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

Christoph Högenauer1, Yashwant Mahida2, Andreas Stallmach3, Philippe Marteau4, Grazyna Rydzewska5, Vladimir Ivashkin6, Panagiotis Gargalianos-Kakolyris7, Ingrid Michon6, Nicholas Adomakoh9, Areti Georgopali9, Reiner Tretter8, Andreas Karas10 and Walter Reinisch11*

1Medical University of Graz, Graz, Austria; 2NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK; 3Jena University Hospital, Jena, Germany; 4Sorbonne Université & APHP, Hôpital Saint Antoine, Paris, France; 5Central Clinical Hospital of the Ministry of the Interior, Warsaw and Jan Kochanowski University, Kielce, Poland; 6I. M. Sechenov University, Moscow, Russian Federation; 7General Hospital of Athens ‘G. Gennimatas’, Athens, Greece; 8Astellas Pharma Europe B.V., Leiden, The Netherlands; 9Astellas Pharma, Inc., Chertsey, UK; 10Astellas Pharma Ltd, Chertsey, UK; 11Medical University of Vienna, Vienna, Austria

*Corresponding author. Department of Internal Medicine III, Division of Gastroenterology & Hepatology, Medical University of Vienna, Vienna, Austria. Tel: +43 1 40400 47410; Fax: +43 1 40400 47350; E-mail: walter.reinisch@meduniwien.ac.at

Received 16 March 2018; returned 10 June 2018; revised 20 July 2018; accepted 17 August 2018

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\textsubscript{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\textsubscript{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 l g/g for fidaxomicin and 0–1940 l g/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. Patients with inflammatory bowel disease (IBD) are at particular risk of developing CDI. 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. Notably, rates of CDI are higher among patients with ulcerative colitis (UC) and Crohn’s disease (CD) with colonic involvement. 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. Furthermore, fidaxomicin achieved significantly lower rates of CDI recurrence and higher rates of sustained clinical cure, compared with vancomycin. 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. It is currently recommended that fidaxomicin is used with caution in patients with IBD and CDI, owing to uncertainty whether absorption of
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 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.

Figure 2. Patient flow diagram. *CDI not confirmed by local testing.
| 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<sup>a</sup>                            |             |             |                |
| 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<sup>b</sup>, n (%)             | 2 (14)      | 2 (18)      | 4 (16)         |
| Pseudomembranous colitis, n (%)                    | 0           | 2 (18)      | 2 (8)          |
| Prior CDI<sup>c</sup>, n (%)                       | 2 (14)      | 3 (27)      | 5 (20)         |
| No. of UBMs per day<sup>d</sup>, 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                                            | 4 (29)      | 8 (73)      | 12 (48)        |
| for conditions other than CDI                      | 1 (7)       | 4 (36)      | 5 (20)         |
| Antibiotic use for CDI within 90 days prior to enrolment by preferred WHO name, n (%) | 3 (21) | 7 (64) | 10 (40) |
| 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.

<sup>a</sup>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.

<sup>b</sup>Leucocyte count >15×10<sup>9</sup>/L.

<sup>c</sup>In the 90 days prior to enrolment. No patient had >1 episode of CDI during this period.

<sup>d</sup>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) | 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 | | | | | | |
| aminosalicylic acid and similar agents | | | | | | |
| mesalazine | 13 (93) | 11 (100) | 24 (96) |
| sulfasalazine | 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) |
| 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 | | | | | | |
| meropenem | 4 (29) | 7 (64) | 11 (44) |
| sulperazon | 1 (7) | 0 | 1 (4) |
| amoxiclavulanico | 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 | | | | | | |
| rifampicin | 0 | 1 (9) | 1 (4) |
| isoniazid | 0 | 1 (9) | 1 (4) |
| Antimycotics for systemic use | | | | | | |
| rynstatin | 0 | 1 (9) | 1 (4) |
| Lactobacillus acidophilus | 0 | 1 (9) | 1 (4) |
| Lactobacillus plantarum | 0 | 1 (9) | 1 (4) |
| VSL #3 | 0 | 1 (9) | 1 (4) |
| Corticosteroids for systemic use | | | | | | |
| budesonide | 8 (57) | 7 (64) | 15 (60) |
| dexamethasone | 3 (21) | 1 (9) | 4 (16) |
| hydrocortisone | 1 (7) | 0 | 1 (4) |
| methylprednisolone | 0 | 4 (36) | 4 (16) |
| prednisolone | 1 (7) | 4 (36) | 5 (20) |
| prednisone | 5 (36) | 1 (9) | 6 (24) |
| Adalimumab | 1 (7) | 2 (18) | 3 (12) |
| Immunosuppressants | | | | | | |
| calcineurin inhibitors | 11 (79) | 5 (46) | 16 (64) |
| ciclosporin | 0 | 2 (18) | 2 (8) |
| other immunosuppressants | 0 | 2 (18) | 2 (8) |
| azathioprine | 8 (57) | 4 (36) | 12 (48) |
| methotrexate | 7 (50) | 4 (36) | 11 (44) |
| TNF-a inhibitors | 2 (14) | 0 | 2 (8) |
| Infliximab | 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**

| 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
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 \(^2\) for patients with UC\(^1\) or Harvey–Bradshaw index (HBI) score \(^5\), excluding points for complications, for patients with CD.\(^1\) 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.\(^1\)

**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 \(T_{\text{max}}\), 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 \(T_{\text{max}}\) (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 \(-70^\circ\) 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\(^\text{®}\), 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...
where

until the end of the study (Day 180); AEs arising during the period from the

Adverse events (AEs) were recorded from the time of informed consent

Safety

studies of fidaxomicin. A secondary endpoint was fidaxomicin and

with full PK profile measurements; (b, c) 14 patients (8 CD, 6 UC) with

Plasma concentration of fidaxomicin by IBD type on (a) Day 1,

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. 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. 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 Cmax or plasma concentrations at Tmax. 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;
One-fifth (5/25; 20%) of patients had a prior history of one CDI episode in the 90 days prior to study enrolment. Of these, 5/25 (20%) patients received antibiotics for the treatment of CDI. Antidiarrhoeals and intestinal ant-inflammatory/anti-infective agents were used by 24/25 (96%) 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.

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

| Day | Parameter | Fidaxomicin | OP-1118 |
|-----|-----------|-------------|---------|
|     | PKAS (all patients) | PKAS-Full Profile | PKAS (all patients) | PKAS-Full Profile |
|     | C_{trough} (ng/mL) | C_{max} (ng/mL) | T_{max} (h) | AUC\(^a\) (ng·h/mL) | C_{trough} (ng/mL) | C_{max} (ng/mL) | T_{max} (h) | AUC\(^a\) (ng·h/mL) |
| 1   | n/median/min-max | 23/9.7/2.5–75.3 | 14/9.9/3.4–75.3 | 14/1.8/0.5–11.5 | 8/67.6/22.7–339 | 23/24.7/4.9–336 | 14/23.7/10.3–336 | 14/1.8/0.5–11.5 | 9/169.0/36.2–1550 |
| 5   | n/median/min-max | 23/4.3/0.7–28.8 | 23/12.2/1.2–154 | 13/17.7/5.3–154 | 13/1.0/0.5–3.0 | 11/116.5/38.0–513 | 12.7/42.7/4.7–555 | 13/13/0.5–5.0 | 10/102–2269 |
| 10  | n/median/min-max | 33/4.3/1.0–11.6 | 24/11.3/4.6–71.3 | 14/13.4/4.6–71.3 | 14/1.8/0.5–5.4 | 11/109.8/19.2–364 | 13.6/45.5/10.6–206 | 14/14/0–5.4 | 12/50–314 |
|     | mean (SD)/min-max | 4.4 (3.2)/5.75–154 | 22.6 (30.4) | 16.3 (15.1)/17.2 (18.6) | 22.2 (1.7)/2.2 (1.7) | 129.1 (115.0)/212.9 (212.9) | 18.2 (15.6)/10.6–206 | 13.5 (5.5)/52.8–1161 |

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. 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 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 $T_{\text{max}}$ across all days was $\sim 1–2$ 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 $C_{\text{max}}$ across all days for the PKAS was 14.6 ng/mL (range 5.8–154 ng/mL). No apparent differences in plasma $C_{\text{max}}$ were observed between patients with a limited PK profile and those with a full profile. The highest observed plasma $C_{\text{max}}$ 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 $\sim 2–6$-fold higher than those of fidaxomicin.

PK parameters of OP-1118 are given in Table 3 and $C_{\text{max}}$ measurements by IBD type are given in Table 4. The median $C_{\text{max}}$ for the PKAS across Days 1, 5 and 10 was 46.1 ng/mL (range 13.5–555 ng/mL). The highest observed plasma $C_{\text{max}}$ 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 $C_{\text{max}}$, 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).

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

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%)
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 studies2 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.5,13,14 This suggests no increase in absorption of fidaxomicin or OP-1118 in patients with active IBD. Based on AUC and Cmax 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 Cmax 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 Cmax of fidaxomicin and OP-1118 were therefore slightly higher in the subgroup of patients with UC compared with patients with CD; median plasma Cmax values obtained from the PKAS-Full Profile were also slightly higher compared with plasma Cmax 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 Closer surveillance study,17 which analysed 2694 C. difficile isolates between 2011 and 2014, determined that the MIC90 (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 MIC90 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 CD suggest no increase in absorption of the parent drug or its primary metabolite, compared with previously published results from patients with CD and no IBD. The similarity of the AE profiles in this study to those previously observed in patients without IBD suggest that fidaxomicin is comparably well tolerated in this patient population.

Acknowledgements
These data were presented in part as a poster at the Twelfth Congress of ECCO—Inflammatory Bowel Diseases, Barcelona, Spain, 2017 (Poster P390).

Funding
This study was initiated and supported by Astellas Pharma, Inc. Medical writing support was funded by Astellas Pharma, Inc.

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 & Doehme, 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 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, Danane Austria, Elian, Ferring, Galapagos, Genentech, Gilead, Grunenthal, ICON, Index Pharma, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robert's Clinical Trial, Schering-Plough, Second Genome, Setpointmedicaal, Takeda, Therakos, Tigenix, UCB, Vifor, Zynegena and 4SC; served as an advisory board member for Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, AstraZeneca, Avexia, Biogen IDEC, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, Elian, Ferring, Galapagos, Genentech, Gilead, Grunenthal, ICON, Index Pharma, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Schering-Plough, Second Genome, Setpointmedicaal, Takeda, Therakos, Tigenix, UCB, Zynegena and 4SC; and received research funding from Abbott Laboratories, AbbVie, Aesca, Centocor, Falk Pharma Gmbh, Immunodiagnostik and MSD.

Medical writing support was provided by Iona Easthope and Rhian Harper Owen for Cello Health MedErgy.

Author contributions
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., Y. M., A. S., P. M., 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.

References
1 Bagwa E. Consequences of Clostridium difficile infection: understanding the healthcare burden. Clin Microbiol Infect 2012; 18 Suppl 6: 5–12.
2 Nitzan O, Elias M, Chazan B et al. Clostridium difficile and inflammatory bowel disease: role in pathogenesis and implications in treatment. World J Gastroenterol 2013; 19: 7577–85.
3 Carpenter B, Hennessey EK, Bryant AM et al. Identification of factors impacting recurrent Clostridium difficile infection and development of a risk evaluation tool. J Pharm Pharm Sci 2016; 19: 349–56.
4 Nguyen GC, Kaplan GG, Harris ML et al. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. Am J Gastroenterol 2008; 103: 1443–50.
5 Zhang T, Lin Q-Y, Fei J-X et al. Clostridium difficile infection worsen outcome of hospitalized patients with inflammatory bowel disease. Sci Rep 2016; 6: 29791.
6 Issa M, Vijayarap A, Graham MB et al. Impact of Clostridium difficile on inflammatory bowel disease. Clin Gastroenterol Hepatol 2007; 5: 345–51.
7 Cornell OA, Crook DW, Esposito R et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012; 12: 819–21.
8 Louie TJ, Miller MA, Mullane K et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011; 364: 422–31.
9 Spiceland CM, Khanna S, Pardi DS. Outcomes with fidaxomicin therapy in Clostridium difficile infection. J Clin Gastroenterol 2018; 52: 151–4.
10 Astellas Pharma Europe B.V. Summary of Product Characteristics: DIFICLIR 200 mg Film-Coated Tablets. 2016. http://www.ema.europa.eu/
Lewis JD, Chuai S, Nessel L et al. Use of the non-invasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis 2009; 14: 1660–6.

12 Harvey RF, Bradshaw JM. A simple index of Crohn’s-disease activity. Lancet 1980; 315: 514.

13 Sears P, Crook DW, Louie TJ et al. Fidaxomicin attains high fecal concentrations with minimal plasma concentrations following oral administration in patients with Clostridium difficile infection. Clin Infect Dis 2012; 55: S116–20.

14 Mullane KM, Gorbach S. Fidaxomicin: first-in-class macrocyclic antibiotic. Expert Rev Anti Infect Ther 2011; 9: 767–77.

15 Debast S, Bauer M, Kuijper E. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect 2014; 20 Suppl 2: 1–26.

16 EMA. Assessment Report: Dificlir. 2011. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002087/WC500119707.pdf.

17 Freeman J, Vernon J, Pilling S et al. The ClosER study: results from a three-year pan-European longitudinal surveillance of antibiotic resistance among prevalent Clostridium difficile ribotypes, 2011–2014. Clin Microbial Infect 2018; 24: 724–31.

18 Bauer MP, Notermans DW, van Benthem BH et al. Clostridium difficile infection in Europe: a hospital-based survey. Lancet 2011; 377: 63–73.

19 Karas JA, Enoch DA, Aliyu SH. A review of mortality due to Clostridium difficile infection. J Infect 2010; 61: 1–8.

20 Khanna S, Shin A, Kelly C. Management of Clostridium difficile infection in inflammatory bowel disease: expert review from the Clinical Practice Updates Committee of the AGA Institute. Clin Gastroenterol Hepatol 2017; 15: 166–74.