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Name of Sponsor/Company: Astellas Pharma Europe Ltd.		
Name of Finished Product DIFICLIR™		
Name of Active Ingredient: Fidaxomicin		

SYNOPSIS

Title of Study:

Open label study to evaluate the pharmacokinetics of fidaxomicin in inflammatory bowel disease (IBD) subjects with C*lostridium difficile* infection (CDI).

Investigators/Coordinating Investigator:

[redacted] M.D.
[redacted], Austria.

Study Center(s):

This was an open-label, single arm, multicenter study with patients allocated to treatment in 9 European countries and regions (hereafter referred to as regions) at 28 sites.

Publication Based on the Study:

N/A

Study Period:

From Q3 2015 to Q4 2016

Study Initiation Date (Date of First Enrollment):

13 August 2015

Study Completion Date (Date of Last Evaluation):

24 October 2016

Phase of Development:

Phase 3b/4

Objectives:

The primary objective of the study was to investigate the plasma pharmacokinetics of fidaxomicin and its primary metabolite OP-1118, in patients with IBD and CDI on day 1, day 5 and day 10 of treatment. Of special interest was to document the maximum observed plasma concentrations in this patient population with a view to comparing the range of maximum observed plasma concentrations recorded to data of patients obtained from earlier phase 1/2 studies with fidaxomicin.

The secondary objectives of this study were:

- Compare CDI clinical response to the microbiological response in terms of magnitude of reduction of *C. difficile* total viable count and spore count during treatment with fidaxomicin and if achieved, the time to microbial eradication.
- Determine time to negative *C. difficile* toxin assay in stool specimens during treatment with fidaxomicin.
- Assess stool concentrations of fidaxomicin and metabolite OP-1118 throughout therapy from day 1, day 5, and day 10 and at any unscheduled failure visit.
- Assess the length of hospital stay, readmissions and resource utilization for IBD patients receiving fidaxomicin throughout the study through the end of study (EoS) visit 8 (day 180).
- Record the incidence and severity of adverse events (AEs) up to EoS visit 8 (day 180).
- Document impact of treatment on quality of life as measured by the changes in short IBD questionnaire (IBDQ) score from baseline (visit 1) to visit 3 (day 10), visit 5 (day 26), visit 6 (day 40) and visit 7 (day 90), EoS visit 8 (day 180) and to any confirmed recurrence episode of CDI.

Methodology:

This was a multicenter, open-label single arm study to evaluate the plasma pharmacokinetics of fidaxomicin and its primary metabolite OP-1118 in with a diagnosis of IBD and CDI confirmed by positive local standard CDI testing for the presence of *C. difficile* (within 48 hours prior to enrollment). Screening and informed consent was to be completed within 48 hours of enrollment. The study comprised of 8 visits: 3 visits during the treatment period: screening/visit 1 (day 1), visit 2 (day 5), end of treatment (EoT) visit 3 (day 10); and 5 visits during follow-up: visit 4 (day 12 [telephone call]), visit 5 (day 26), visit 6 (day 40), visit 7 (day 90) and visit 8 (day 180).

Patients were treated for 10 days with fidaxomicin 200 mg tablets twice daily, and blood samples were taken on day 1, day 5 and day 10 (predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) to determine pharmacokinetic parameters of fidaxomicin and OP-1118 in plasma and to test for biomarkers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR] and neutrophil gelatinase-associated lipocalin [NGAL]) at screening, day 5, day 10, day 26, at unscheduled visits and via fecal sampling for fecal calprotectin and lactoferrin. Stool samples were collected at, or as close as possible to, all visits. These samples were used to test for biomarkers (fecal calprotectin and lactoferrin), microbiome assessment, *C. difficile* spore count, *C. difficile* total viable count and toxin detection. Patients in this study were followed until EoS at visit 8 (day 180) to collect safety, efficacy and health outcomes data.

Patients with increased unformed bowel movements (UBM) following CDI clinical response at Test of Cure (ToC) (UBMs greater than the frequency recorded at visit 4) had to attend an unscheduled visit to evaluate the recurrence of CDI/IBD flare based on clinical symptoms, frequency of UBM and a stool sample. The need for additional CDI/IBD therapy was to be recorded. During the treatment period and up to the ToC visit, patients had to complete a daily bowel movement diary and enter stool type classification as defined in the Bristol Stool Chart for each bowel movement. Short IBDQs were collected during screening at baseline, at visits 3, 5, 6, 7, 8 and at unscheduled visits for treatment failure or recurrence of CDI.

Number of Patients (Planned, Enrolled and Analyzed):

The total number of patients to be included based on the initial sample size (30 patients) was not met before the end of the recruitment date on 30 Apr 2016. A total of 25 patients enrolled in the study: 14 Crohn's disease and

11 ulcerative colitis patients who were analyzed according to the following analysis sets: Safety Analysis Set (SAF), modified Full Analysis Set (mFAS) and Per Protocol set (PPS).

For pharmacokinetic analysis: Pharmacokinetic Analysis Set (PKAS) with a total number of patients of 24 (14 Crohn's disease patients and 10 ulcerative colitis patients) and PKAS-Full Profile with a total number of patients of 14 (8 Crohn's disease patients and 6 ulcerative colitis patients).

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

1. Patient was aged at least 18 years.
2. Confirmed diagnosis or history of IBD for at least 3 months.
3. Patient had active IBD defined by:
    - Partial Mayo Score (ulcerative colitis patients) of 2 or more, where at least 1 point had to originate from blood in stool.
    - Harvey-Bradshaw index (HBI) (Crohn's disease patients) of 5 or more, excluding points for complications.
4. CDI confirmed positive according to local standard testing for the *C. difficile* within 48 hours prior to enrollment.
5. IEC approved written informed consent and privacy language as per national regulations was obtained from the patient or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
6. Female patient was either:

- Of non-childbearing potential:
    - Post-menopausal (defined as at least 1 year without any menses) prior to screening,
    or
    - Documented surgically sterile (at least 1 month prior to screening) or status posthysterectomy
- Or in case of childbearing potential:
    - Had a negative urine pregnancy test at screening
    and
    - Had to use 2 forms of birth control † (at least 1 should have been a barrier method) starting at screening or throughout the investigational period.

7. Female patient was not breastfeeding at screening or during the investigational period.
8. Male patient and their female spouse/partners who were of childbearing potential should have used highly effective contraception consisting of 2 forms of birth control † (1 of which should have been a barrier method) starting at screening and continuing throughout the investigational period.
    † Acceptable forms of birth control included:
    - Established use of oral, injected or implanted hormonal methods of contraception
    - Placement of an intrauterine device or intrauterine system
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps with spermicidal foam/gel/film/cream/suppository)
9. Male partner agreed not to donate sperm starting at screening and throughout the investigational period.
10. Patient agreed not to participate in another interventional study while participating in this study.

Exclusion criteria:

1. Patient had received more than 1 day of dosing of any CDI therapy within the 48 hours prior to enrollment.
2. Patient was unable to swallow oral study drug.
3. Presence of an ostomy or short bowel syndrome.
4. Patient had a current diagnosis of toxic megacolon.
5. Patient was not willing to adhere to the provisions of treatment and observation specified in the protocol.

6. Patient had been enrolled into this study previously, had taken any investigational drug within 28 days or 5 half-lives, whichever is longer, prior to enrollment, or was currently participating in another clinical study which may influence the assessment of efficacy and/or safety endpoints of this study, in the opinion of the sponsor.
7. Patient had previously participated in a CDI vaccine study.
8. Patient had hypersensitivity to fidaxomicin or any of its components
9. Patient had a condition, which, in the investigator's opinion, made the patient unsuitable for study participation.

Waivers to the inclusion/exclusion criteria were NOT allowed.

Test Product, Dose and Mode of Administration, Batch Numbers:

Commercially available fidaxomicin immediate-release tablets were white to off-white capsule-shaped, film-coated tablets (batch number: [redacted]). Study drug administration started on day 1 following enrollment via IWRS, within 24 hours of enrollment. Patients received oral fidaxomicin 200 mg tablets twice daily (every 12 hours) beginning day 1 for 10 treatment days. Special considerations were given to the review of patients with plasma fidaxomicin levels in excess of 3000 ng/mL, taking into account the clinical context of the patient.

Duration of Treatment and Duration of Study:

The average treatment duration for all patients was 10 days with a mean total of 4016 mg of study drug used. The study duration for all patients was 180 days.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Not used in this study.

Criteria for Evaluation:

Primary endpoint:

Primary endpoints were pharmacokinetic parameters derived from plasma concentrations of both fidaxomicin and OP-1118 on days 1, 5 and 10. Of special interest was the upper limit of maximum plasma concentration in this population.

The following pharmacokinetic parameters were to be calculated for each patient with a complete pharmacokinetic profile:

- Day 1: C_{max}, AUC_{12}, t_{max}
- Day 5 and day 10: C_{max}, AUC_{tau}, t_{max}, apparent total systemic clearance after single or multiple extra-vascular dosing (CL/F) and C_{trough} (predose to first daily dose)

The following pharmacokinetic parameters were to be calculated for each patient who might have had a reduced profile:

- Day 1: C_{max}, AUC_{12}, t_{max}
- Day 5 and day 10: C_{trough} (prior to first daily dose) and the maximum observed plasma concentrations in time window (±1 hour) for t_{max}, based on mean t_{max} estimate derived from cumulative data of patients with a full pharmacokinetic profile

Other pharmacokinetic parameters were to be calculated when possible. The upper limit of the maximal observed plasma concentrations was the maximum plasma concentration value observed for any patient at any time point in the study.

Secondary endpoints:

- CDI clinical response at ToC on visit 4 (day 12)
- Microbiological response at visit 2 (day 5) and visit 3 (day 10)
    - *C. difficile* total viable count †,
    - *C. difficile* spore count †
    - Percentage of patients with microbial ‡ eradication †
- Percentage for patients with negative C. difficile toxin assay †
- Stool concentrations of fidaxomicin and its metabolite OP-1118 throughout fidaxomicin treatment
- Length of hospital stay, readmissions and resource utilization throughout the study
- Health-related Quality of Life (HRQoL) as measured by the short IBDQ score

† Data was not available before finalization of this clinical study report (CSR) and will be reported separately.
‡ The term 'microbial' was replaced by 'bacterial'.

Statistical Methods:

Demography and baseline characteristics were presented for the SAF, mFAS, PPS, PKAS and PKAS Full-Profile. Medical history, previous and concurrent medications were coded using MedDRA (v14.1), and summarized by system organ class (SOC) and, as well as by preferred term (PT) alone, for the SAF. Individual listings were provided. The duration of exposure was summarized by descriptive statistics for number of treatment-exposure days as continuous variable, and exposure time categorized according to the following categories by treatment group: less than 3 days, 3 days to less than 8 days, 8 days, 9 days, and 10 days.

Percentages of overall compliance were summarized for the SAF and mFAS by descriptive statistics and the number and percentage of patients within the following categories: < 20%, ≥ 20% to < 50%, ≥ 50% to < 70%, ≥ 70% to < 90%, ≥ 90% to < 100%, = 100%, > 100%.

For the primary pharmacokinetic endpoint the individual plasma concentrations for fidaxomicin and the primary metabolite OP-1118 were listed and summarized by sampling day and time point for the PKAS and a subset of patients with a full pharmacokinetic profile. In addition, for continuous pharmacokinetic parameters, the coefficient of variation (CV) was calculated and for C_{max} and AUC, the geometric mean was calculated. Boxplots and scatter plots (both normal and semi-log) of plasma fidaxomicin concentrations by visit and time point were also generated. Similar descriptive statistics were shown for measurements of fidaxomicin and OP-1118 in feces, and if available, also for intestinal mucosa. Non-compartmental analyses were performed to estimate the pharmacokinetic parameters. Scatterplots were generated for the PKAS to explore whether maximum plasma concentration measurements of fidaxomicin were associated with the severity of IBD, and to distinguish between responders and nonresponders in clinical cure of CDI at ToC (visit 4, day 12).

Efficacy analyses for secondary endpoints were performed on the mFAS; PPS was used to assess the robustness of the results. All 95% CIs were calculated according to the Wilson method, without continuity correction. For continuous variables, descriptive statistics included the number of patients (n), mean (SD), median, minimum and maximum. For continuous efficacy parameters, short IBDQ and duration of hospitalization, also the lower and upper quartiles (Q1, Q3) were presented. Short IBDQ total scores and dimensional subscale scores were summarized by descriptive statistics at each visit for the mFAS. Change from baseline was presented for visits

prior to ToC (visit 4, day 12), thereafter change from visit 3 (day 10) was presented. Variables collected for health economics were analyzed in terms of length of hospital stay, readmissions and resource utilization using mFAS as detailed in the statistical analysis plan (SAP). Health economic and resource variables were stratified by clinical response of CDI at ToC visit 4 on day 12 (yes/no/total). Detailed percentiles were calculated for the time-to-event analyses, dependent on the observed data.

Summary of safety variables were presented for the SAF and AEs were coded using MedDRA (v14.1) and summarized by SOC as well as by PT alone. No formal statistical testing was performed on these data. AEs were summarized for treatment-emergent adverse events (TEAEs) and additional summaries were provided for AEs that started in the long-term follow-up period beyond 30 days after the EoT until the EoS visit on day 180. Local laboratory safety variables (biochemistry, hematology, urinalyses) were summarized by visit as absolute measurement and their change from baseline. Shift tables for the number and percentage of patients with baseline and corresponding postbaseline values classified as less then lower limit, normal, or above upper limit were summarized for visit 2 (day 5) and visit 3 (day 10). Additional descriptive analyses were performed for parameters indicative of potential drug-induced-liver-injury (DILI). Vital signs (blood pressure, pulse rate, body temperature) were summarized by descriptive statistics at each visit. Additionally, a within-patient change was calculated as the postbaseline measurement minus the baseline measurement and summarized at each visit. Number and percentage of patients with fever (core body temperature > 38.5°C) were summarized by visit. The number and percentage of patients with potentially clinically significant values in liver function tests (i.e., alkaline phosphatase [ALP], alanine aminotransferase [ALT], total bilirubin, aspartate aminotransferase [AST]) during the investigational period were summarized. Listings were provided for all safety variables.

Changes from the planned statistical analyses:

- CIs were not provided for time-to-event variables since calculations based on dummy data showed that the number of patients included in this study was too small for getting meaningful CIs for this type of data. Detailed descriptive summaries by visit for viable count, spore count, microbial eradication and presence of toxin data were restricted to the treatment period, without showing CIs.
- Data not analyzed before the finalization of this CSR included: microbial response data for total viable and spore count, CDI relapse rate and inflammatory biomarkers in plasma and stool. These data will be reported separately.
- The definitions for TEAEs was added: 1) AEs which started later than 30 days after EoT were not considered to be treatment-emergent and were summarized in a separate set of tables for the long-term follow-up period (> 30 days after EoT to EoS (visit 8, day 180), and 2) TEAEs are defined as an AE starting or a condition existing pretreatment that worsens after first study drug intake and until 30 days after the EoT.
- The protocol specified as 1 way of identifying a flare of Crohn's disease was "Worsening of endoscopic lesions (based on simple endoscopic score for Crohn's disease [SES CD] or Crohn's Disease Endoscopic Index of Severity [CDEIS]), where this was performed and could have been compared with baseline". However, endoscopic lesions were not recorded in the electronic case report form (eCRF) for Crohn's disease patients; therefore this clause did not apply.
- The total number of patients to be included based on the sample size (30 patients) was not met before the end of the recruitment date on 30 Apr 2016. As indicated in the protocol the number of patients was not based on any intended statistical power calculation but rather selected based on the feasibility of recruiting

a sufficient number of patients with IBD to be able to demonstrate the pharmacokinetics of fidaxomicin in this patient group.

- Pharmacokinetic predose sampling on days 5 and 10 for the reduced pharmacokinetic profile as described in the study protocol was changed from t_{max} ± 1 hour to t_{max} 2 hours ± 30 minutes (Investigator Letter Reduced PK Profile dated 9 Feb 2016).
- According to standard practice, SAEs were followed-up 30 days after EoT and until the EoS visit.
- The term ‘ microbial’ as used in the study protocol should have been replaced by ‘bacterial’ and included all references to ‘microbial groups’, ‘microbial diversity’, ‘microbial composition’, ‘microbial abundance’ and ‘microbial population’ in this study. This change was due to the method used to determine the composition and diversity of the fecal microbiota in stool samples. In this study a 16S rRNA sequencing technique was used that could only detect and classify bacteria and no other microorganism like parasites, fungi and viruses.
- In addition to the rules specified in the SAP, 2 more rules were added (between ‘C’ and ‘D’ in the original list). These were added because all anatomic therapeutic chemical classification (ATC) codes were used irrespective of the route of administration. However, IBD medications (such as steroids) were incorrectly also being included in the ATC code ‘Dermatologicals’ and also ‘Nasal preparations’, even though they were given systemically (oral or intravenously) and did not have a dermatological or nasal action.
    - If (the ATC level 1 code was ‘Dermatologicals’ (i.e., ATC code starting with ‘D’) and the route of administration was not ‘Topical’ then this was flagged as a violation.
    - If the route of administration was ‘Other’ or ‘Missing’, this was not counted as a violation.
  - If the ATC code started with ‘D10B’ this was not a violation.
    - If the ATC code contained ‘Topical’ and the route of administration was not ‘Topical’ then it was a violation.
    - If the route of administration was ‘Other’ or ‘Missing’, this was not counted as a violation.
- The timing for the exploratory endpoint ‘CDI disease-free survival at day 10’ was changed to ‘CDI disease-free survival’ because this was counted from the day at which the patient was free of disease which could be prior or after 10 days.
- It was decided that patients with an investigator reported recurrence of CDI who also received treatment for CDI, should be counted as a CDI recurrence even if the local laboratory test for CDI was missing. The SAP was not updated to clarify this decision.

Interim analysis:

The study team together with the pharmacokineticist, continued to review the pharmacokinetics parameters on a case-by-case basis. Should the pharmacokinetic analysis at any time reveal exceptionally high plasma concentrations (in excess of the 3000 ng/mL based on the no observed adverse effect level (NOAEL) from dog 3-month toxicology studies) of fidaxomicin or its primary metabolite OP-1118 and within the range recorded from historical studies of fidaxomicin in non-IBD CDI patients, or the safety data raised concerns, then the study was to be discontinued. Therefore a formal interim analysis report was not produced; a pharmacokinetic interim analysis was performed instead.

Summary of Results/Conclusions:

Population:

Subject disposition and analysis sets can be found in Figure 1 and Table 1. Demographics and baseline characteristics of the patients in the SAF can be found in Table 2 and Table 3, and for patients in the PKAS Full Profile in Table 4 and Table 5.

Of the 25 patients in the SAF, 18 (72%) were classified as nonsevere CDI based on the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) score, of which 12 of 14 (85.7%) patients with Crohn's disease and 6 of 11 (54.5%) patients with ulcerative colitis. Pseudomembranous colitis was diagnosed only in 2 patients with ulcerative colitis (2 out of 11 patients [8%]) at baseline. Most of the patients (20 out of 25 [80%]) had no previous CDI episodes (85.7% patients with Crohn's disease and 72.7% patients with ulcerative colitis), and the remaining 5 patients (20%) had 1 previous CDI episode within the previous 3 months. Only 5 of 25 (20%) patients used antibiotics to treat CDI 90 days prior to the study, of which metronidazole and vancomycin were mostly used (12% of patients), and 1 patient took both metronidazole and vancomycin. Two of 25 (8%) patients used antibiotics 2 days prior to the first study drug intake (1 Crohn's disease patient using vancomycin and 1 ulcerative colitis patient using moxifloxacin).

Additional IBD specific medical history by IBD type for patients in the SAF and PKAS Full Profile is summarized in Table 6 and Table 7. Medications used prior to the first study drug dosing were used by all patients in both IBD types (25/25 [100%]).

During the follow-up period from EoT (day 10) to the EoS visit (day 180), all patients (100%) received medications. Antidiarrheals, intestinal antiinflammatory or anti-infective agents were used in 24 out of 25 patients (96%) of both ulcerative colitis and Crohn's disease patients. These agents were used in 16 out 17 (94.41%) patients with sustained clinical cure at EoS and 8 out of 8 (100%) patients without sustained clinical cure at EoS, respectively. Systemic corticosteroids were used in 82.4% and 37.5% of patients with and without sustained clinical cure respectively.

A total of 4 out of 25 (16%) patients were administered with medications to treat CDI after EoT until the EoS visit (1/17 [5.9%] patient with sustained clinical cure and 3/8 [37.5%] patients without sustained clinical cure). During this period, only 1 out of 14 patients with Crohn's disease (without sustained clinical cure) used medications, and not more than 3 of 11 patients with ulcerative colitis (1 patient with sustained clinical cure; 2 patients without sustained clinical cure).

Pharmacokinetic Results:

- Mean plasma concentration time profiles of fidaxomicin for all patients in the PKAS are presented in Figure 2 and Figure 4. Overall, plasma fidaxomicin concentrations reached a maximum after approximately 3 hours on day 1 and 10. On day 5 an earlier peak was observed at approximately 1.5 hours after fidaxomicin dosing Figure 3. The maximum plasma concentrations across days for the 24 patients was 22.6 (SD: 30) ng/mL with a range of 5.8 to 154 ng/mL. Plasma concentrations obtained from the PKAS Full Profile were higher due to 1 patient with ulcerative colitis that had relatively high fidaxomicin concentrations during the study period.
- The overall plasma OP-1118 concentrations had a similar profile as fidaxomicin. The maximum plasma concentration across days for the 24 patients in the PKAS was 78 (SD: 112) ng/mL with a range of 13.5 to 555 ng/mL.

- The maximum values for C_{max} of fidaxomicin across days were consistent with the plasma concentrations Table 8. On average, the observed AUC for fidaxomicin in plasma increased between day 1 and day 5, and then decreased slightly at day 10. The observed t_{max} was approximately 1 to 2 hours, but varied widely between 0 and 11.5 hours Table 9.
- All OP-1118 pharmacokinetic results did not showed apparent differences to that of fidaxomicin pharmacokinetic parameters. All results were similar to that of fidaxomicin pharmacokinetic parameters. The mean exposure of OP-1118 was 3.0 (389.1 ng·h/mL/129.1 ng·h/mL) to 4.3 (668.7 ng·h/mL/155.6 ng·h/mL) fold higher than for fidaxomicin Table 10 and Table 11.

Secondary pharmacokinetic results:

- Stool concentrations of fidamoxicin (secondary endpoint) were assessed at days 1, 5 and 10 Table 12. At day 1, a total of 17 patients (10 with Crohn's disease and 7 with ulcerative colitis) had a mean (SD) fidaxomicin stool concentration of 141.34 (243.18) mcg/g, and the stool samples obtained > 12 hours postdose (n = 7) had a mean (SD) fidaxomicin concentration of 305.40 (306.24) mcg/g (range: 17.8 to 804 mcg/g). The concentration increased during the treatment period to a mean (SD) of 749.77 (410.53) mcg/g on day 5 (n = 21) and 844.52 (614.28) mcg/g on day 10 (n = 22).
- Stool concentrations of OP-1118 (secondary endpoint) were assessed at days 1, 5 and 10 Table 13. At day 1, a total of 17 patients (10 with Crohn's disease vs 7 with ulcerative colitis) had a mean (SD) OP-1118 stool concentration of 59.04 (99.37) mcg/g and the stool samples obtained > 12 hours postdose (n = 7) had a mean (SD) OP-1118 concentration of 126.81 (123.29) mcg/g (range: 0 to 318 mcg/g). The concentration increased during the treatment period to a mean (SD) of 495.27 (420.46) mcg/g on day 5 (n = 21) and 466.95 (449.00) mcg/g on day 10 (n = 22).

Efficacy Results (secondary endpoints):

- Clinical response at visit 4, 48 to 72 hours after EoT was observed in 80% of patients (all ulcerative colitis patients and 9/14 Crohn's disease patients) with an overall 95% CI of 60.9%, 91.1% Table 14.
- A total of 13 out of 19 responding patients (68.4%) were negative for *C. difficile* at baseline and included all nonresponding patients (4/4 [100%] Crohn's disease patients and 0 ulcerative colitis patients) and 9 out of 15 responding patients (6/8 [75%] Crohn's disease patients and 3/7 [42.9%] ulcerative colitis patients). At all other visits, all Crohn's disease patients remained negative for *C. difficile* while from visit 5 through visit 7 ulcerative colitis patients (only responders) were found to be positive for *C. difficile* Table 15.
- The overall length of hospital stay for the total number of patients (21 of 25 patients) was on average 32.2 days and 18 patients were hospitalized prior to or at the start of the fidaxomicin therapy. Patients with Crohn's disease (12/14 patients) had a mean hospital stay of 35 days (range: 6 to 146 days) while ulcerative colitis patients had a mean stay of 29 days (range: 1 to 127 days) Table 16.
- The mean (SD) total short IBDQ score was 3.07 (0.92) (range: 1.3 to 4.9). The mean total score increased during the study and at the EoS visit the mean (SD) total score was 4.98 (1.32) (range: 1.9 to 6.7).
    - In the bowel dimension the mean (SD) score at baseline was 3.44 (1.10; range: 1.7 to 5.7) and increased each visit with a mean (SD) score at EoS of 5.28 (1.32; range: 2.7 to 7.0).
    - In the systemic dimension the mean (SD) score at baseline was 2.90 (1.60; range: 1.0 to 6.5) and increased each visit with a mean (SD) score at EoS of 4.60 (1.32; range: 1.0 to 7.0).
    - In the emotional dimension the mean (SD) score at baseline was 3.13 (1.27; range: 1.0 to 6.3) and increased each visit with a mean (SD) score at EoS of 4.83 (1.53; range: 1.7 to 7.0).

- In the social dimension the mean (SD) score at baseline was 2.60 (1.19; range: 1.0 to 4.5) and increased each visit with a mean (SD) score at EoS of 5.10 (1.66; range: 2.0 to 7.0).

Safety Results:

- There were no deaths, SAEs or TEAEs leading to permanent discontinuation of study drug or of the clinical study during the conduct of this clinical study Table 17. Overall, 15 of 25 (60.0%) patients experienced 43 TEAEs up to 30 days after EoT, and 8 serious TEAEs up to 30 days after EoT were experienced by 6 out of 25 (24%) patients. Most events occurred in the SOC of Gastrointestinal (GI) Disorders Table 18 and Table 19.
- A total of 6 of 25 (24%) patients had an AE of special interest. None of the patients were hypersensitive to fidaxomicin or needed an ECG to assess QT interval prolongation. More patients with Crohn's disease (3/14 of patients) had decreased WBC and neutrophil counts. One patient with ulcerative colitis was a potential DILI case Table 20.
- Long term follow-up (> 30 days) after EoT showed that 11 of 25 (44%) patients had 50 AEs of which 1 event was a related AE (1/25 [4%] patient). The main events were for IBD (5 events; 3/25 [12%] patients). One event in the long term follow-up was drug-related (ulnar nerve injury) and experienced by 1 of 25 (4%) patients. A single severe event was reported for colitis ulcerative (1/25 [5.9%] patient with sustained clinical cure Table 21.
- SAEs in the long term follow-up (> 30 days) after EoT were experienced by 7 of 25 (28%) patients. None of the SAEs were drug-related Table 22.
- Clinically significant abnormalities in liver enzymes and total bilirubin were found in samples from 1 patient with ulcerative colitis that were collected at visit 7 (ALT: 20.0 U/L; AST: 29.0 U/L; total billirubin: 16.3 µmol/L; ALP: 80.0) and at an unscheduled visit (ALT: 17.0 U/L; AST: 29.0 U/L; total billirubin: 17.4 µmol/L; ALP: 81.0) to assess recurrence of CDI.
- A total of 10 of 25 (40%) patients experienced 19 drug-related TEAEs up to 30 days after EoT and were most often in the SOC of GI Disorders (4/25 [16%] patients and 10 drug-related TEAEs). The severity was mostly moderate (6 events) or mild (4 events). Severe events were reported for insomnia (1/25 [4%] patients and 1 event), hypoxia (1/25 [4%] patients and 1 event) and skin ulcer (1/25 [4%] patients and 1 event).
- Overall, there were no notable changes in the numbers of abnormal values observed for hematological and biochemistry and most results were within the normal reference range. None of the patients had a body temperature > 38.5°C during any of the study visits.

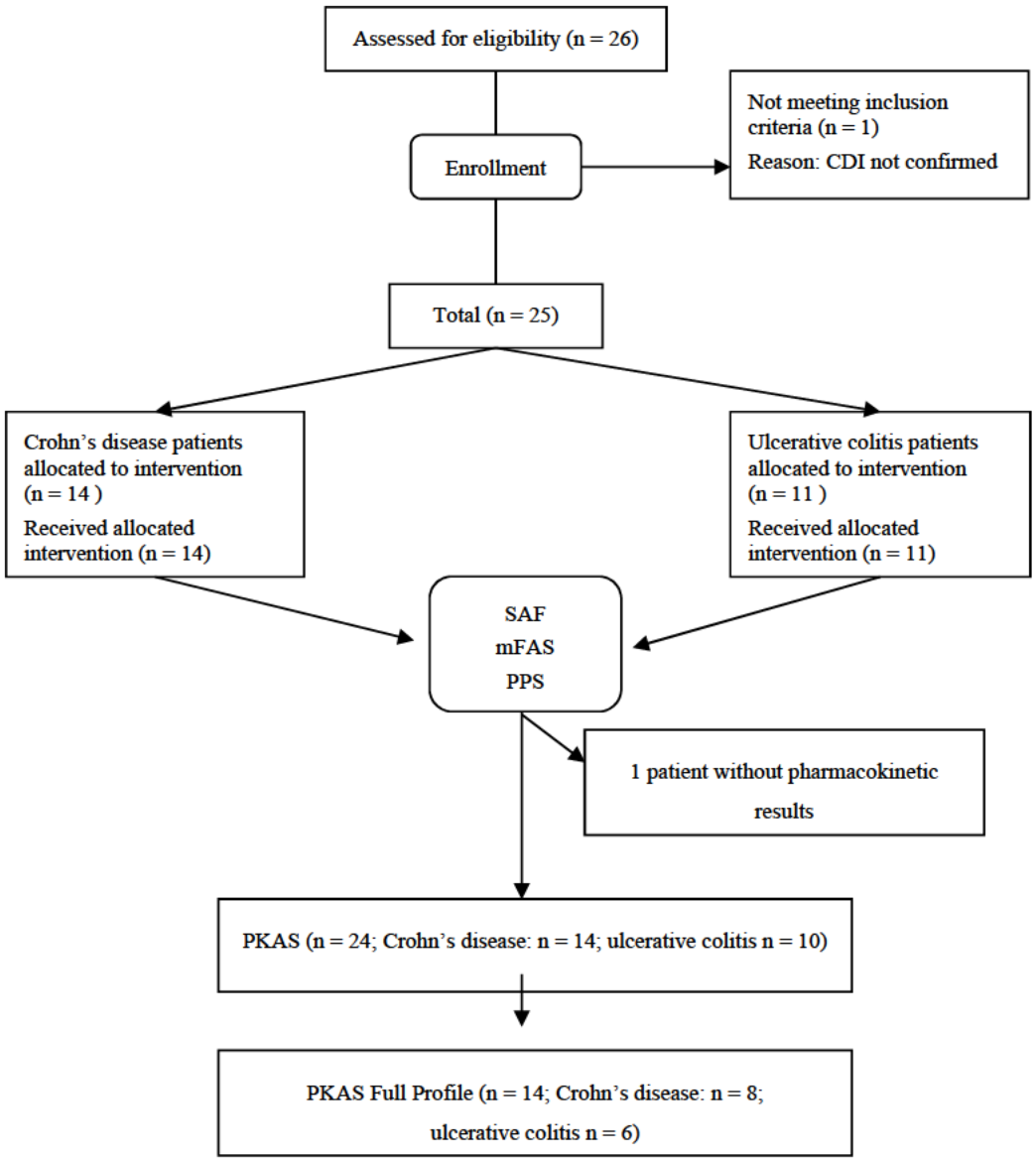
CONCLUSIONS:

- Plasma fidaxomicin concentrations reached a maximum after approximately 3 hours on day 1 and day 10. This peak was higher in the PKAS-Full Profile subset. Overall, plasma OP-1118 concentrations had a similar profile as observed for plasma fidaxomicin. Maximum plasma concentrations of fidaxomicin and its active metabolite OP-1118 in patients with active IBD and CDI were within the measured range of concentration values found in earlier studies of fidaxomicin and OP-1118 involving CDI patients without IBD. This suggests that there was no increase in absorption of fidaxomicin or OP-1118 in this patient population with IBD. The maximum concentration of fidaxomicin measured was 154 ng/mL, which was well below the human equivalent to NOAEL in 3-month dog toxicology studies (3000 ng/mL) and within the range recorded from historical studies of fidaxomicin in non-IBD CDI patients.
- Fidaxomicin and OP-1118 in stool demonstrated that mean concentration of these tended to be higher in Crohn's disease than in ulcerative colitis patients and attained supra-therapeutic levels within the GI tract, and the data showed that mean fecal concentrations consistently have a factor of 2 to 3 log greater than the minimum inhibitory concentrations.
- Assessment of initial clinical response based on local standards suggested high rates of efficacy in both Crohn's disease (9/14; 64.3%) and ulcerative colitis (11/11; 100%) patients at day 12, i.e., 2 days after EoT. This was accompanied by a reduction in mean stool frequency for responders over the treatment period versus an increase in the mean stool frequency for non-responders, all of whom were Crohn's disease patients. Interestingly, the Bristol stool chart scores did not change significantly during this time, highlighting the clinical challenges in assessing response to therapy in this patient population.
- Disease activity assessment revealed a reduction in the Partial Mayo Score for ulcerative colitis patients over the treatment period, mirroring the initial clinical response; however, through day 180, 5 of 11 patients had elevations in disease activity score suggesting IBD flare. This occurred in association with recurrence of CDI in 1 patient, and the remaining 4 patients were found to have generally more extensive ulcerative colitis disease and a higher frequency of IBD flare at baseline. Of the Crohn's disease patients, 6 of 9 responders experienced a reduction in HBI score of >3 units, with only 1 of 5 nonresponders having a similar change at day 10.
- There were 6 patients that neither had toxin nor organism information for screening from the central laboratory (1 nonresponder) due to missing samples. Eight patients did not have *C difficile* detected (neither toxin nor organism) by the central laboratory (1 nonresponder). *C. difficile* was detected (organism with or without toxin) in 11 patients by the central laboratory (3 nonresponders). All enrolled patients had a positive local test for CDI. The accuracy of subsequent evaluations that were performed by a central lab may have been compromised by sample degradation during storage or shipment to the testing facility. Additional microbiological analysis (to be provided separately) may help to explain, for example, the observed low levels of CDI positivity at baseline in the central laboratory tests.
- Fidaxomicin was well tolerated in this small patient population as most AEs were mild or moderate in severity and there were no instances of hypersensitivity or AEs that resulted in discontinuation of fidaxomicin treatment.

Date of Report:

01 Aug 2017

Figure 1 Disposition of Subjects



CDI: *Clostridium difficile* infection; IBD: inflammatory bowel disease; mFAS: modified full analysis set; PK: pharmacokinetic; PKAS: pharmacokinetic analysis set; PP: per protocol analysis set; SAF: safety analysis set.

Source: Tables 12.1.1.1, 12.1.1.2 and 12.1.1.3 and Appendix 13.2.1.1

Table 1 Patient Disposition and Analysis Sets

Analysis Set	Crohn's Disease (n = 14) n (%)	Ulcerative Colitis (n = 11) n (%)	Total (n = 25) n (%)
Safety analysis set †	14 (100)	11 (100)	25 (100)
Modified full analysis set	14 (100)	11 (100)	25 (100)
Per protocol set	14 (100)	11 (100)	25 (100)
Pharmacokinetic analysis set (all patients)	14 (100)	10 (90.9)	24 (96)
Pharmacokinetic analysis set Full Profile	8 (57.1)	6 (54.5)	14 (56)
Treatment discontinuation			
Yes	0	0	0
No	14 (100)	11 (100.0)	25 (100)
Study discontinuation			
Yes	3 (21.4)	1 (9.1)	4 (16)
No	11 (78.6)	10 (90.9)	21 (84)

IBD: inflammatory bowel disease; SAF: safety analysis set.

† All patients who received at least 1 dose of study drug (SAF), for whom sufficient serum concentration data was available to facilitate derivation of at least 1 primary pharmacokinetic parameter

Source: Tables 12.1.1.1, 12.1.1.2, 12.1.1.3 and 12.1.1.4 and Appendices 13.2.1 and 13.2.3.1

Table 2 Summary of Demographics and Baseline Characteristics (SAF)

Parameter Category/ Statistics	Crohn's Disease (n = 14) n (%)	Ulcerative Colitis (n = 11) n (%)	Total (n = 25) n (%)
Sex			
Male	8 (57.1)	5 (45.5)	13 (52)
Female	6 (42.9)	6 (54.5)	12 (48)
Race			
White	13 (100)	9 (90)	22 (95.7)
Black	0	0	0
Asian	0	1 (10)	1 (4.3)
Other	0	0	0
Missing	1	1	2
Age, years			
Mean (SD)	35.4 (10.9)	43.3 (21.6)	38.9 (16.5)
Median	34.5	32.0	32.0
Min to Max	19 to 55	21 to 81	19 to 81
Age categories, years			
18 to 64	14 (100)	8 (72.7)	22 (88)
65 to 74	0	1 (9.1)	1 (4)
> 74	0	2 (18.2)	2 (8)
Weight (kg)			
Mean (SD)	67.49 (16.40)	62.25 (12.29)	65.18 (14.68)
Median	65.00	68.00	66.00
Min to Max	43.0 to 96.0	45.0 to 79.7	43.0 to 96.0
Height (cm)			
Mean (SD)	175.14 (9.31)	170.36 (8.55)	173.04 (9.13)
Median	176.00	172.00	175.00
Min to Max	158.0 to 192.0	160.0 to 183.0	158.0 to 192.0
BMI (kg/m^2)			
Mean (SD)	22.09 (5.88)	21.35 (3.39)	21.76 (4.87)
Median	20.50	20.60	20.60
Min to Max	14.6 to 35.2	17.2 to 27.3	14.6 to 35.2
BMI (kg/m^2) categories			
< 18.5	4 (28.6)	3 (27.3)	7 (28)
18.5 to < 25	7 (50)	6 (54.5)	13 (52)
25 to < 30	1 (7.1)	2 (18.2)	3 (12)
≥ 30	2 (14.3)	0	2 (8)
Baseline CDI Severity by ESCMID Score			
Severe	2 (14.3)	5 (45.5)	7 (28)
Non severe	12 (85.7)	6 (54.5)	18 (72)
Physical examinations [§]	0	0	0
Laboratory examinations			
Marked leucocytosis	2 (14.3)	2 (18.2)	4 (16)
Marked left shift	0	0	0
Rise in serum creatinine	0	0	0
Elevated serum lactate	0	0	0
Markedly reduced serum albumin	1 (7.1)	2 (18.2)	3 (12)
Colonoscopy or sigmoidoscopy			
Pseudomembranous colitis	0	2 (18.2)	2 (8)

Table continued on next page

Parameter Category/ Statistics	Crohn's Disease (n = 14) n (%)	Ulcerative Colitis (n = 11) n (%)	Total (n = 25) n (%)
Imaging			
Distention of large intestine	0	0	0
Colonic wall thickening	0	1 (9.1)	1 (4)
Pericolonic fat stranding	0	0	0
Ascites	0	0	0
Number of previous CDI episodes †			
0	12 (85.7)	8 (72.7)	20 (80)
1	2 (14.3)	3 (27.3)	5 (20)
≥ 2	0	0	0
Use of antibiotics for conditions other than CDI within 90 days prior to enrollment	3 (21.4)	7 (63.6)	10 (40)
Use of antibiotics for any reason within 90 days prior to enrollment	4 (28.6)	8 (72.7)	12 (48)
Use of antibiotics for CDI within 90 days prior to enrollment	1 (7.1)	4 (36.4)	5 (20)
Use of antibiotics for CDI within 90 days prior to enrollment, preferred WHO name			
Metronidazole	1 (7.1)	2 (18.2)	3 (12)
Rifaximin	0	1 (9.1)	1 (4)
Vancomycin	0	3 (27.3)	3 (12)
Use of antibiotics 2 days prior to first study drug intake	1 (7.1)	1 (9.1)	2 (8)
Use of medications for the treatment of diarrhea ‡	13 (92.9)	11 (100)	24 (96)
Number of UBMs ‡			
n	14	10	24
Mean (SD)	6.2 (3.7)	6.6 (3.5)	6.4 (3.5)
Median	6.0	6.5	6.0
Min to Max	3 to 15	3 to 15	3 to 15

SAF: All patients who received at least 1 dose of study drug

BMI: is calculated as body weight in kilograms divided by height in meters squared

BMI: body mass index; CDI: *Clostridium difficile*; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; Max: maximum; Min: minimum; NA: not applicable; SAF: safety analysis set; UBMs: unformed bowel movements.

† The number of previous CDI episodes was derived from the general medical history page for the time period of 90 days prior to enrollment.

‡ In the last 24 hours before treatment allocation.

§ All results for physical examination (fever, rigors, hemodynamic instability, respiratory failure, signs and symptoms of peritonitis and signs and symptoms of ileus) were 0 in both patients with Crohn's disease and ulcerative colitis.

¶ Data for race was not provided by all patients as information on race was not allowed to be collected in some sites/countries (a total of 2 patients were classified as "missing").

Source: Tables 12.1.2.1.1, 12.1.2.2.1

Table 3 Summary of Baseline Characteristics by IBD Type (SAF)

Parameter Category/ Statistics	**Crohn's Disease (n = 14) n (%)**	**Ulcerative Colitis (n = 11) n (%)**	**Total (n = 25) n (%)**
Partial Mayo Score total	NA	11	11
Mean (SD)	NA	5.3 (1.6)	5.3 (1.6)
Median	NA	5.0	5.0
Min to Max	NA	3 to 8	3 to 8
Partial Mayo Score total categories			
≤ 1 (with rectal bleeding score 0 [remission])	NA	0	0
2 to 6 (mild – moderate disease) or a score of 1 due to rectal bleeding	NA	9 (81.8)	9 (36)
≥ 7 (severe disease)	NA	2 (18.2)	2 (8)
Partial Mayo Score stool			
Normal numbers of stools for patient	NA	0	0
1 to 2 stools per day more than normal	NA	1 (9.1)	1 (4)
3 to 4 stools more than normal	NA	4 (36.4)	4 (16)
≥ 5 stools more than normal	NA	6 (54.5)	6 (24)
Partial Mayo Score rectal bleeding			
No blood seen	NA	3 (27.3)	3 (12)
Streaks of blood with stool most of the time	NA	4 (36.4)	4 (16)
Obvious blood with stool most of the time	NA	3 (27.3)	3 (12)
Blood alone passes	NA	1 (9.1)	1 (40)
Partial Mayo endoscopic findings			
Normal or inactive disease	NA	0	0
Mild disease	NA	0	0
Moderate disease	NA	2 (18.2)	2 (8)
Severe disease	NA	1 (9.1)	1 (4)
Partial Mayo physician's global assessment			
Normal	NA	0	0
Mild disease	NA	5 (45.5)	5 (20)
Moderate disease	NA	5 (45.5)	5 (20)
Severe disease	NA	1 (9.1)	1 (4)
Harvey Bradshaw index total score	14	NA	14
Mean (SD)	10.2 (4.7)	NA	10.2 (4.7)
Median	8.0	NA	8.0
Min to Max	5 to 20	NA	5 to 20
Harvey Bradshaw index total score categories			
< 5 (remission)	0	NA	0
5 to 7 (mild disease)	6 (42.9)	NA	6 (24)
8 to 16 (moderate disease)	6 (42.9)	NA	6 (24)
16 (severe disease)	2 (14.3)	NA	2 (8)
Harvey Bradshaw index general well-being (yesterday)			
Very well	0	NA	0
Slightly below par	5 (35.7)	NA	5 (20)
Poor	5 (35.7)	NA	5 (20)
Very poor	2 (14.3)	NA	2 (8)
Terrible	2 (14.3)	NA	2 (8)

Table continued on next page

Parameter **Category/ Statistics**	**Crohn's Disease (n = 14) n (%)**	**Ulcerative Colitis (n = 11) n (%)**	**Total (n = 25) n (%)**
Harvey Bradshaw index abdominal pain (yesterday)			
None	2 (14.3)	NA	2 (8)
Mild	5 (35.7)	NA	5 (20)
Moderate	6 (42.9)	NA	6 (24)
Severe	1 (7.1)	NA	1 (4)
Harvey Bradshaw index number of soft stools per day (yesterday)			
	14	NA	14
Mean (SD)	6.1 (3.8)	NA	6.1 (3.8)
Median	5.5	NA	5.5
Min to Max	3 to 15	NA	3 to 15
Harvey Bradshaw index abdominal mass			
None	13 (92.9)	NA	13 (52)
Dubious	1 (7.1)	NA	1 (4)
Definite	0	NA	0
Definite and tender	0	NA	0
Harvey Bradshaw index complications			
None	9 (64.3)	NA	9 (36)
Arthralgia	6 (42.9)	NA	6 (24)
Aphthous ulcers	1 (7.1)	NA	1 (4)
Anal fissure	1 (7.1)	NA	1 (4)
Charlson co-morbidity index score	14	11	25
Mean (SD)	0.9 (1.2)	1.7 (2.6)	1.3 (2)
Median	0.5	0	0
Min to Max	0 to 4	0 to 8	0 to 8
Type of hospitalization			
Intensive care unit	0	0	0
Non-intensive care unit	11 (78.6)	7 (63.6)	18 (72)
Type of hospital ward			
Isolated	1 (7.1)	1 (9.1)	2 (8)
Non-isolated	10 (71.4)	6 (54.5)	16 (64)

SAF: All patients who received at least 1 dose of study drug.

BMI: Is calculated as body weight in kilograms divided by height in meters squared

BMI: body mass index; CDI: *Clostridium difficile* infection; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; Max: maximum; Min: minimum; NA: not applicable; SAF: safety analysis set; UBMs: unformed bowel movements.

Source: Table 12.1.2.2.1

Table 4 Summary of Demographics and Baseline Characteristics (PKAS Full Profile)

Parameter Category/ Statistics	Crohn's Disease (n = 8) n (%)	Ulcerative Colitis (n = 6) n (%)	Total (n = 14) n (%)
Sex			
Male	4 (50)	2 (33.3)	6 (42.9)
Female	4 (50)	4 (66.6)	8 (57.1)
Race			
White	7 (100)	6 (100)	13 (100)
Black	0	0	0
Asian	0	0	0
Other	0	0	0
Missing	1	0	1
Age, years			
Mean (SD)	31.6 (9)	37.0 (17.7)	33.9 (13.1)
Median	30.5	30.5	30.5
Min to Max	19 to 47	21 to 66	19 to 66
Age categories, years			
18 to 64	8 (100)	5 (83.3)	13 (92.9)
65 to 74	0	1 (16.7)	1 (7.1%)
> 74	0	0	0
Weight (kg)			
Mean (SD)	70.63 (17.06)	58.17 (12.06)	65.29 (15.92)
Median	67.00	59.50	66.00
Min to Max	43.0 to 96.0	45.0 to 70.0	43.0 to 96.0
Height (cm)			
Mean (SD)	174.63 (11.65)	168.50 (9.95)	172.00 (11)
Median	176.00	166.00	173.00
Min to Max	158.0 to 192.0	160.0 to 183.0	158.0 to 192.0
BMI (kg/m^2)			
Mean (SD)	23.39 (6.70)	20.45 (3.85)	22.13 (5.67)
Median	20.95	19.30	20.70
Min to Max	17.2 to 35.2	17.2 to 27.3	17.2 to 35.2
Baseline CDI Severity by ESCMID Score			
Severe	1 (12.5)	4 (66.6)	5 (35.7)
Non severe	7 (87.5)	2 (33.3)	9 (64.3)
Physical examinations [§]	0	0	0
Laboratory examinations			
Marked leucocytosis	1 (12.5)	2 (33.3)	3 (21.4)
Marked left shift	0	0	0
Rise in serum creatinine	0	0	0
Elevated serum lactate	0	0	0
Markedly reduced serum albumin	1 (12.5)	1 (16.7)	2 (14.3)
Colonoscopy or sigmoidoscopy			
Pseudomembranous colitis	0	2 (33.3)	2 (14.3)
Imaging, n (%)			
Distention of large intestine	0	0	0
Colonic wall thickening	0	1 (16.7)	1 (7.1)
Pericolonic fat stranding	0	0	0
Ascites	0	0	0

Table continued on next page

Parameter Category/ Statistics	Crohn's Disease (n = 8) n (%)	Ulcerative Colitis (n = 6) n (%)	Total (n = 14) n (%)
Number of previous CDI episodes †			
0	7 (87.5)	3 (50)	10 (71.4)
1	1 (12.5)	3 (50)	4 (28.6)
≥ 2	0	0	0
Use of antibiotics for conditions other than CDI within 90 days prior to enrollment			
Yes	0	5 (83.3)	5 (35.7)
No	8 (100)	1 (16.7)	9 (64.3)
Use of antibiotics for any reason within 90 days prior to enrollment			
Yes	1 (12.5)	6 (100)	7 (50)
No	7 (87.5)	0	7 (50)
Use of antibiotics for CDI within 90 days prior to enrollment			
Yes	1 (12.5)	4 (66.7)	5 (35.7)
No	7 (87.5)	2 (33.3)	9 (64.3)
Use of antibiotics for CDI within 90 days prior to enrollment, preferred WHO name			
Metronidazole	1 (12.5)	2 (33.3)	3 (21.4)
Rifaximin	0	1 (16.7)	1 (7.1)
Vancomycin	0	3 (50)	3 (21.4)
Use of antibiotics 2 days prior to first study drug intake			
Yes	0	0	0
No	8 (100)	6 (100)	14 (100)
Use of medications for the treatment of diarrhea ‡			
Yes	8 (100)	6 (100)	14 (100)
No	0	0	0
Number of UBMs ‡	8	6	14
Mean (SD)	6.9 (4.4)	7.0 (4.6)	6.9 (4.3)
Median	6.0	6.0	6.0
Min to Max	3 to 15	3 to 15	3 to 15

Patients in the PKAS Full Profile included only those patients who participated in the full pharmacokinetics sampling profile and had sufficient plasma concentration data available to facilitate the measurement of at least 1 maximum plasma concentration (day 1, day 5 or day 10) for fidaxomicin and its metabolite OP-1118, and for whom the time of dosing on the day of sampling was known.

BMI: is calculated as body weight in kilograms divided by height in meters squared.

BMI: body mass index; CDI: *Clostridium difficile* infection;; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; Max: maximum; Min: minimum; NA: not applicable; PKAS: pharmacokinetic analysis set; SAF: safety analysis set; UBMs: unformed bowel movements.

† The number of previous CDI episodes was derived from the general medical history page for the time period of 90 days prior to enrollment.

‡ In the last 24 hours before treatment allocation.

§ All results for physical examination (fever, rigors, hemodynamic instability, respiratory failure, signs and symptoms of peritonitis and signs and symptoms of ileus) were 0 in both patients with Crohn's disease and ulcerative colitis.

¶ Data for race was not provided by all patients as information on race was not allowed to be collected in some sites/countries (a total of 1 patient were classified as "missing").

Source: Tables 12.1.2.1.3, 12.1.2.2.3

Table 5 Summary of Baseline Characteristics by IBD Type (PKAS Full Profile)

Parameter Category/ Statistics	Crohn's Disease (n = 8) n (%)	Ulcerative Colitis (n = 6) n (%)	Total (n = 14) n (%)
Partial Mayo Score total (n)	NA	6	6
Mean (SD)	NA	4.3 (1.2)	4.3 (1.2)
Median	NA	4.5	4.5
Min to Max	NA	3 to 6	3 to 6
Partial Mayo Score total categories			
≤ 1 (with rectal bleeding score 0 [remission])	NA	0	0
2 to 6 (mild to moderate disease) or a score of 1 due to rectal bleeding	NA	6 (100)	6 (42.9)
≥ 7 (severe disease)	NA	0	0
Partial Mayo Score stool			
Normal number of stools for patient	NA	0	0
1 to 2 stools per day more than normal	NA	1 (16.7)	1 (7.1)
3 to 4 stools more than normal	NA	2 (33.3)	3 (14.3)
≥ 5 stools more than normal	NA	3 (50)	3 (21.4)
Partial Mayo Score rectal bleeding			
No blood seen	NA	3 (50)	3 (21.4)
Streaks of blood with stool most of the time	NA	3 (50)	3 (21.4)
Obvious blood with stool most of the time	NA	0	0
Blood alone passes	NA	0	0
Partial Mayo endoscopic findings			
Normal or inactive disease	NA	0	0
Mild disease	NA	0	0
Moderate disease	NA	0	0
Severe disease	NA	1 (16.7)	1 (7.1)
Partial Mayo physician's global assessment			
Normal	NA	0	0
Mild disease	NA	3 (50)	3 (21.4)
Moderate disease	NA	3 (50)	3 (21.4)
Severe disease	NA	0	0
Harvey Bradshaw index total score	8	NA	8
Mean (SD)	11.4 (5.4)	NA	11.4 (5.4)
Median	9.5	NA	9.5
Min to Max	5 to 20	NA	5 to 20
Harvey Bradshaw index total score categories			
< 5 (remission)	0	NA	0
5 to 7 (mild disease)	2 (25)	NA	2 (14.3)
7 to 16 (moderate disease)	4 (50)	NA	4 (28.6)
16 (severe disease)	2 (25)	NA	2 (14.3)
Harvey Bradshaw index general well-being (yesterday)			
Very well	0		0
Slightly below par	3 (37.5)	NA	3 (21.4)
Poor	2 (25)	NA	2 (14.3)
Very poor	1 (12.5)	NA	1 (7.1)
Terrible	2 (25)	NA	2 (14.3)

Table continued on next page

Parameter Category/ Statistics	Crohn's Disease (n = 8) n (%)	Ulcerative Colitis (n = 6) n (%)	Total (n = 14) n (%)
Harvey Bradshaw index abdominal pain (yesterday)			
None	1 (12.5)	NA	1 (7.1)
Mild	2 (25)	NA	2 (14.3)
Moderate	4 (50)	NA	4 (28.6)
Severe	1 (12.5)	NA	1 (7.1)
Harvey Bradshaw index number of soft stools per day (yesterday)	8	NA	8
Mean (SD)	6.8 (4.4)	NA	6.8 (4.4)
Median	5.5	NA	5.5
Min to Max	3 to 15	NA	3 to 15
Harvey Bradshaw index abdominal mass			
None	7 (87.5)	NA	7 (50)
Dubious	1 (12.5)	NA	1 (7.1)
Definite	0	NA	0
Definite and tender	0	NA	0
Harvey Bradshaw index complications			
None	5 (62.5)	NA	5 (35.7)
Arthralgia	3 (37.5)	NA	3 (21.4)
Aphthous ulcers	1 (12.5)	NA	1 (7.1)
Anal fissure	1 (12.5)	NA	1 (7.1)
Charlson co-morbidity index score	8	6	14
Mean (SD)	0.8 (0.9)	1.0 (1.3)	0.9 (1.0)
Median	0.5	0.5	0.5
Min to Max	0 to 2	0 to 3	0 to 3
Type of hospitalization			
Intensive care unit	0	0	0
Non-intensive care unit	6 (75.0)	4 (66.7)	10 (71.4)
Type of hospital ward			
Isolated	1 (12.5)	1 (16.7)	2 (14.3)
Non-isolated	5 (62.5)	3 (50)	8 (57.1)

PKAS Full Profile: Patients in the PKAS Full Profile included only those patients who participated in the full pharmacokinetic sampling profile and had sufficient plasma concentration data available to facilitate the measurement of at least 1 maximum plasma concentration (day 1, day 5 or day 10) for fidaxomicin and its metabolite OP-1118, and for whom the time of dosing on the day of sampling was known.

BMI: is calculated as body weight in kilograms divided by height in meters squared

BMI: body mass index; CDI: *Clostridium difficile* infection; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; Max: maximum; Min: minimum; NA: not applicable; PKAS: pharmacokinetic analysis set; UBMs: unformed bowel movements.

Source: Table 12.1.2.2.3

Table 6 Additional IBD Specific Medical History by IBD Type (SAF)

Parameter	Category/Statistic	Crohn's Disease (n = 14) n (%)	Ulcerative Colitis (n = 11) n (%)	Total (n = 25) n (%)
Ulcerative colitis extent	Proctitis (E1)	NA	1 (9.1)	NA
	Left-sided - extending to the splenic flexure (E2)	NA	1 (9.1)	NA
	More extensive disease (E3)	NA	9 (81.8)	NA

Table continued on next page

Parameter	Category/Statistic	Crohn's Disease (n = 14) n (%)	Ulcerative Colitis (n = 11) n (%)	Total (n = 25) n (%)
Crohn's disease age category for onset	≤ 16 years (A1)	4 (28.6)	NA	NA
	17 to 40 years (A2)	6 (42.9)	NA	NA
	> 40 years (A3)	4 (28.6)	NA	NA
Crohn's disease location †‡	Ileal (L1)	7 (50)	NA	NA
	Colonic (L2)	1 (7.1)	NA	NA
	Ileo colonic (L3)	6 (42.9)	NA	NA
	Isolated upper gastrointestinal disease (L4) ‡	1 (7.1)	NA	NA
Crohn's disease behavior	Non-stricturing nonpenetrating (B1)	8 (57.1)	NA	NA
	Stricturing (B2)	4 (28.6)	NA	NA
	Penetrating (B3)	2 (14.3)	NA	NA
Time since diagnosis (years)	Mean (SD)	4.7 (7.45)	5.9 (3.31)	5.2 (5.92)
	Median	1.2	6.2	2.9
	Min to Max	0 to 28	1 to 10	0 to 28
Average frequency of flares per year	Mean (SD)	2. 0 (1.24)	1.7 (0.79)	1.9 (1.05)
	Median	2.0	2.0	2.0
	Min to Max	0 to 4	1 to 3	0 to 4
Extraintestinal manifestations by IBD type §	Crohn's disease	14 (100)	0	14 (56)
	Ulcerative colitis	0	11 (100)	11 (44)
	Arthritis	5 (35.7)	2 (18.2)	7 (28)
	Aphthous ulcers	1 (7.1)	0	1 (4)
	Kidney stones	1 (7.1)	1	1 (4)
	Gall stones	2 (14.3)	1 (9.1)	3 (12)
	Urinary tract infection	0	2 (18.2)	2 (8)
Disease symptoms of IBD	Abdominal cramps and pain	13 (92.9)	10 (90.9)	23 (92)
	Diarrhea	14 (100)	9 (81.8)	23 (92)
	Blood in the stool	6 (42.9)	9 (81.8)	15 (60)
	Severe urgency to have a bowel movement	7 (50)	9 (81.8)	16 (64)
	Weight loss	9 (64.3)	8 (72.7)	17 (68)
	Loss of appetite	9 (64.3)	6 (54.5)	15 (60)
	Fever	3 (21.4)	1 (9.1)	4 (16)
	Fatigue	9 (64.3)	8 (72.7)	17 (68)
	Joint pain	7 (50)	2 (18.2)	9 (36)
Baseline frequency of UBMs per day	Mean (SD)	2.6 (2.24)	1.8 (1.40)	2.3 (1.93)
	Median	2.0	2.0	2.0
	Min to Max	0 to 7	0 to 4	0 to 7

SAF: All patients who received at least 1 dose of study drug.

IBD: inflammatory bowel disease; Max: maximum; Min: minimum; NA: not applicable; SAF: safety analysis set; UBMs: unformed bowel movements.

† Two Crohn's disease patients also had perianal disease and ileocolonic L3 locations

‡ Crohn's disease patient also had isolated upper gastrointestinal disease in addition to ileo colonic disease.

§ Results for extraintestinal manifestations were 0 for the following indications in both Crohn's disease and ulcerative colitis patients: stomatitis, uveitis, episcleritis, erythema nodosum, ankylosing spondylitis, psoriasis, pyoderma gangrenosum and primary sclerosing cholangitis hepatic.

Source: Table 12.1.4.1

Table 7 Additional IBD Specific Medical History by IBD Type (PKAS Full Profile)

Parameter	Category/Statistic	Crohn's Disease (n = 8) n (%)	Ulcerative Colitis (n = 6) n (%)	Total (n = 14) n (%)
Ulcerative colitis extent	Proctitis (E1)	NA	1 (16.7)	NA
	Left-sided - extending to the splenic flexure (E2)	NA	0	NA
	More extensive disease (E3)	NA	5 (83.3)	NA
Crohn's disease age category for onset	≤ 16 years (A1)	2 (25)	NA	NA
	17 to 40 years (A2)	5 (62.5)	NA	NA
	> 40 years (A3)	1 (12.5)	NA	NA
Crohn's disease location †	Ileal (L1)	5 (62.5)	NA	NA
	Colonic (L2)	1 (12.5)	NA	NA
	Ileo colonic (L3)	2 (25)	NA	NA
	Isolated upper gastrointestinal disease (L4)	0	NA	NA
Crohn's disease behavior	Non-stricturing nonpenetrating (B1)	6 (75)	NA	NA
	Stricturing (B2)	1 (12.5)	NA	NA
	Penetrating (B3)	1 (12.5)	NA	NA
Time since diagnosis (years)	Mean (SD)	3.3 (3.58)	5.2 (3.53)	4.1 (3.55)
	Median	1.3	5.1	2.7
	Min to Max	0 to 10	1 to 10	0 to 10
Average frequency of flares per year	Mean (SD)	2.0 (1.31)	1.3 (0.52)	1.7 (1.07)
	Median	1.5	1.0	1.0
	Min to Max	1 to 4	1 to 2	1 to 4
Extraintestinal manifestations by IBD type ‡	Crohn's disease	8 (100)	0	8 (57.1)
	Ulcerative colitis	0	6 (100)	6 (42.9)
	Arthritis	2 (25)	0	2 (14.3)
	Aphthous ulcers	1 (12.5)	0	1 (7.1)
Disease symptoms of IBD	Abdominal cramps and pain	8 (100)	5 (83.3)	13 (92.9)
	Diarrhea	8 (100)	4 (66.7)	12 (85.7)
	Blood in the stool	3 (37.5)	4 (66.7)	7 (50)
	Severe urgency to have a bowel movement	3 (37.5)	4 (66.7)	7 (50)
	Weight loss	5 (62.5)	4 (66.7)	9 (64.3)
	Loss of appetite	5 (62.5)	4 (66.7)	9 (64.3)
	Fever	2 (25)	1 (16.7)	3 (21.4)
	Fatigue	6 (75)	4 (66.7)	10 (71.4)
	Joint pain	4 (50)	0	4 (28.6)
Baseline frequency of UBMs per day	Mean (SD)	1.4 (1.19)	1.5 (1.52)	1.4 (1.28)
	Median	1.0	1.5	1.0
	Min to Max	0 to 3	0 to 4	0 to 4

Footnotes appear on next page

PKAS: consisted of the subset of the safety analysis set (SAF) population for which at least 1 blood plasma measurement of fidaxomicin and its metabolite OP-1118, regardless of whether the value of the measurement was above or below lower limit of quantification and whether the patient had a full pharmacokinetic sampling profile or a limited pharmacokinetic sampling profile.

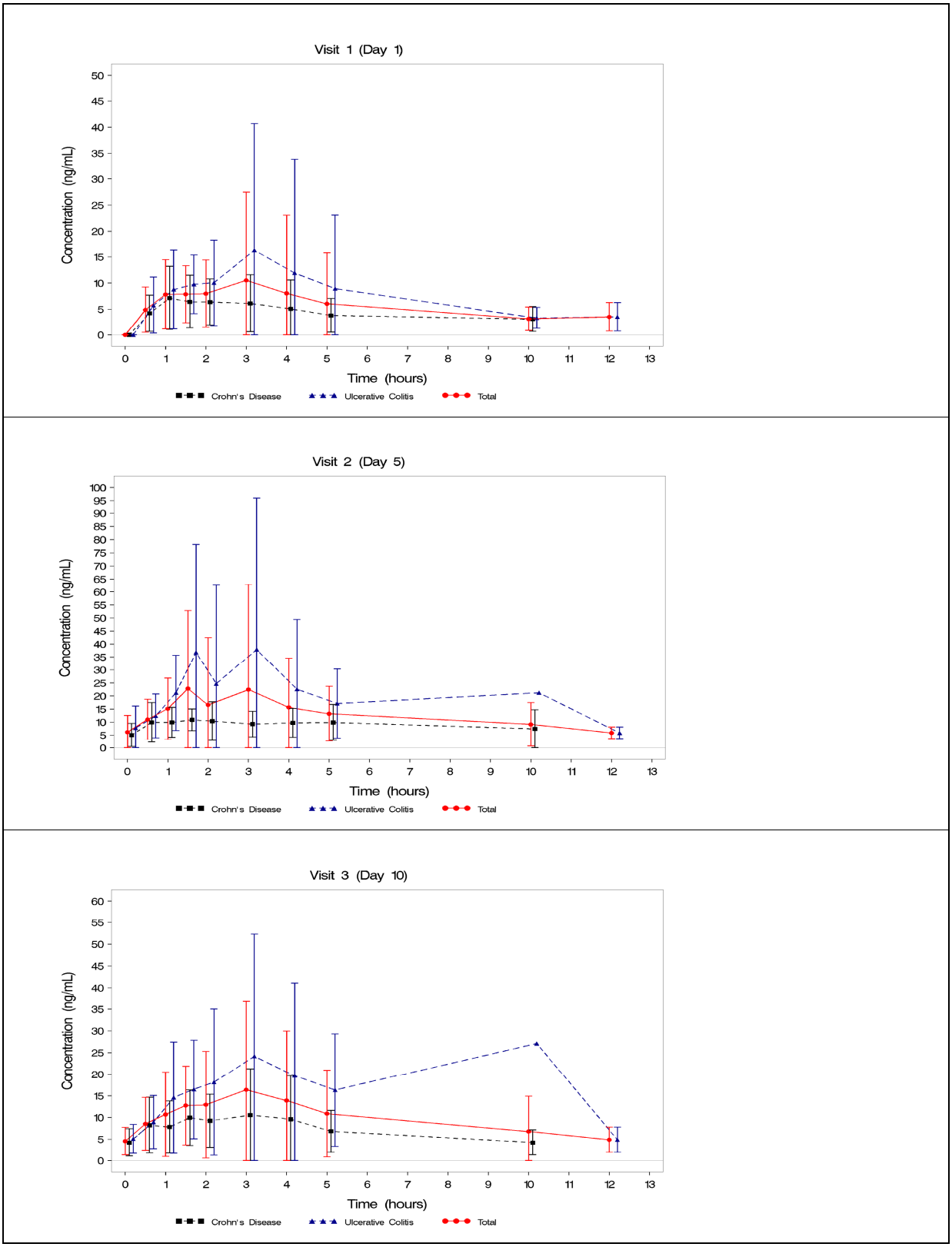
IBD: inflammatory bowel disease; Max: maximum; Min: minimum; NA: not applicable;
PKAS: pharmacokinetic analysis set; UBMs: unformed bowel movements.

† One Crohn's disease patients also had perianal disease (ileocolonic L3 location)

‡ Results for extraintestinal manifestations were 0 for the following indications in both Crohn's disease and ulcerative colitis patients: stomatitis, uveitis, episcleritis, erythema nodosum, ankylosing spondylitis, psoriasis, pyoderma gangrenosum, primary sclerosing cholangitis hepatic, steatitis, gall stones, urinary tract infection and kidney stones.

Source: Table 12.1.4.3

Figure 2 Mean (SD) Plasma Concentration of Fidaxomicin, by IBD Type (PKAS All Patients)



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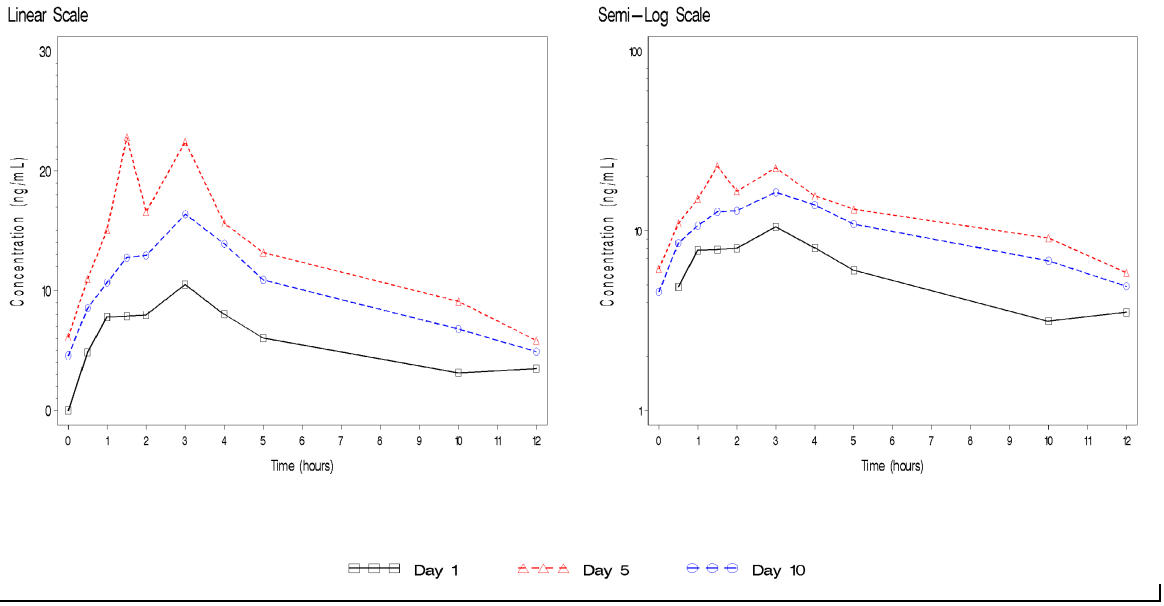
PKAS: consisted of the subset of the safety analysis set (SAF) population for which at least 1 blood plasma measurement of fidaxomicin and its metabolite OP-1118, regardless of whether the value of the measurement was above or below lower limit of quantification and whether the patient had a full pharmacokinetic sampling profile or a limited pharmacokinetic sampling profile.

IBD: inflammatory bowel disease; PKAS: pharmacokinetic analysis set.

Source: Figure 12.4.3.1

Figure 3 **Mean (SD) Plasma Concentration of Fidaxomicin (Linear and Semi-Log Scale Plot), At Day 1, 5 and 10 (PKAS-Full Profile)**

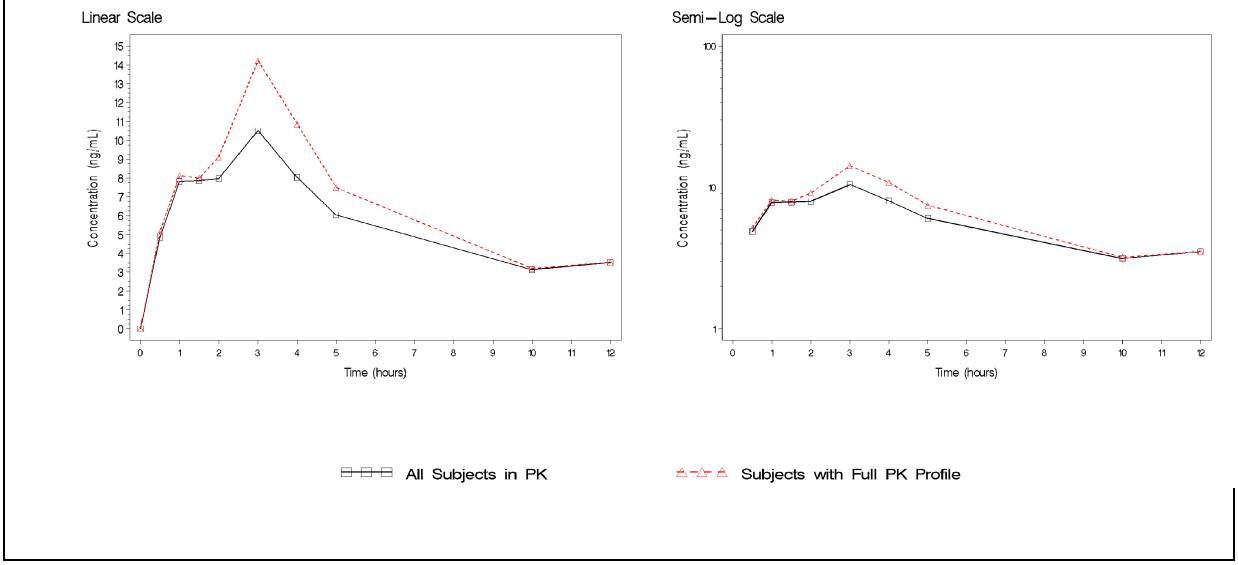


PKAS-Full Profile: a subset of the PKAS which included only those patients who participated in the full pharmacokinetic sampling profile and had sufficient plasma concentration data available to facilitate measurement of at least 1 maximum plasma concentration (day 1, day 5 or day10) for fidaxomicin and its metabolite OP-1118 and for whom the time of dosing on the day of sampling was known.

PKAS-FP: pharmacokinetic Full Profile analysis set.

Source: Figure 12.4.4.1

Figure 4 **Mean (SD) Plasma Concentration of Fidaxomicin (Linear and Semi-Log Scale Plot), At Day 1 (PKAS all patients vs PKAS-Full Profile)**



PKAS: consisted of the subset of the safety analysis set (SAF) population for which at least 1 blood plasma measurement of fidaxomicin and its metabolite OP-1118, regardless of whether the value of the measurement was above or below lower limit of quantification and whether the patient had a full pharmacokinetic sampling profile or a limited pharmacokinetic sampling profile.

PKAS-FP: a subset of the PKAS which included only those patients who participated in the full pharmacokinetic sampling profile and had sufficient plasma concentration data available to facilitate measurement of at least 1 maximum plasma concentration (day 1, day 5 or day10) for fidaxomicin and its metabolite OP-1118 and for whom the time of dosing on the day of sampling was known.

IBD: inflammatory bowel disease; PKAS: pharmacokinetic analysis set; PKAS FP: pharmacokinetic Full Profile analysis set.

Source: Figure 12.4.4.2

Table 8 **Maximum Plasma Concentration of Fidaxomicin Day 1, 5, 10 and Overall, (PKAS All Patients)**

Parameter Statistic	Day 1	Day 5	Day 10	Maximum across days
C_{max} (ng/mL)				
n	23	23	24	24
Mean (SD)	14.61 (16.10)	20.33 (31.80)	16.25 (15.06)	22.57 (30.42)
% CV	110.2	156.4	92.7	134.8
Median	9.680	12.20	11.30	14.55
Min to Max	2.54 to 75.3	1.17 to 154	4.64 to 71.3	5.75 to 154

For patients with limited PK sampling, C_{max} on Days 5 and 10 was estimated by value from scheduled time window for t_{max} (2 hours ± 30 minutes).

Source: Tables 12.4.3.1 (days 1, 5 and 10) and 12.4.1.1 (maximum across days)

Table 9 Plasma Pharmacokinetic Parameters of Fidaxomicin Day 1, 5 and 10 (PKAS All Patients)

Parameter Statistic	Day 1	Day 5	Day 10
t_{max} (h)			
n	23	13	14
Median	1.500	1.033	1.750
Min to Max	0.450 to 11.5	0.500 to 3.00	0.00 to 5.35
AUC† (h·ng/mL)			
n	14	11	11
Mean (SD)	77.70 (79.77)	155.6 (150.9)	129.1 (115.0)
% CV	102.7	97.0	89.1
Median	60.2	116.5	109.8
Min to Max	22.7 to 339	38.0 to 513	19.2 to 364
C_{max} (ng/mL)			
n	23	23	24
Mean (SD)	14.61 (16.10)	20.33 (31.80)	16.25 (15.06)
% CV	110.2	156.4	92.7
Median	9.680	12.20	11.30
Min to Max	2.54 to 75.3	1.17 to 154	4.64 to 71.3
CL/F (L/h) ‡			
n	NA	11	11
Mean (SD)	NA	2306 (1556)	3228 (3037)
% CV	NA	67.5	94.1
Median	NA	1717	1821
Min to Max	NA	390 to 5268	549 to 10392
C_{trough} (ng/mL)			
n	NA	23	22
Mean (SD)	NA	6.183 (6.521)	4.414 (3.173)
% CV	NA	105.5	71.9
Median	NA	4.280	3.325
Min to Max	NA	0.740 to 28.8	1.03 to 11.6

PKAS: consisted of the subset of the safety analysis set (SAF) population for which at least 1 blood plasma measurement of fidaxomicin and its metabolite OP-1118, regardless of whether the value of the measurement was above or below lower limit of quantification and whether the patient had a full pharmacokinetic sampling profile or a limited pharmacokinetic sampling profile.

For patients with limited PK sampling, C_{max} on Days 5 and 10 was estimated by value from scheduled time window for t_{max} (2 hours ± 30 minutes).

AUC: area under the curve; %CV: coefficient of variation; Max: maximum; Min: minimum; NA: not applicable

PKAS: pharmacokinetic analysis.

† AUC for day 1 was the time curve from the time of dosing to 12 hours postdose, and AUC for days 5 and 10 was time curve from the time of dosing to the start of the next dosing interval.

‡ CL/F (L/h) for day 1 was not defined in the study protocol.

Source: Tables 12.4.3.1

Table 10 Maximum Plasma Concentration of OP-1118 Day 1, 5, 10 and Overall (PKAS All Patients)

Parameter Statistic	Day 1	Day 5	Day 10	Maximum across days
C_{max} (ng/mL)				
N	23	23	24	24
Mean (SD)	45.26 (67.48)	70.28 (116.7)	53.10 (43.54)	78.50 (111.58)
% CV	149.1	166.1	82.0	142.2
Median	24.7	42.7	45.5	46.1
Min to Max	4.93 to 336	4.74 to 555	10.6 to 206	13.5 to 555

For patients with limited PK sampling, C_{max} on Days 5 and 10 was estimated by value from scheduled time window for t_{max} (2 hours ± 30 minutes).

Source: Tables 12.4.3.2 (days 1, 5 and 10) and 12.4.1.2 (maximum across days)

Table 11 Plasma Pharmacokinetic Parameters of OP-1118 Day 1, 5 and 10 (PKAS All Patients)

Parameter Statistic	Day 1	Day 5	Day 10
t_{max} (h)			
n	23	13	14
Median	1.500	1.033	2.042
Min to Max	0.450 to 11.5	0.500 to 5.00	0.00 to 5.35
AUC[†] (h·ng/mL)			
n	13	10	12
Mean (SD)	283.5 (400.8)	668.7 (726.0)	389.1 (364.7)
% CV	141.4	108.6	93.7
Median	169.0	415.5	301.4
Min to Max	36.2 to 1550	102 to 2269	52.8 to 1161
C_{max} (ng/mL)			
n	23	23	24
Mean (SD)	45.26 (67.48)	70.28 (116.7)	53.10 (43.54)
% CV	149.1	166.1	82.0
Median	24.70	42.70	45.50
Min to Max	4.93 to 336	4.74 to 555	10.6 to 206
CL/F (L/h) [‡]			
n	NA	10	12
Mean (SD)	NA	630.1 (541.0)	1083 (1072)
% CV	NA	85.9	99.0
Median	NA	450.7	620.9
Min to Max	NA	82.4 to 1838	161 to 3545
C_{trough} (ng/mL)			
n	NA	23	22
Mean (SD)	NA	22.08 (22.21)	18.24 (15.63)
% CV	NA	100.6	85.7
Median	NA	12.70	13.55
Min to Max	NA	2.28 to 88.9	2.52 to 62.8

PKAS: consisted of the subset of the safety analysis set (SAF) population for which at least 1 blood plasma measurement of fidaxomicin and its metabolite OP-1118, regardless of whether the value of the measurement was above or below lower limit of quantification and whether the patient had a full pharmacokinetic sampling profile or a limited pharmacokinetic sampling profile.

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AUC: area under the curve; %CV: coefficient of variation; Max: maximum; Min: minimum; NA: not applicable; PKAS: pharmacokinetic analysis.

C_{max} was estimated by value from scheduled time window for t_{max} (2 hours ± 30 minutes).

† AUC for day 1 was the time curve from the time of dosing to 12 hours postdose, and AUC for days 5 and 10 was time curve from the time of dosing to the start of the next dosing interval.

‡ CL/F (L/h) for day 1 was not defined in the study protocol.

Source: Tables 12.4.3.2

Table 12 Summary of Feces Concentration of Fidaxomicin on Day 1, 5 and 10, by IBD Type (PKAS All Patients)

IBD Type Statistic	Day 1 As per protocol †	Day 1	Day 5	Day 10
Total				
n	7	17	21	22
Mean (SD)	305.40 (306.24)	141.34 (243.18)	749.77 (410.53)	844.52 (614.28)
Median	217.0	0.0	697.00	692.50
75%	611.0	217.0	967.0	1350.0
Min to Max	17.8 to 804.0	0.0 to 804.0	42.1 to 1640	71.4 to 2170
Crohn's Disease				
n	5	10	12	13
Mean (SD)	348.80 (341.17)	174.40 (292.45)	840.50 (397.55)	894.23 (687.71)
Median	217.0	18.0	778.0	564.0
75%	611.0	217.0	1080.5	1470.0
Min to Max	36.0 to 804.0	0.0 to 804.0	403.0 to 1640	162.0 to 2170
Ulcerative Colitis				
n	2	7	9	9
Mean (SD)	196.90 (253.29)	94.11 (158.07)	628.79 (418.57)	772.71 (520.85)
Median	196.9	0.0	621.0	821.0
75%	376.0	265.0	967.0	1090.0
Min to Max	17.8 to 376.0	0.0 to 376.0	42.1 to 1240	71.4 to 1570

Feces concentration expressed as mcg/g. Concentrations below the limit of quantification (10 ng/mL of diluted fecal homogenate or about 2 mcg/g fecal concentrations) were set to zero.

PKAS: consisted of the subset of the safety analysis set (SAF) population for which at least 1 blood plasma measurement of fidaxomicin and its metabolite OP-1118, regardless of whether the value of the measurement was above or below lower limit of quantification and whether the patient had a full pharmacokinetic sampling profile or a limited pharmacokinetic sampling profile.

Max: maximum; Min: minimum; PKAS: pharmacokinetic analysis.

† Excluding fecal samples taken less than 12 hours after the first dose.

Source: Table 12.4.2.1

Table 13 Summary of Feces Concentration of OP-1118 on Day 1, 5 and 10, by IBD Type (PKAS All Patients)

IBD Type Statistic	Day 1 As per protocol †	Day 1	Day 5	Day 10
Total				
n	7	17	21	22
Mean (SD)	126.81 (123.29)	59.04 (99.37)	495.27 (420.46)	466.95 (449.00)
Median	116.0	0.0	395.0	370.50
75%	242.0	116.0	659.0	639.0
Min to Max	0.0 to 318.0	0.0 to 318.0	26.6 to 1940	25.9 to 1830
Crohn's Disease				
n	5	10	12	13
Mean (SD)	143.54 (134.04)	71.77 (117.08)	618.08 (492.88)	496.29 (558.32)
Median	116.0	0.0	470.0	287.0
75%	242.0	116.0	780.0	531.0
Min to Max	0.0 to 318.0	0.0 to 318.0	198.0 to 1940	25.9 to 1830
Ulcerative Colitis				
n	2	7	9	9
Mean (SD)	85.00 (120.21)	40.86 (71.50)	331.51 (234.82)	424.58 (241.24)
Median	85.0	0.0	268.0	434.0
75%	170.0	116.0	489.0	639.00
Min to Max	0.0 to 170.0	0.0 to 170.0	26.6 to 662.0	82.2 to 777.0

OP-1118 concentration expressed as mcg/g. Concentrations below the limit of quantification (50 ng/mL of diluted fecal homogenate or about 10 mcg/g fecal concentrations) were set to zero.

PKAS: consisted of the subset of the safety analysis set (SAF) population for which at least 1 blood plasma measurement of fidaxomicin and its metabolite OP-1118, regardless of whether the value of the measurement was above or below lower limit of quantification and whether the patient had a full pharmacokinetic sampling profile or a limited pharmacokinetic sampling profile.

Max: maximum; Min: minimum; PKAS: pharmacokinetic analysis.

† Excluding fecal samples taken less than 12 hours after the first dose.

Source: Table 12.4.2.2

Table 14 Clinical Response at Visit 4 (Day 12) ToC After EoT, Sustained Clinical Cure and Recurrence of CDI at EoS, by IBD Type (mFAS)

Parameter/statistic	Crohn's Disease (n = 14) n (%)	Ulcerative Colitis (n = 11) n (%)	Overall (n = 25) n (%)
Clinical response (day 12) † 95% CI §	9/14 (64.3) (38.8, 83.7)	11/11 (100) (74.1, 100.0)	20/25 (80.0) (60.9, 91.1)
Sustained clinical cure at EoS (day 180) ‡¶ 95% CI §	8/9 (88.9) †† (56.5, 98.0)	9/11 (81.8) (52.3, 94.9)	17/20 (85) (64.0, 94.8)
Recurrence at EoS (day 180) ¶ 95% CI §	1/8 (12.5) (2.2, 47.1)	2/10 (20) (5.7, 51.0)	3/18 (16.7) (5.8, 39.2)

mFAS: all patients with confirmed CDI that were enrolled, received at least 1 dose of study treatment and had a valid assessment of TOC.

Footnotes continue on next page

CDI clinical response (ToC) was as per clinical judgment of the investigator based on the ESCMID criteria.

CDI clinical response (ToC) was as per clinical judgment of the investigator based on the ESCMID criteria.

CDI: *Clostridium difficile* infection; EoT: end of treatment; ESCMID: European Society of Clinical Microbiology and Infectious Diseases IBD: inflammatory bowel disease; mFAS: modified full analysis set; ToC: test of cure; UBM unformed bowel movement..

† Clinical response of CDI at visit 4 ToC (day 12), 48 to 72 hours after EoT by IBD type (secondary endpoint).

‡ Sustained clinical cure of CDI was defined as clinical response to fidaxomicin (as determined by the investigator) at ToC and no recurrence of CDI from ToC until time of assessment (only for patients who responded at ToC).

§ Two-sided CI (exploratory endpoint).

¶ Recurrence was according to the investigator's judgement, and confirmed by local test where available. Sustained clinical cure and recurrence of CDI were calculated based on responders.

†† Data for race was not provided by all patients as information on race was not allowed to be collected in some sites/countries (a total of 2 patients were classified as “missing”).

Source: Tables 12.3.1.1, 12.3.2.1 and 12.3.3.1

Table 15 Central Laboratory CDI Toxin Assay by CDI Response at ToC (mFAS)

Visit	Responders (n = 20) n (%)		Nonresponders (n = 5) n (%)		Overall (n = 25) n (%)	
	Positive	Negative	Positive	Negative	Positive	Negative
Baseline	6/15 (40)	9/15 (60)	0/4 (0)	4/4 (100)	6/19 (32)	13/19 (68)
Visit 2 (day 5)	0/17 (0)	17/17 (100)	0/5 (0)	5/5 (100)	0/22 (0)	22/22 (100)
Visit 3 (day 10)	9/19 (0)	19/19 (100)	0/5 (0)	5/5 (100)	0/24 (0)	24/24 (100)
Visit 5 (day 26)	5/19 (26)	14/19 (74)	0/4 (0)	4/4 (100)	5/23 (22)	18/23 (78)
Visit 6 (day 40)	2/15 (13)	13/15 (87)	0/5 (0)	5/5 (100)	2/20 (10)	18/20 (90)
Visit 7 (day 90)	1/15 (7)	14/15 (93)	0/5 (0)	5/5 (100)	1/20 (5)	19/20 (95)
Visit 8 (day 180)	0/15 (0)	15/15 (100)	0/4 (0)	4/4 (100)	0/19 (0)	19/19 (100)
Recurrence (unscheduled visit)	0/3 (0)	3/3 (100)	NA	NA	0/3 (0)	3/3 (100)
Unscheduled visit †	0/1 (0)	1/1 (100)	NA	NA	0/1 (0)	1/1 (100)

mFAS: all patients with confirmed CDI that were enrolled, received at least 1 dose of study treatment and had a valid assessment of TOC.

Responders/nonresponders: patients assessed as cured/not cured for clinical response for CDI at day 12. If there was more than 1 test for a visit, ‘positive’ was taken if there was at least 1 positive.

CDI: *Clostridium difficile* infection; mFAS: modified full analysis set; NA: not applicable; ToC: test of cure.

† This was an unscheduled visit on [redacted], which was positive for *C. difficile* at the local laboratory but negative for toxin (PCR), and therefore not a recurrence.

Source: Table 12.3.6.1

Table 16 Health Economic and Resource Variables By CDI Response at ToC on Day 12 (mFAS)

Variable	Category/statistic	CDI response at ToC †		
		Responders (n = 20)	Nonresponders (n = 5)	Total (n = 25)
Type of hospitalization	Nonintensive care unit	17 (85)	4 (80)	21 (84)
Isolated ward	Isolated ward	3 (15)	1 (20)	4 (16)
	Nonisolated ward	16 (80)	4 (80)	20 (80)
Reason for hospitalization ‡				
Adverse event	n/N (%)	8/39 (20.5)	7/10 (70)	15/49 (30.6)
CDI recurrence	n/N (%)	2/39 (5.1)	0	2/49 (4.1)
CDI at study entry	n/N (%)	8/39 (20.5)	2/10 (20)	10/49 (20.4)
Medical history	n/N (%)	8/39 (20.5)	1/10 (10)	9/49 (18.4)
Other	n/N (%)	13/39 (33.3)	0	13/49 (26.5)
Length of hospital stay (days)				
Overall	n	17	4	21
	Mean	34.8	21.5	32.2
	SD	41.6	13.2	37.9
	Min	1	13	1
	Median	20	16	19
	Max	146	41	146
Non intensive care unit	n	17	4	21
	Mean	34.8	21.5	32.2
	SD	41.6	13.2	37.9
	Min	1	13	1
	Median	20	16	19
	Max	146	41	146
Isolated ward	n	3	1	4
	Mean	19.3	3	15.3
	SD	8.4	0	10.7
	Min	14	3	3
	Median	15	3	14.5
	Max	29	3	29
Non isolated ward	n	16	4	20
	Mean	33.3	21.3	30.9
	SD	44	12.7	39.7
	Min	1	13	1
	Median	19	16	18
	Max	146	40	146

Table continued on next page

Variable	Category/statistic	CDI response at ToC †		
		Responders (n = 20)	Nonresponders (n = 5)	Total (n = 25)
Length of hospital stay with reason CDI recurrence (days)				
Overall	n	2	0	2
	Mean	6	0	6
	SD	0	0	0
	Min	6	0	6
	Median	6	0	6
	Max	6	0	6
Non intensive care unit	n	2	0	2
	Mean	3	0	3
	SD	0	0	0
	Min	3	0	3
	Median	3	0	3
	Max	3	0	3
Isolated ward	n	1	0	1
	Mean	3	0	3
	SD	0	0	0
	Min	3	0	3
	Median	3	0	3
	Max	3	0	3
Non isolated ward	n	1	0	1
	Mean	3	0	3
	SD	0	0	0
	Min	3	0	3
	Median	3	0	3
	Max	3	0	3
Number of hospitalizations	0	3 (15)	1 (20)	4 (16)
	1	8 (40)	1 (20)	9 (36)
	2	5 (25)	1 (20)	6 (24)
	> 2	4 (20)	2 (40)	6 (24)
Hospital admissions	n	17	4	21
	Mean	2.3	2.5	2.3
	SD	1.8	1.3	1.7
	Min	1	1	1
	Median	2.0	2.5	2.0
	Max	6	4	6

CDI: *Clostridium difficile* infection; IBD: inflammatory bowel disease; mFAS: modified full analysis set; ToC: test of cure.

† Responders/nonresponders: patients assessed as cured/not cured for clinical response for CDI at day 12.

‡ Patients might had more than 1 hospitalization record so frequencies for each category of this variable could be higher than the total number of patients.
Source: Table 12.3.16

Table 17 Overview of TEAEs and Deaths up to 30 Days After EoT (SAF)

	Fidaxomicin (n = 25) n (%)	**Number of events**
TEAE	15 (60)	43
Drug-related TEAE †	10 (40)	19
Serious TEAE ‡	6 (24)	8
Drug-related † **serious TEAEs**‡	2 (8)	2
TEAEs leading to death	0	0
Drug-related † **TEAE leading to death**	0	0
TEAE leading to withdrawal of treatment	0	0
Drug-related† **TEAEs leading to withdrawal of treatment**	0	0
Death §	0	0

SAF: All patients who received at least 1 dose of study drug.

Within an SOC, a patient may have reported more than 1 type of adverse event.

An AE was defined as any untoward medical occurrence in a patient administered a study drug or who underwent study procedures and which did not necessarily have a causal relationship with this treatment.

TEAEs were defined as an AE starting or a condition existing pretreatment that worsens after first study drug intake and until 30 days after EoT. AEs with onset or worsening > 30 days after last intake of the study drug are presented in separate tables.

AE: adverse event; EoT: end of the treatment; n: number of patients; SAF: Safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

† Possible or probable, as assessed by the investigator, or records where relationship is missing.

‡ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.

§ All reported deaths after the first study drug administration.

Source: Table 12.6.1.1

Table 18 TEAEs Up to 30 Days After EoT (SAF)

MedDRA v14.1 System Organ Class **Preferred Term**	**Fidaxomicin (n = 25)**	
	n (%)	**Number of events**
Overall	**15 (60)**	**43**
Blood and lymphatic system disorders	**3 (12)**	**3**
Anaemia	2 (8)	2
Leukopenia	1 (4)	1
Gastrointestinal disorders	**10 (40)**	**19**
Abdominal pain	3 (12)	3
Abdominal pain upper	1 (4)	1
Colitis ulcerative	1 (4)	1
Crohn's disease	2 (8)	2
Defaecation urgency	1 (4)	1
Dry mouth	1 (4)	3
Flatulence	2 (8)	3
Inflammatory bowel disease	2 (8)	3
Nausea	1 (4)	1
Rectal tenesmus	1 (4)	1

Table continued on next page

MedDRA v14.1 System Organ Class **Preferred Term**	**Fidaxomicin (n = 25)** **n (%)**	**Number of events**
General disorders and administration site conditions	**5 (20)**	**6**
Chills	1 (4)	1
Fatigue	3 (12)	3
Oedema peripheral	1 (4)	1
Pyrexia	1 (4)	1
Infections and infestations	**2 (8)**	**2**
Clostridial infection	1 (4)	1
Upper respiratory tract infection	1 (4)	1
Investigations	**2 (8)**	**2**
Alanine aminotransferase increased	1 (4)	1
C-reactive protein increased	1 (4)	1
Musculoskeletal and connective tissue disorders	**1 (4)**	**1**
Arthralgia	1 (4)	1
Nervous system disorders	**1 (4)**	**2**
Headache	1 (4)	2
Psychiatric disorders	**1 (4)**	**2**
Insomnia	1 (4)	1
Stress	1 (4)	1
Renal and urinary disorders	**1 (4)**	**1**
Dysuria	1 (4)	1
Respiratory, thoracic and mediastinal disorders	**1 (4)**	**1**
Hypoxia	1 (4)	1
Skin and subcutaneous tissue disorders	**3 (12)**	**3**
Rash	2 (8)	2
Skin ulcer	1 (4)	1
Vascular disorders	**1 (4)**	**1**
Venous thrombosis limb	1 (4)	1

SAF: All patients who received at least 1 dose of study drug.

Within an SOC, a patient may have reported more than 1 type of adverse event.

An AE was defined as any untoward medical occurrence in a patient administered a study drug or who underwent study procedures and which did not necessarily have a causal relationship with this treatment.

TEAEs were defined as an AE starting or a condition existing pretreatment that worsens after first study drug intake and until 30 days after EoT. AEs with onset or worsening > 30 days after last intake of the study drug are presented in separate tables.

AE: adverse event; EoT: end of the treatment; n: number of patients; SAF: Safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.2

Table 19 Serious TEAEs Up to 30 Days After EoT (SAF)

MedDRA v14.1 System Organ Class Preferred Term	Fidaxomicin (n = 25)	
	n (%)	Number of events
Overall	**6 (24)**	**8**
Blood and lymphatic system disorders	**1 (4)**	**1**
Anaemia	1 (4)	1
Gastrointestinal disorders	**3 (12)**	**3**
Colitis ulcerative	1 (4)	1
Crohn's disease	2 (8)	2
Infections and infestations	**1 (4)**	**1**
Clostridial infection	1 (4)	1
Investigations	**1 (4)**	**1**
Alanine aminotransferase increased	1 (4)	1
Respiratory, thoracic and mediastinal disorders	**1 (4)**	**1**
Hypoxia	1 (4)	1
Skin and subcutaneous tissue disorders	**1 (4)**	**1**
Skin ulcer	1 (4)	1

SAF: All patients who received at least 1 dose of study drug.

TEAEs were defined as an AE starting or a condition existing pretreatment that worsens after first study drug intake and until 30 days after EoT. AEs with onset or worsening > 30 days after last intake of the study drug are presented in separate tables.

AE: Adverse event; EoT: end of the treatment; n: number of patients; SAF: Safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.6

Table 20 Summary of Events of Special Interest

	Crohn's Disease (n=14) n (%)	Ulcerative Colitis (n=11) n (%)	Total (n=25) n (%)
Any event of special interest	3 (21.4)	3 (27.3)	6 (24)
Development of microbial resistance to fidaxomicin	Antimicrobial resistance to fidaxomicin were assessed when microbial data was available and reported separately		
Hypersensitivity to fidaxomicin	0	0	0
GI hemorrhage	0	1 (9.1)	1 (4)
Decreases in WBC, neutrophil counts	3 (21.4)	1 (9.1)	4 (16)
Hepatic laboratory value abnormalities (>3 x ULN ALT/AST and/or >2 x ULN total bilirubin)	0	1 (9.1)	1 (4)
Renal laboratory value abnormalities	1 (7.1)	1 (9.1)	2 (8)
QT-interval prolongation	0	0	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GI: gastrointestinal; WBC: white blood cell.

Source: Attachment 1

Table 21 AEs in Long Term Follow-up of > 30 days After EoT, Overview by Sustained Clinical Cure of CDI at EoS (SAF)

	Patients with sustained clinical cure at EoS n = 17		**Patients without sustained clinical cure at EoS n = 8**		**Total n = 25**	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
AEs	9 (52.9)	43	2 (25)	7	11 (44)	50
Related AEs †	1 (5.9)	1	0	0	1 (4)	1
SAEs‡	5 (29.4)	8	2 (25)	3	7 (28)	11
Drug-related † **SAEs** ‡	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

SAF: All patients who received at least 1 dose of study drug.

Sustained clinical cure at EoS was defined as clinical response at ToC and no recurrence of CDI until the EoS visit.

An AE was defined as any untoward medical occurrence in a patient administered a study drug or who underwent study procedures and which did not necessarily have a causal relationship with this treatment.

AE: adverse event; CDI: *Clostridium difficile* infection; EoS: end of study; EoT: end of treatment; n: number of patients; SAE: serious adverse event; SAF: Safety analysis set; ToC: test.

† Possible or probable, as assessed by the investigator, or records where relationship is missing.

‡ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.

Source: Table 12.6.1.12

Table 22 SAEs in Long Term Follow-Up > 30 Days After EoT by Sustained Clinical Cure of CDI at EoS (SAF)

MedDRA v14.1 System Organ class Preferred Term	**Patients with sustained clinical cure at EoS n = 17**		**Patients without sustained clinical cure at EoS n = 8**		**Total n = 25**	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
Overall	**5 (29.4)**	**8**	**2 (25)**	**3**	**7 (28)**	**11**
Gastrointestinal disorders	**4 (23.5)**	**4**	**2 (25)**	**2**	**6 (24)**	**6**
Colitis ulcerative	1 (5.9)	1	0	0	1 (4)	1
Crohn's disease	1 (5.9)	1	1 (12.5)	1	2 (8)	2
Inflammatory bowel disease	2 (11.8)	2	0	0	2 (8)	2
Pancreatitis	0	0	1 (12.5)	1	1 (4)	1
Infections and infestations	**2 (11.8)**	**2**	**0**	**0**	**2 (8)**	**2**
Lung abscess	1 (5.9)	1	0	0	1 (4)	1
Pyelonephritis acute	1 (5.9)	1	0	0	1 (4)	1
Metabolism and nutrition disorders	**1 (5.9)**	**1**	**0**	**0**	**1 (4)**	**1**
Dehydration	1 (5.9)	1	0	0	1 (4)	1
Surgical and medical procedures	**0**	**0**	**1 (12.5)**	**1**	**1 (4)**	**1**
Respiratory therapy	0	0	1 (12.5)	1	1 (4)	1
Vascular disorders	**1 (5.9)**	**1**	**0**	**0**	**1 (4)**	**1**
Deep vein thrombosis	1 (5.9)	1	0	0	1 (4)	1

SAF: All patients who received at least 1 dose of study drug.

Sustained clinical cure at EoS was defined as clinical response at ToC and no recurrence of CDI until the EoS visit.

SAEs: An AE was considered "serious" if, in the view of either the investigator or sponsor, it resulted in any of the following outcomes: resulted in death, was life threatening (an AE was considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence placed the patient at immediate risk of death. It did not include an AE that, had it occurred in a more severe form, might have caused death), resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, resulted in congenital anomaly, or birth defect, required inpatient hospitalization or led to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE was to be considered as serious) or other medically important events.

AE: adverse event; CDI: *Clostridium difficile* infection; EoS: end of study; EoT: end of treatment; n: number of patients; SAE: serious adverse event; SAF: Safety analysis set; ToC: test of cure.

Source: Table 12.6.1.16

Table 23 Drug-related TEAEs Up to 30 Days After EoT (SAF)

MedDRA v14.1 System Organ Class Preferred Term	**Fidaxomicin n = 25**	
	n (%)	**Number of events**
Overall	**10 (40)**	**19**
Blood and lymphatic system disorders	**1 (4)**	**1**
Leukopenia	1 (4)	1
Gastrointestinal disorders	**4 (16)**	**10**
Abdominal pain	1 (4)	1
Abdominal pain upper	1 (4)	1
Dry mouth	1 (4)	3
Flatulence	2 (8)	3
Nausea	1 (4)	1
Rectal tenesmus	1 (4)	1
General disorders and administration site conditions	**2 (8)**	**2**
Fatigue	1 (4)	1
Oedema peripheral	1 (4)	1
Nervous system disorders	**1 (4)**	**2**
Headache	1 (4)	2
Psychiatric disorders	**1 (4)**	**1**
Insomnia	1 (4)	1
Respiratory, thoracic and mediastinal disorders	**1 (4)**	**1**
Hypoxia	1 (4)	1
Skin and subcutaneous tissue disorders	**2 (8)**	**2**
Rash	1 (4)	1
Skin ulcer	1 (4)	1

SAF: All patients who received at least 1 dose of study drug.

Within an SOC, a patient may have reported more than 1 type of adverse event.

TEAEs were defined as an AE starting or a condition existing pretreatment that worsens after first study drug intake and until 30 days after EoT. AEs with onset or worsening > 30 days after last intake of the study drug are presented in separate tables.

AE: adverse event; EoT: end of the treatment; n: number of patients; SAF: Safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.3