydrocortisone	0	1 (9)	1 (4)
methylprednisolone	1 (7)	5 (46)	6 (24)
prednisolone	2 (14)	3 (27)	5 (20)
prednisone	1 (7)	2 (18)	3 (12)
Immunosuppressants	8 (57)	5 (46)	13 (52)
calcineurin inhibitors	0	1 (9)	1 (4)
ciclosporin	0	1 (9)	1 (4)
other immunosuppressants	7 (50)	4 (36)	11 (44)
azathioprine	6 (43)	4 (36)	10 (40)
methotrexate	1 (7)	0	1 (4)
TNF-α inhibitors	3 (21)	0	3 (12)
adalimumab	1 (7)	0	1 (4)
infliximab	2 (14)	0	2 (8)

ATC, Anatomical Therapeutic Chemical; SAF, all patients who received at least one dose of study drug. A medication which could be classified into several therapeutic subgroups (ATC level 2) was programmatically coded to each subgroup without consideration of the indication provided by the investigator.

[a]Not shown under the following therapeutic subgroups: antibacterials for systemic use; antimycobacterials; antimycotics for systemic use; antivirals for systemic use; and corticosteroids for systemic use.

[b]Includes up to Day 11 for patients who completed the course on Day 11.

at least 3 months; active IBD (as recorded at enrolment); and positive confirmation of CDI by local standard testing within 48 h prior to enrolment (Table S2). Active IBD was initially defined by either Partial Mayo Score $\geq$2 for patients with UC[11] or Harvey–Bradshaw index (HBI) score $\geq$5, excluding points for complications, for patients with CD.[12] Following initiation of the study, the protocol was amended to include a requirement for patients with UC that at least one point should originate from blood in stool. Therefore, not all patients with UC have one point originating from blood in stool at baseline.

Patients were excluded if they had received any CDI therapy for more than 1 day within 48 h prior to enrolment, or had a diagnosis of toxic megacolon. Screening and informed consent were completed within 48 h of enrolment.

Treatment procedures

Fidaxomicin 200 mg tablets were administered orally, twice daily, from Day 1 (within 24 h of enrolment) to Day 10. Fidaxomicin was administered in accordance with the current Summary of Product Characteristics.[10]

Previous and concurrent medications

Prior medication recorded included antibiotic, immunosuppressive or IBD medication taken within 90 days prior to enrolment. All relevant concurrent medications were recorded for the duration of the study. Treatment of underlying IBD during this period was at the discretion of the site investigator. Owing to their potential impact on the evaluation of study endpoints and the composition of the gut microbiota, it was recommended to avoid the following medications throughout the study period: non-study oral fidaxomicin, metronidazole, vancomycin, oral bacitracin, fusidic acid, rifaximin and rifampicin, nitazoxanide, tigecycline, teicoplanin and prebiotics or probiotics. It was also recommended to avoid faecal microbiota transplantation throughout the study period.

Blood and stool sampling

Blood samples were taken on Days 1, 5 and 10 (pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5 and 10 h post-dose) for PK analysis at a central laboratory. After review of the cumulative PK data from the first 15 patients to establish T_{max}, subsequent patients enrolled into the study could have a limited PK sampling schedule: full PK profile on Day 1 only and sampling on Days 5 and 10 at pre-dose and at the anticipated T_{max} (2 ± 0.5 h).

Stool samples for the measurement of fidaxomicin and OP-1118 concentrations were obtained on Day 1 (no earlier than 12 h following first dose of fidaxomicin), Day 5 and Day 10. These underwent PK analysis at a central laboratory. Stool samples obtained at screening were stored at -70°C, then transported to a central laboratory for further assessment. Central laboratory assessments included toxin A/B ELISA, bacterial culture and *C. difficile* toxin A/B PCR screening (BioFire FilmArray®, GI Panel, bioMérieux).

Outcomes

PK

The primary endpoint was the plasma PK of fidaxomicin and OP-1118, in patients with IBD and CDI, on Days 1, 5 and 10 of treatment. A particular aim was to compare the maximum observed plasma concentrations in this patient population with those observed for patients without IBD in previous

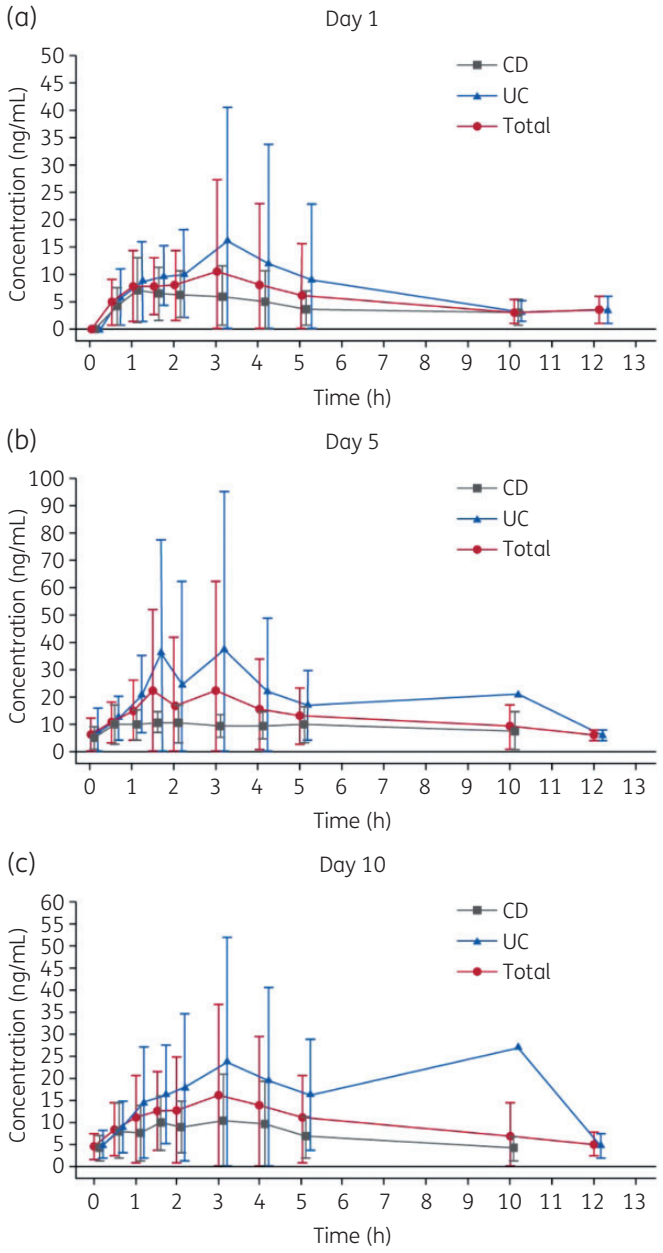

Figure 3. Plasma concentration of fidaxomicin by IBD type on (a) Day 1, (b) Day 5 and (c) Day 10 [PKAS (all patients)]. (a) 23 patients (13 CD, 10 UC) with full PK profile measurements; (b, c) 14 patients (8 CD, 6 UC) with full profile and 10 patients (6 CD, 4 UC) with reduced PK profile (pre-dose, 2±0.5 h). Data are mean ± SD. SDs have been plotted for all timepoints where $n > 1$. For three patients with deviations from the visit schedule, pre-dose samples were collected on a day other than the planned visit day. Final blood samples for each patient were taken at 10 or 12 h post-dose; data have therefore been plotted at the respective timepoints.

studies of fidaxomicin.[8,13,14] A secondary endpoint was fidaxomicin and OP-1118 stool concentrations at Days 1, 5 and 10.

Safety

Adverse events (AEs) were recorded from the time of informed consent until the end of the study (Day 180); AEs arising during the period from the first dose until 30 days following the end of treatment (EoT) were considered treatment-emergent AEs (TEAEs). AEs of special interest included: hypersensitivity to fidaxomicin (angioedema, dyspnoea); gastrointestinal (GI) haemorrhage; decrease in white blood cell (WBC) count; abnormal liver or kidney function tests; and QT interval prolongation (assessed using ECG only in the case of a suspected AE).

Efficacy

Assessment of clinical response to treatment at test of cure (ToC; Day 12, 48–72 h after EoT) was based on investigator assessment using the ESCMID criteria (Supplementary Methods).[15] Patients who did not meet the criteria for CDI clinical response, as determined by the investigator, remained in the study for safety assessments. For patients with a CDI clinical response, recurrence of CDI was defined as re-establishment of diarrhoea after ToC to an extent (judged by the frequency of unformed bowel movements) greater than the frequency recorded on Day 12 and requiring further CDI therapy.

Statistical analyses

It was planned to enrol 40 patients to achieve 30 evaluable patients with either measurements of fidaxomicin and OP-1118 C_{max}, or plasma concentrations at T_{max}. The planned sample size was chosen based on the feasibility of recruiting a sufficient number of patients with IBD to be able to demonstrate the PK of fidaxomicin in this patient population and was not based on intended statistical power calculation.

The safety analysis set (SAF) consisted of all enrolled patients who received at least one dose of study medication. The modified full analysis set (mFAS) consisted of all enrolled patients who received at least one dose of study medication and had a valid ToC assessment. The PK analysis set (PKAS) consisted of patients from the SAF for whom at least one blood plasma measurement of fidaxomicin and OP-1118 was available and the PKAS-Full Profile included only those patients from the PKAS who participated in the full PK sampling profile. Further details of the statistical methods used are described in the Supplementary Methods.

Results

Patient characteristics

The planned number of patients intended to be enrolled was not achieved before the end of the recruitment period (30 April 2016). Eligible patients were recruited from seven countries and 12 sites: 14 with CD and 11 with UC. All 25 patients completed the full 10 days of fidaxomicin treatment and were included in the SAF and mFAS (Figure 2). PK results were missing for one patient in the mFAS; 24 patients were therefore included in the PKAS (14 patients with CD and 10 with UC), of whom 10 patients underwent reduced PK profiling. Thus, 14 patients were included in the PKAS-Full Profile.

Twenty-one of the 25 patients completed the investigational period (Days 1–180): 3 patients with CD chose to withdraw from the study and 1 patient with UC was lost to follow-up. Five patients had a minor protocol deviation: four patients entered the study although the local CDI test was not conducted within 48 h of the first dose and one patient took two additional (commercially available) fidaxomicin tablets.

Patient baseline characteristics for the SAF are shown in Table 1. Most patients were in the category of 'mild' or 'moderate' disease for CD (12/14; 86%) or 'mild–moderate disease' for UC (9/11; 82%) (Table 1). Two patients with CD and five with UC (7/25;

Table 3. Plasma PK parameters of fidaxomicin and OP-1118 [PKAS (all patients) and PKAS-Full Profile]

		Fidaxomicin					OP-1118				
		PKAS (all patients)		PKAS-Full Profile			PKAS (all patients)		PKAS-Full Profile		
Day	Parameter	C_{trough} (ng/mL)	C_{max} (ng/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC[a] (ng·h/mL)	C_{trough} (ng/mL)	C_{max} (ng/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC[a] (ng·h/mL)
1	*n*		23	14	14	8	—	23	14	14	9
	median	—	9.7	9.9	1.8	67.6	—	24.7	23.7	1.8	169.0
	min–max		2.5–75.3	3.4–75.3	0.5–11.5	22.7–339	—	4.9–336	10.3–336	0.5–11.5	36.2–1550
	mean (SD)	—	14.6 (16.1)	17.9 (19.8)	2.5 (2.8)	98.3 (102.2)	—	45.3 (67.5)	57.5 (84.7)	2.6 (2.9)	323.0 (482.4)
5	*n*	23	23	13	13	11	23	23	13	13	10
	median	4.3	12.2	17.7	1.0	116.5	12.7	42.7	45.8	1.0	415.5
	min–max	0.7–28.8	1.2–154	5.3–154	0.5–3.0	38.0–513	2.3–88.9	4.7–555	15.2–555	0.5–5.0	102–2269
	mean (SD)	6.2 (6.5)	20.3 (31.8)	30.0 (40.1)	1.3 (0.7)	155.6 (150.9)	22.1 (22.2)	70.3 (116.7)	99.0 (149.5)	1.5 (1.3)	668.7 (726.0)
10	*n*	22	24	14	14	11	22	24	14	14	12
	median,	3.3	11.3	13.4	1.8	109.8	13.6	45.5	45.8	2.0	301.4
	min–max	1.0–11.6	4.6–71.3	4.6–71.3	0–5.4	19.2–364	2.5–62.8	10.6–206	10.6–206	0–5.4	52.8–1161
	mean (SD)	4.4 (3.2)	16.3 (15.1)	20.2 (18.6)	2.2 (1.7)	129.1 (115.0)	18.2 (15.6)	53.1 (43.5)	61.5 (52.0)	2.4 (1.7)	389.1 (364.7)
Max across days	median	—	14.6	—	—	—	—	46.1	—	—	—
	min–max	—	5.75–154	—	—	—	—	13.5–555	—	—	—
	mean (SD)		22.6 (30.4)	—	—	—	—	78.5 (111.6)	—	—	—

PKAS (all patients), patients from the SAF for whom at least one blood plasma measurement of fidaxomicin and OP-1118 was available; PKAS-Full Profile, including only those patients from the PKAS who participated in the full PK sampling profile. PKAS (all patients) and PKAS-Full Profile exclude the one patient with UC who took an extra two (commercially available) fidaxomicin tablets in addition to those prescribed.

[a]AUC_{12} (from the time of dosing to 12 h post-dose), Day 1; AUC_{tau} (from the time of dosing to the start of the next dosing interval), Days 5 and 10. As fidaxomicin is minimally absorbed and the T_{max} is variable, the terminal $t_{1/2}$ and AUC could not be estimated in all cases; additional comparisons showed no resultant bias.

28%) had a primary diagnosis of severe CDI based on ESCMID criteria.[15] One-fifth (5/25; 20%) of patients had a prior history of one CDI episode in the 90 days prior to study enrolment.

Antibiotics were used by 12/25 (48%) patients in the 90 days prior to enrolment (Table 1). Of these, 5/25 (20%) patients received antibiotics for the treatment of CDI. Antidiarrhoeals and intestinal anti-inflammatory/anti-infective agents were used by 24/25 (96%) patients in the 90 days prior to enrolment, 23/25 (92%) patients during the treatment period (Days 1–10 inclusive) and 24/25 (96%) patients during follow-up [Days 11–180, end of study inclusive (Table 2 and Supplementary Table S3)]. Immunosuppressants, including TNF-α inhibitors, were used by 16/25 (64%) of all patients in the 90 days prior to enrolment and 13/25 (52%) of all patients concurrently with fidaxomicin treatment (Table 2).

All 25 patients tested positive for CDI by local laboratory assessment at screening. With regard to the further tests conducted at the central laboratory, results from toxin A/B ELISA were available for 19 patients, of whom 6 (32%) tested positive for CDI. Of the remaining 13/19 (68%) patients who were negative for CDI by central laboratory toxin A/B ELISA, 4 were confirmed positive both by anaerobic culture and for toxigenic *C. difficile* by PCR (BioFire FilmArray, GI Panel), 1 was confirmed positive by PCR (BioFire FilmArray, GI Panel) alone and 2 were confirmed positive by anaerobic culture alone. A total of 13/19 (68%) patients were therefore confirmed positive for CDI by both local assessment and at least one central laboratory test. For the remaining 6/19 patients who tested negative for CDI by central laboratory toxin A/B ELISA, specimens for further microbiological investigation were not available. Of the 6/25 patients for whom central laboratory toxin A/B ELISA results were not available, 2 had anaerobic culture performed from samples taken approximately (and no earlier than) 12 h after the first dose of fidaxomicin, 1 of whom was positive.

Fidaxomicin exposure

All enrolled patients completed the treatment period of 10 days, with a mean total dosage of 4016 mg of fidaxomicin per patient. One patient with CD missed 1 dose on Day 3, but took all 20 doses of fidaxomicin, completing the course on Day 11. One patient with UC took an extra two (commercially available) fidaxomicin tablets in addition to those prescribed; this patient was excluded from the PKAS (all patients) and PKAS-Full Profile.

PK

Missing PK samples

A pre-dose sample was missing from the full PK profiles of Day 1 for a single patient; this had no implications for the PK analysis. For one patient with a reduced profile, the 2 h sample at Day 5 was missing and no C_{max} or T_{max} could be estimated. One pre-dose sample on Day 10 from a patient with a reduced profile was also missing; no C_{trough} could be estimated for this patient.

Fidaxomicin plasma concentrations

The mean plasma concentrations of fidaxomicin for all 24 patients in the PKAS are given in Figure 3 and the fidaxomicin PK parameters are provided in Table 3. The median T_{max} across all days was ~1–2 h, but varied widely between 0 and 11.5 h (Table 3 and Figure 3). On Day 5 in patients with UC, an additional earlier peak was observed at approximately 1.5 h after fidaxomicin dosing (Figure 3).

The median plasma C_{max} across all days for the PKAS was 14.6 ng/mL (range 5.8–154 ng/mL). No apparent differences in plasma C_{max} were observed between patients with a limited PK profile and those with a full profile. The highest observed plasma C_{max} were all from one patient with UC who had relatively high fidaxomicin concentrations throughout the study period (Day 1, 75.3 ng/mL; Day 5, 154 ng/mL; Day 10, 71.3 ng/mL).

OP-1118 plasma concentrations

Mean plasma concentration–time profiles of OP-1118 (Figure 4) were similar to those of fidaxomicin. Overall, the observed plasma concentrations of OP-1118 were ~2–6-fold higher than those of fidaxomicin.

PK parameters of OP-1118 are given in Table 3 and C_{max} measurements by IBD type are given in Table 4. The median C_{max} for the PKAS across Days 1, 5 and 10 was 46.1 ng/mL (range 13.5–555 ng/mL). The highest observed plasma C_{max} values for OP-1118 (Day 1, 336 ng/mL; Day 5, 555 ng/mL; Day 10, 206 ng/mL) were all from the same patient with UC who also experienced the highest fidaxomicin plasma concentrations.

Stool concentrations of fidaxomicin and OP-1118

The mean concentrations of fidaxomicin and OP-1118 in stool samples rose over the treatment period (Table 5). Median fidaxomicin concentrations increased from 217.0 μg/g on Day 1 to 692.5 μg/g on Day 10 and median OP-1118 concentrations increased from 116.0 μg/g on Day 1 to 370.5 μg/g on Day 10. For the one patient with UC who had the highest fidaxomicin and OP-1118 plasma C_{max}, stool concentrations of fidaxomicin were 221 μg/g on Day 5 and 415 μg/g on Day 10, and OP-1118 concentrations were 132 μg/g on Day 5 and 434 μg/g on Day 10 (no Day 1 post-first-dose sample was available).

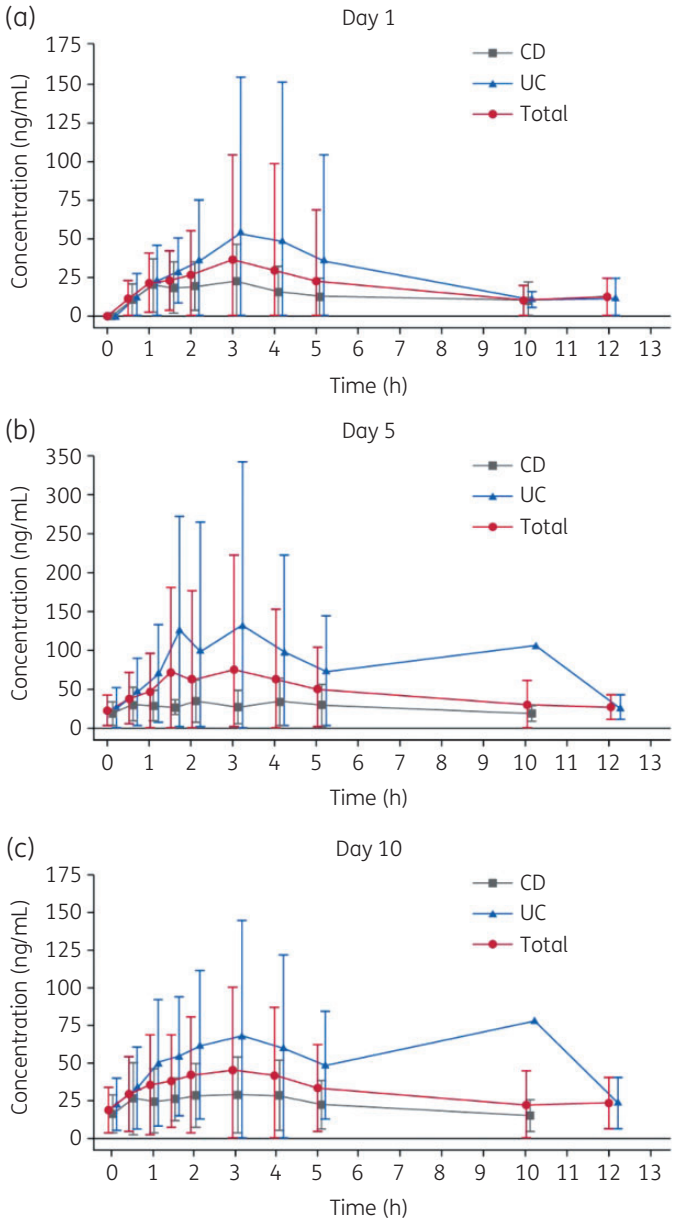

Figure 4. Plasma concentration of OP-1118 by IBD type on (a) Day 1, (b) Day 5 and (c) Day 10 [PKAS (all patients)]. (a) 23 patients (13 CD, 10 UC) with full PK profile measurements; (b, c) 14 patients (8 CD, 6 UC) with full profile and 10 patients (6 CD, 4 UC) with reduced PK profile (pre-dose, 2±0.5 h). Data are mean ± SD. SDs have been plotted for all timepoints where $n > 1$. For three patients with deviations from the visit schedule, pre-dose samples were collected on a day other than the planned visit day. Final blood samples for each patient were taken at 10 or 12 h post-dose; data have therefore been plotted at the respective timepoints.

Safety

AEs

Of patients in the SAF set, 15/25 (60%) experienced TEAEs within 30 days after EoT (Table S4). The majority (35/43, 81%) of TEAEs were mild or moderate. Of 25 patients, 10 (40%) experienced a total of 19 drug-related TEAEs (Table S4). There were no TEAEs or drug-related TEAEs that resulted in permanent discontinuation of the study drug. Serious TEAEs ($n = 8$) were experienced by 6/25 (24%) patients, half of which were GI related (Table S4).

Two (8%) patients experienced serious drug-related TEAEs (Table S4). Of these, one patient experienced severe hypoxia on Day 40, which subsequently resolved on Day 58. This was judged by the investigator to be possibly related to both fidaxomicin and treatment with infliximab for IBD flare-ups, as the patient had received infliximab both before and after the fidaxomicin treatment period. One patient developed a severe skin ulcer starting on Day 24; the event resolved on Day 54 and was considered by the investigator to be possibly related to treatment with fidaxomicin.

Six (24%) patients had an AE of special interest (Table S4). Of these, one patient with UC had elevated ALT at baseline (91 U/L) and throughout the treatment period, but resolved at Day 86 (20 U/L) after the withdrawal of concomitant azathioprine; this

Table 4. Plasma C_{max} of fidaxomicin and OP-1118 by IBD type [PKAS (all patients)]

		Fidaxomicin C_{max} (ng/mL)			OP-1118 C_{max} (ng/mL)		
Day	Parameter	CD	UC	total	CD	UC	total
1	*n*	13	10	23	13	10	23
	median	7.4	10.9	9.7	22.4	25.6	24.7
	min–max	2.5–25.9	6.1–75.3	2.5–75.3	4.9–84.7	15.6–336	4.9–336
	mean (SD)	9.9 (6.7)	20.7 (22.4)	14.6 (16.1)	30.3 (23.3)	64.7 (98.3)	45.3 (67.5)
5	*n*	13	10	23	13	10	23
	median	12.4	11.4	12.2	37.0	44.3	42.7
	min–max	2.2–28.2	1.2–154	1.2–154	5.7–99.4	4.7–555	4.7–555
	mean (SD)	13.1 (7.4)	29.8 (47.1)	20.3 (31.8)	42.8 (28.4)	106.0 (172.4)	70.3 (116.7)
10	*n*	14	10	24	14	10	24
	median	11.0	16.1	11.3	38.4	48.1	45.5
	min–max	4.6–33.5	5.8–71.3	4.6–71.3	10.6–94.7	12.3–206	10.6–206
	mean (SD)	12.1 (7.7)	22.0 (20.7)	16.3 (15.1)	41.6 (26.5)	69.3 (57.7)	53.1 (43.5)

PKAS (all patients), patients from the SAF for whom at least one blood plasma measurement of fidaxomicin and OP-1118 was available; PKAS-Full Profile, including only those patients from the PKAS who participated in the full PK sampling profile. PKAS (all patients) and PKAS-Full Profile exclude the one patient with UC who took an extra two (commercially available) fidaxomicin tablets in addition to those prescribed.

Table 5. Stool concentrations of fidaxomicin and OP-1118 on Days 1, 5 and 10 by IBD type [PKAS (all patients)]

		Fidaxomicin (μg/g)			OP-1118 (μg/g)		
Day	Parameter	CD	UC	total	CD	UC	total
1[a]	*n*	5	2	7	5	2	7
	median	217.0	196.9	217.0	116.0	85.0	116.0
	min–max	36.0–804.0	17.8–376.0	17.8–804.0	0.0–318.0	0.0–170.0	0.0–318.0
	mean (SD)	348.8 (341.2)	196.9 (253.3)	305.4 (306.2)	143.5 (134.0)	85.0 (120.2)	126.8 (123.3)
5	*n*	12	9	21	12	9	21
	median	778.0	621.0	697.0	470.0	268.0	395.0
	min–max	403.0–1640	42.1–1240	42.1–1640	198.0–1940	26.6–662.0	26.6–1940
	mean (SD)	840.5 (397.6)	628.8 (418.6)	749.8 (410.5)	618.1 (492.9)	331.5 (234.8)	495.3 (420.5)
10	*n*	13	9	22	13	9	22
	median	564.0	821.0	692.5	287.0	434.0	370.5
	min–max	162.0–2170	71.4–1570	71.4–2170	25.9–1830	82.2–777.0	25.9–1830
	mean (SD)	894.2 (687.7)	772.7 (520.9)	844.5 (614.3)	496.3 (558.3)	424.6 (241.2)	467.0 (449.0)

PKAS (all patients), patients from the SAF for whom at least one blood plasma measurement of fidaxomicin and OP-1118 was available; PKAS-Full Profile, including only those patients from the PKAS who participated in the full PK sampling profile. PKAS (all patients) and PKAS-Full Profile exclude the one patient with UC who took an extra two (commercially available) fidaxomicin tablets in addition to those prescribed. Concentrations below the limit of quantification (10 ng/mL of diluted stool homogenate or about 2 μg/g stool concentrations) were set to zero.
[a]On Day 1, a total of 18 stool samples were collected, but only results for the 7 samples collected in the protocol-specified time period (>12 h) post-dose are included.

event was considered unrelated to fidaxomicin treatment. There were no instances of hypersensitivity to fidaxomicin or of QT interval prolongation.

During long-term follow-up >30 days after EoT, 11/25 (44%) patients reported 50 AEs. The majority of these events were GI related. One event experienced by 1/25 (4%) patients was considered possibly related to fidaxomicin (ulnar nerve injury). Serious AEs ($n = 11$) were experienced by 7/25 (28%) patients, but none was considered to be related to fidaxomicin. There were no deaths during the study.

Clinical laboratory evaluations and vital signs

Most patients were within the normal reference ranges for haematological, biochemistry, WBC and neutrophil counts (Table S5). No notable changes were observed in blood pressure, temperature or pulse rate throughout the study.

Efficacy

Of all patients in the mFAS, 20/25 (80%) patients experienced clinical response according to ESCMID criteria at Day 12: 9/14 (64%)

Table 6. Clinical outcomes by IBD type (mFAS)

Clinical outcome, *n* (%)	CD (*N* = 14)	UC (*N* = 11)	Total (*N* = 25)
Clinical response at Day 12	9/14 (64)	11/11 (100)	20/25 (80)
Clinical failure at Day 12	5/14 (36)	0	5/25 (20)
Sustained clinical cure at Day 180	7/9 (78)	8/11 (73)	15/20 (75)
Cumulative recurrence[a] until Day 180	1/8 (13)[b]	2/10 (20)[c]	3/18 (17)[b,c]

n, number of observations; *N*, number of patients.
[a]Relapse or reinfection.
[b]Excludes one patient with CD who discontinued on Day 28 with sustained clinical cure.
[c]Excludes one patient with UC who discontinued on Day 91 with sustained clinical cure.

patients with CD and 11/11 (100%) of patients with UC (Table 6). One patient with CD (13%, 1/8) and two with UC (20%, 2/10) experienced recurrence of CDI.

Discussion

To date, the use of fidaxomicin in patients with CDI and IBD has been described only in retrospective studies[9] and data regarding the safety and utility of fidaxomicin in these patients are limited. There is an unmet need to explore the PK profile of fidaxomicin in patients with IBD and to determine whether chronic intestinal inflammation and disturbance of GI barriers alter the absorption of the drug. The current investigation is, to our knowledge, the first prospective study of fidaxomicin in patients with IBD and CDI, and the first to explore fidaxomicin PK in this setting.

Previous analysis in patients with CDI and no IBD confirmed that fidaxomicin has minimal systemic absorption and the plasma concentrations of the parent drug and its primary metabolite remain low throughout the dosing period.[13] In this study, maximum plasma concentrations of fidaxomicin and OP-1118 in patients with active IBD and CDI were within the measured ranges of concentrations found in patients with CDI, but without IBD.[8,13,14] This suggests no increase in absorption of fidaxomicin or OP-1118 in patients with active IBD. Based on AUC and C_{max} results across Days 1, 5 and 10, there was no evidence of accumulation of fidaxomicin or OP-1118 in plasma over the treatment period. The maximum measured plasma concentration of fidaxomicin was 154 ng/mL, well below the human equivalent of the no-observed-adverse-effect limit of 3000 ng/mL extrapolated from dog toxicology studies.[16] The C_{max} of 154 ng/mL was observed in a patient with UC who had relatively high plasma concentrations throughout the study period, compared with other patients in the study. The median plasma C_{max} of fidaxomicin and OP-1118 were therefore slightly higher in the subgroup of patients with UC compared with patients with CD; median plasma C_{max} values obtained from the PKAS-Full Profile were also slightly higher compared with plasma C_{max} from the PKAS (all patients), due to the inclusion of this patient in the PKAS-Full Profile. Of note, the patient with UC who experienced the highest fidaxomicin and OP-1118 plasma concentrations had a Partial Mayo Score of 5 at baseline, within the range of disease severity recorded in the subgroup of patients with UC.

The concentrations of fidaxomicin and OP-1118 found in stool were lower in our study compared with a previous clinical trial of patients without IBD.[13] However, it should be noted that for both fidaxomicin and OP-1118, there was substantial variability between patients in our study; relatively high standard deviations were also observed in the previous trial.[13] Nevertheless, stool concentrations of fidaxomicin and OP-1118 consistently attained supra-therapeutic levels in excess of the MIC for *C. difficile*. The *Clos*ER surveillance study,[17] which analysed 2694 *C. difficile* isolates between 2011 and 2014, determined that the MIC_{90} (the lowest concentration at which the growth of 90% of isolates was inhibited) of fidaxomicin for *C. difficile* was 0.125 mg/L. Mean stool concentrations of fidaxomicin observed in the IBD patient population in the present study ranged from 305.4 μg/g on Day 1 to 844.5 μg/g on Day 10, which (assuming a stool density of ∼1 g/mL) were well in excess of the MIC_{90} for *C. difficile*.

Our PK findings are also supported by the accompanying safety data. Although we expected some AEs to be associated with the underlying active IBD, overall incidences of TEAEs (60%) and serious TEAEs (24%) observed in this study were similar to those observed during previous Phase III trials in patients with CDI, but no IBD.[7,8] The majority of AEs were mild or moderate in severity and there were no cases of hypersensitivity to fidaxomicin or AEs that resulted in discontinuation of treatment. Incidence of drug-related TEAEs (40%) was higher than that reported by Cornely *et al.*[7] (11.7%), although the assessment period was longer in the present study. Two serious AEs reported within 30 days after EoT (hypoxia and skin ulcer) were assessed by the investigator as possibly related to fidaxomicin treatment; however, there is no other pre-clinical or clinical evidence to suggest a causal association of these events with fidaxomicin. There were no deaths during this study and the clinical laboratory evaluations conducted suggested no safety concerns regarding the use of fidaxomicin in patients with IBD.

Regarding limitations, this study was an uncontrolled study in which all patients had both IBD and CDI. The sample size was small and was chosen based on clinical and practical considerations with the aim of obtaining a sufficient number of evaluable PK profiles. The age range of patients enrolled (range 19–81 years) included a relatively young population, with only three patients older than 65 years; additional studies may therefore be required to ascertain safety in patients older than 65 years, who are at highest risk of CDI complications.[15,18,19]

Furthermore, the diagnosis of CDI poses particular challenges in patients with IBD, partly due to the overlap in clinical presentation of the two diseases.[20] Individual diagnostic tests can also produce

differing results: in our study, 7/13 patients with a negative central laboratory toxin A/B ELISA were confirmed positive for CDI by additional PCR and/or anaerobic culture. Moreover, in the present study, there were proportionally more patients with severe CDI (by ESCMID score) among those with UC than CD. All the patients with UC had a clinical response and it remains to be determined whether, in patients with UC, *C. difficile* positivity has a more pronounced impact on symptoms than in patients with CD.

In conclusion, the PK properties of fidaxomicin and OP-1118 in this study of patients with IBD and CDI suggest no increase in absorption of the parent drug or its primary metabolite, compared with previously published results from patients with CDI and no IBD. The similarity of the AE profiles in this study to those previously observed in patients without IBD suggest that fidaxomicin is comparatively well tolerated in this patient population.

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Transparency declarations

C. H. has received grants and personal fees from Astellas in relation to the study. Y. M. has received consulting fees related to this study via an agreement between his university and Astellas Pharma Europe Ltd. A. S. has received: consulting fees from AbbVie, Astellas, Biogen, Janssen, MSD, Mundipharma, Summit Therapeutics and Takeda; lecture fees and support for travel accommodation from AbbVie, FalkFoundation, Janssen, MSD, Mundipharma and Takeda; and research funding from AbbVie and Pentax. P. M. has received personal fees from Astellas in relation to the study and consultation or lecture fees from AbbVie, Astellas, Biocodex, Danone, Hospira-Pfizer, Janssen, Merck Sharp & Dohme, Ferring Pharmaceuticals and Takeda. G. R. has received clinical study fees, lecture fees and conference funding from Astellas Pharma, Inc. V. I. has none to declare. P. G.-K. has received investigator fees from Astellas Pharma, Inc. I. M. and R. T. are full-time employees of Astellas Pharma Europe B.V. N. A. was a full-time employee of Astellas Pharma, Inc. at the time of the study. A. G. is a full-time employee of Astellas Pharma, Inc. A. K. is a full-time employee of Astellas Pharma Ltd and has patents WO2015169451 A1 and EP17167541.6 pending to Astellas Pharma Europe Ltd. W. R. has received personal fees from Astellas in relation to the study and has served as a consultant and advisory board member for Astellas. He has: served as a speaker for Abbott Laboratories, AbbVie, Aesca, Aptalis, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, Schering-Plough, Shire, Takeda, Therakos, Vifor and Yakult; served as a consultant for Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, AstraZeneca, Avaxia, Bioclinica, Biogen IDEC, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trial, Schering-Plough, Second Genome, Setpointmedical, Takeda, Therakos, Tigenix, UCB, Vifor, Zyngenia and 4SC; served as an advisory board member for Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, AstraZeneca, Avaxia, Biogen IDEC, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Schering-Plough, Second Genome, Setpointmedical, Takeda, Therakos, Tigenix, UCB, Zyngenia and 4SC; and received research funding from Abbott Laboratories, AbbVie, Aesca, Centocor, Falk Pharma GmbH, Immundiagnostik and MSD.

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Conception: N. A. and A. K. Study design and conduct: C. H., Y. M., A. S., P. M., G. R., V. I., P. G.-K., I. M., N. A., R. T., A. K. and W. R. Data acquisition: C. H., G. R., V. I., P. G.-K., I. M., N. A., A. G. and A. K. Analysis and interpretation: C. H., Y. M., A. S., P. M., G. R., V. I., P. G.-K., I. M., N. A., A. G., R. T., A. K. and W. R. Writing: C. H., Y. M., A. S., P. M., G. R., V. I., P. G.-K., I. M., N. A., A. G., R. T., A. K. and W. R.

Supplementary data

Supplementary Methods and Tables S1 to S5 are available as Supplementary data at *JAC* Online.

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