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Name of Finished Product: DIFICLIR™		
Name of Active Ingredient: Fidaxomicin		

SYNOPSIS

Title of Study:

A phase IIIb/IV randomized, controlled, open-label, parallel group study to compare the efficacy of vancomycin therapy to extended duration fidaxomicin therapy in the sustained clinical cure of *Clostridium difficile* infection in an older population.

Investigators/Coordinating Investigator:

[redacted]
[redacted]
[redacted] Germany

Study Center(s):

This was multinational, multicenter study with patients randomized at 86 clinical sites in 21 countries in Europe and Asia

Publication Based on the Study:

NA

Study Period:

From Q4 2014 to Q2 2016

Study Initiation Date (Date of First Enrollment):

06 Nov 2014

Study Completion Date (Date of Last Evaluation):

05 May 2016

Phase of Development:

Phase 3b/4

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Objectives:

Primary Objective:

To evaluate the efficacy of extended pulsed fidaxomicin (EPFX) in the treatment of *C. difficile* infection (CDI) in male and female patients aged 60 years and older compared with standard vancomycin therapy.

Secondary Objectives:

The main secondary objectives of the study were to compare EPFX and standard vancomycin treatments on sustained clinical cure, clinical response and the rate of relapse. Other secondary objectives included: compare EPFX and standard vancomycin treatment on clinical response after end of treatment (EoT), time to resolution of diarrhea (TTROD), recurrence rate of CDI and only for patients with clinical response the time to recurrence of CDI after EoT and disease-free survival after day 10.

Exploratory Objectives:

Evaluation of the number or volume of unformed bowel movements (UBMs), CDI toxin in fecal samples, quality of life and health economic and resource variables were included in the exploratory objectives.

Safety Objectives:

The incidence of mortality and severity of adverse events (AEs) were followed-up until day 90.

Methodology:

This was a phase 3b/4 randomized, controlled, parallel-group, open-label study with female and male patients of ≥ 60 years of age with CDI confirmed positive for presence of *C. difficile* toxin A or B in stool (within 48 hours prior to randomization). The study also included 2 sub-studies to analyze microbiome profiles and/or pharmacokinetics (plasma and stool) of fidaxomicin. After screening, patients were randomized to either the extended pulsed fidaxomicin (EPFX) arm or the standard vancomycin arm. Table 1 shows the dosing regimen for day 1 to day 25 of the study for both treatment arms. Patients visited the clinic at screening (visit 1), at day 12 (visit 2) and 27 (visit 3) for the assessment of test of cure (TOC) and clinical response as determined by the investigator. Safety was followed from the time of written informed consent until end of study (EoS) visit 6 (day 90) for all patients.

Patients with increased UBMs following clinical response at TOC (UBMs greater than the frequency recorded on day 10 for the standard vancomycin arm or day 25 for the EPFX arm), had to attend an unscheduled visit for the assessment of recurrence of CDI. The study also included 2 sub-studies to analyze microbiome profiles and/or pharmacokinetics of the concentration of fidaxomicin in blood (plasma) and stool. Both assessments were carried out on day 5, and visits 2, 3, 4 and 5.

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Name of Finished Product: DIFICLIR™		
Name of Active Ingredient: Fidaxomicin		

In the case of treatment failure or any confirmed recurrence of CDI after assessment of clinical response from day 12 (visit 2), stool samples were collected for laboratory testing. All samples underwent culture, ribotyping and susceptibility testing. In order to distinguish between relapse and re-infection in patients with a recurrence of CDI after TOC, whole genome sequencing of isolates was carried out on samples from both day 1 and confirmed recurrence. From visit 1 (day 1) to TOC visit 2 (day 12) for the standard vancomycin arm, or visit 3 (day 27) for the EPFX arm, patients completed a Subject Diary to record the total number of UBMs passed each day, along with the time of the last UBM for each day, or the daily volume of stool (for patients with rectal collection devices), and intake of the number of tablets/capsules of study drug taken each day. At baseline, visit 2, 3, 4 and 5 and at unscheduled visits for assessment of recurrence, patients completed in EuroQoL 5 Dimensions Questionnaire (EQ-5D-5L). If a patient was discharged from the hospital and was not participating in the sub-study, they could complete the questionnaires for visit 4 and visit 5 at home. Following completion of the treatment period, safety, efficacy and health economics outcomes were followed-up until EoS visit 6 (day 90). Patients were to be followed-up at least every 2 weeks to check for CDI recurrence, AEs and concomitant medications.

Table 1 Dosing Regimens

Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Vancomycin	*am*	V	V	V	V	V	V	V	V	V	V															
		V	V	V	V	V	V	V	V	V	V															
	pm	V	V	V	V	V	V	V	V	V	V															
		V	V	V	V	V	V	V	V	V	V															
EPFX	*am*	F	F	F	F	F		F		F		F		F		F		F		F		F		F		F
	pm	F	F	F	F	F																				

EPFX: extended pulsed fidaxomicin arm.
F = fidaxomicin 200 mg oral tablets
V = vancomycin 125 mg oral capsules

An interim analysis was performed after approximately 190 patients had completed day 40 (visit 4) on standard vancomycin or day 55 (visit 5) on EPFX treatment (i.e., had an assessment of sustained clinical cure at 30 days after EoS).

Number of Patients (Planned, Enrolled and Analyzed):

In total, 364 randomized patients were enrolled (183 in the EPFX arm and 181 in the standard vancomycin arm). Of these, a total of 49 patients enrolled in the microbiological sub-study (27 in the EPFX arm and 22 in the standard vancomycin arm), and 14 patients of the EPFX arm enrolled in the pharmacokinetic sub-study.

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Name of Finished Product: DIFICLIR™		
Name of Active Ingredient: Fidaxomicin		

Diagnosis and Main Criteria for Inclusion:

Patients were eligible for inclusion if they were male or female patients, ≥ 60 years of age, and if CDI was confirmed by clinical symptoms either > 3 UMBs or ≥ 200 mL of unformed stool (for patients having rectal collection devices) in the 24 hours prior to randomization and a CDI test confirmed positive for presence of *C. difficile* toxin A or B in stool within 48 hours prior to randomization.

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

Fidaxomicin (commercial), 200 mg, immediate-release tablets, Numbers: [redacted].

Duration of Treatment (or Duration of Study, if applicable):

Patients received either fidaxomicin twice daily from day 1 to day 5, followed by once daily every other day from day 6 to day 25, or vancomycin 4 times daily from day 1 to day 10.

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

Vancomycin (commercial), 125 mg capsules, Number: [redacted].

Criteria for Evaluation:

Primary efficacy variable

- Rate of sustained clinical cure of CDI at 30 days after EoT (day 40 or day 55)

Main Secondary Efficacy Variables

- Sustained clinical cure of CDI at day 40, day 55 and day 90
- Clinical response of CDI at day 12
- Rate of relapse at day 90 as determined by whole genome sequencing of *C. difficile* isolates from patients who had documented recurrence after treatment of cure (TOC)

Other Secondary Efficacy Variables

- Clinical response of CDI at 2 days after EoT (day 12 or day 27 for standard vancomycin and EPFX, respectively)
- Time to resolution of diarrhea (TTROD) in hours
- Rate of recurrence of CDI at day 40, day 55 and day 90
- Time to recurrence after EoT (only for patients with clinical response)
- Disease-free survival after day 10 (only for patients with clinical response)

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Name of Finished Product: DIFICLIR™		
Name of Active Ingredient: Fidaxomicin		

Exploratory Efficacy Variables†

- The number or volume of UBMs per day (from day 1 to 25)
- CDI toxin in fecal samples (sub-study visit 5 and unscheduled visit for recurrence of CDI)
- Viable count and spore burden †
- Microbial diversity in fecal samples †
- Change in Health-Related Quality of Life (HRQoL) using the Euro Quality of Life 5 Dimension questionnaire (EQ-5D-5L) visual analysis score (VAS) per visit and change from baseline
- Health economic and resource utilization variables

† Data were not available for viable count and spore burden and for microbial diversity data as assessed with polymerase chain reaction (PCR) amplification of the bacterial 16SrRNA hypervariable region at the time of clinical study report finalization but will be reported separately.

Pharmacokinetic Variables

- Plasma concentrations fidaxomicin
- Plasma concentrations of OP-1118 metabolite
- Stool concentrations fidaxomicin
- Stool concentrations of OP-1118 metabolite

Safety Variables

- Incidence of mortality and severity of AEs at day 90
- Clinical laboratory evaluations
- Vital signs
- Other safety related observations

Statistical Methods:

There were 5 analysis sets:

- modified Full Analysis Set (mFAS): consisted of eligible randomized patients who had received a least 1 dose of study drug (EPFX or standard vancomycin), had a confirmed CDI positive for presence *C. difficile* toxin A or B in stool within 48 hours prior to randomization and clinical symptoms of CDI in the 24 hours prior to randomization. Patients in the mFAS were analyzed with the treatment arm they were randomized to even if the actual treatment received was different.
- Per protocol set (PPS): consisted of eligible patients from the mFAS who did not have major protocol deviations before the assessment of the primary clinical endpoint, received at least 70% of the study drug according to the allocated treatment regimen (EPFX or standard vancomycin).

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

- Safety analysis set (SAF): consisted of patients who received at least 1 dose of study drug (EPFX or standard vancomycin).
- Pharmacokinetic analysis set (PKAS): consisted of all patients who completed the EPFX treatment and had at least 2 plasma pharmacokinetic samples taken within the defined study visit windows.
- Microbiologically evaluable analysis set (MEAS): consisted of all patients who received at least 1 dose of study drug (EPFX or standard vancomycin) and provided at least 2 complete microbiome profiles within the specified windows.

Demographic and other baseline characteristics were summarized and presented by study treatment using descriptive statistics, frequencies and percentages. Descriptive statistics for age (years), weight (kg), height (cm) and BMI (kg/m^2) at clinical study entry were presented. Frequency tabulations for sex, ethnicity, age group and race were presented. Additional listings were provided for randomization, inclusion and exclusion criteria and treatment compliance. Medical history was coded in the MedDRA (v14.1), and listed by SOC and preferred term (PT). Previous medication was summarized for each treatment arm by therapeutic subgroup (Anatomical therapeutic chemical [ATC] second level) and chemical subgroup (ATC fourth level) and preferred WHO name for the SAF. Listings contained all medication data, nonmedication and only contained data for patients who reported taking medication.

Study drug exposure duration (days) was summarized using descriptive statistics by treatment arm and overall for SAF and mFAS. Treatment compliance was summarized by treatment arm for SAF and mFAS. The percentage of treatment compliance during the entire standard vancomycin treatment period and separately for the 'induction' and 'maintenance' phase of the EPFX treatment were summarized by descriptives, number and percentage of patients.

All efficacy data were presented using descriptive statistics and summarized in tabular and/or graphical form. The primary analysis of the primary efficacy variable was performed for the mFAS. The rate of sustained clinical cure of CDI was stratified by CDI severity (severe/non-severe), presence or absence of cancer, age ($\geq$ 75 or < 75 years) and number of previous recurrences (0, 1 or 2) in the 3 months prior to the study. The difference in the sustained clinical cure rates between the standard vancomycin and EPFX treatment arms was compared across the strata using the Cochran-Mantel-Haenszel (CMH) test. Also the estimate of the common odds ratio (OR) and the corresponding 95% CI for the sustained cure rates of the 2 therapies were provided. The secondary analysis of the primary efficacy variable was repeated using the PPS. Additionally, the OR and 95% CIs for the success rates were calculated using the logistic regression analysis technique.

All the subgroup analyses were conducted using the mFAS, using for each subgroup category the same analysis as performed for the primary efficacy variables.

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

An interim analysis was performed after approximately 190 patients had completed day 40 on standard vancomycin or day 55 on EPFX treatment. Only the primary analysis of the primary efficacy variable was performed.

If the primary efficacy variable was statistically significant for sustained clinical cure of CDI at visit 4 (day 40) and visit 5 (day 55), the main secondary efficacy variables were analyzed with the Hochberg procedure to obtain adjusted P values for the main secondary efficacy variables results for the mFAS.

All exploratory efficacy variables were analyzed using the mFAS, except for the number and volume of UBMs per day which was also analyzed for the PPS.

Safety data of AEs was summarized with use of the coding dictionary MedDRA v14.1. All safety and tolerability data was descriptively analyzed and listed and summarized in tabular and/or graphical form using the SAF. No formal statistical testing was performed on these data except otherwise specified.

Vital signs were summarized by treatment arm and visit, and a summary of within-patient change from baseline for each post-baseline measurement and listings were provided.

Pharmacokinetic data of individual plasma concentrations of fidaxomicin were summarized by scheduled time point (1 to 5 hours post-dose), depending on the time of start with fidaxomicin on day 1. For patients starting with the EPFX regimen in the morning (day 1), TOC was assessed at day 11 or 13, and day 25 was the target day for TOC. For patients starting in the afternoon with the EPFX regimen (day 1), TOC was assessed at day 12 and day 26 was the target day for pharmacokinetic evaluation. Values below the lower limit of quantification (BLQ) were set to 0 for calculation of descriptive statistics. Box-plots and scatter plots (both normal and semi-log) of 1 to 5 hours post-dose fidaxomicin plasma concentrations by visit were produced. All the analyses were performed for the PKAS and were provided in listings.

Each of the 5 dimensions for EQ-5D-5L questionnaire were summarized by treatment arm and visit as categorical variables and compared using the Chi-square test for the mFAS. The items of hospital resource use and diagnostic procedures associated with CDI were summarized by treatment arm and compared between arms with the Chi-square test for categorical variables and with the t-test for continuous variables using the mFAS.

Summary of Results/Conclusions:

Population:

Patient disposition and analysis sets are summarized in Table 2. Patient demographics and baseline characteristics are summarized in Table 3.

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Name of Finished Product: DIFICLIR™		
Name of Active Ingredient: Fidaxomicin		

Efficacy/Clinical Results:

Efficacy variables:

- Sustained clinical cure of CDI at 30 days after EoT was reached at a significantly higher rate in patients treated with EPFX compared with patients treated with standard vancomycin (P = 0.030), with a treatment difference of 10.8% (95% CI:1.0%, 27.0%).
- The odds of achieving sustained clinical cure of CDI at 30 day after EoT in the EPFX arm was 1.6 times the odds in the standard vancomycin arm (OR = 1.62 [95% CI: 1.04, 2.54].
- Results from multivariate analysis (logistic regression) for sustained clinical cure of CDI adjusted to the stratification factors (CDI severity, presence/absence of cancer, age group and number of previous recurrences) showed that patients with severe CDI were significantly less likely to achieve sustained clinical cure compared with patients who had non-severe CDI (P = 0.019) (OR = 0.57 [95% CI: 0.36, 0.91]).
- The rate of sustained clinical cure at days 40, 55 and 90 (main secondary efficacy variables) were significantly higher in the EPFX arm compared with standard vancomycin arm (each with a P < 0.01). In addition, the adjusted P value obtained for each of these was also statistically significant with an adjusted P value less than 0.015 for each.
- The rate of clinical response of CDI at day 12 (main secondary efficacy variables), and at 2 days after EoT were not statistically significantly different between the 2 treatments (80.2% vs 82.1% for EPFX and standard vancomycin, respectively). For the EPFX arm, at day 27 (2 days after EoT) the clinical response rate was 78.0% which was comparable to the rate obtained for the standard vancomycin arm at day 12 (of 82.1%). The majority of the patients in the EPFX arm with clinical response of CDI at day 27 achieved this by day 12 (128 of 138 patients [92.8%]).
- The rate of sustained clinical cure of CDI in the EPFX arm was significantly higher than in the standard vancomycin arm at day 40 (75.1% vs 59.2% patients, P = 0.001), at day 55 (70.1% vs 55.3% patients, P = 0.004) and at day 90 (65.5% vs 51.4% patients, P = 0.007). For the secondary efficacy variable of recurrence of CDI, significantly fewer patients had CDI recurrence in the EPFX arm compared with the standard vancomycin arm at day 40 (1.7% vs 16.8% patients, P < 0.001), day 55 (4.0% vs 17.9% patients, P < 0.001) and day 90 (6.2% vs 19.0% patients, P < 0.001).
- A total of 45 patients experienced a recurrent CDI episode. Of these, 11 patients had paired samples of whole genome sequence data available. Two of these patients were in the EPFX arm (1 classified as ‘reinfection’, 1 classified as ‘relapse’) and 9 patients were in the standard vancomycin arm (5 classified as ‘reinfected’, 3 classified as ‘relapse’, and 1 classified as ‘indeterminate’).

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Name of Finished Product: DIFICLIR™		
Name of Active Ingredient: Fidaxomicin		

- The time to resolution of diarrhea was reached just over 5 days (123 hours [95% CI: 123.00, 494.00]) for the majority of patients (75%) treated with EPFX. The majority of patients on standard vancomycin reached resolution of diarrhea within 3.5 days (81 hours [95% CI: 61.00, 172.00]).
- Recurrence of CDI observed at visit 4, 5 and 6 was significantly different in favor of the EPFX arm with a P value of < 0.001 at each visit. Treatment differences between the 2 arms at visit 4, 5 and 6 were -15.1%, -13.9%, and -12.8%, respectively. Recurrence of CDI after EoT with EPFX was observed after 28 days of TOC in the first 5% patients compared with 7 days after TOC for the first 5% of patients treated with standard vancomycin. The difference in time to recurrence was statistically different (P < 0.001).
- A larger proportion of patients treated with EPFX were disease-free up to 30 days. For the EPFX arm, the time taken after day 10 for the first 5% of patients to have CDI recurred was 47 days (percentile 5, 95% CI: 23.00, -). For the standard vancomycin arm, the time taken after day 10 for the first 5% of patients to show symptoms of CDI was 9 days (percentile 5, [95% CI: 4.0, 10.0]). The overall difference in disease-free survival was statistically significant (P < 0.001).
- At baseline the mean (SD) number of UBMs were comparable between the 2 treatment arms: 6.4 (3.4) (range: 4 to 20) for standard vancomycin and 6.8 (4.7) (range: 4 to 50) for EPFX. By day 10, the mean (SD) was 0.8 (1.7) and 0.7 (1.5) for standard vancomycin and EPFX arm, respectively. The majority of the patients had 2 or fewer UBMs per day by day 10; 144 (80.4%) of 179 patients and 139 (78.5%) of 177 patients in standard vancomycin and EPFX arm, respectively. .
- Overall, at screening 231 (69.2%) patients from the SAF were positive for CDI toxin, of which 116 (69%) in the EPFX arm and 115 (69.3%) in the standard vancomycin arm. Of the 40 patients with CDI recurrence who were assessed for *C. difficile* toxin, 28 (70.0%) had a positive toxin test result. Based on the central laboratory test results, 8 of 12 (66.7%) patients) in the EPFX arm and 20 of 28 (71.4%) patients in the standard vancomycin arm, had a positive toxin test result. .
- A total of 10 (20.8%) patients who enrolled in the sub-study tested positive for CDI toxin (EPFX: 5/27 [18.5%] patients vs standard vancomycin: 5/21 [23.8%] patients). At visit 5 (day 55), a total of 5 (15.2%) of patients tested positive (EPFX: 3/19 [15.8%] patients vs standard vancomycin: 2/14 [14.3%] patients). The HRQoL assessed with the EQ-E5-5L questionnaire demonstrated that the QoL of patients in both treatment arms increased (eg 'no problems' with any of the dimensions of the questionnaire) from baseline through day 55. Apart from an instance at day 40 (visit 4) for the dimension "Usual activities" (P = 0.04), the distribution in the level of the 5 domains did not show a difference in their distribution at the standard level of statistical significance (e.g., P = ≥ 5%).

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

- Statistical significant differences in quality of life based on the VAS were observed for the difference between baseline and visit 3 (P = 0.02), visit 4 (P = 0.002) and visit 5 (P = 0.003) for patients treated with EPFX. This indicated that the QoL as measured by the VAS was better in patients on EPFX compared with patients treated with standard vancomycin.

Pharmacokinetic results

- The current dataset did not show accumulation of fidaxomicin or OP-1118 plasma levels over 25 or 26 days depending on the time point of starting the EPFX regimen. The metabolite to parent ratio in plasma did not seem to be affected by the extended dosing scheme.
- The current dataset did not show accumulation of fidaxomicin or OP-1118 fecal levels over 27 days. The metabolite to parent ratio in feces did not seem to be affected by the extended dosing scheme.
- The levels of fidaxomicin observed in plasma were very low.

Safety Results:

- A total 69 (19.1%) of 364 randomized patients died; 33 (18.2%) of 181 EPFX patients and 36 (19.7%) of 181 standard vancomycin patients. Of the 69 deaths in the randomized patients, 43 (66.15%) deaths occurred after day 27. For the standard vancomycin arm, the majority of the deaths occurred after day 27 (27 [75%] of 36 deaths) while for the EPFX arm, most of the deaths occurred before day 27 (16 [55.2%] of 33 deaths). Only 1 patient's death in the standard vancomycin arm was reported as probably related to the study drug. None of the deaths in the EPFX arm were reported as related to the study drug.
- Overall, 66.9% of EPFX patients and 70.7% of standard vancomycin patients reported at least 1 TEAE. The percentage of patients who reported SAEs were 37.6% and 43.1% for the EPFX and standard vancomycin arms, respectively. Three patients (1.7%) in the EPFX arm and 6 patients (3.3%) in the standard vancomycin arm experienced drug-related SAEs of which 2 (1.1%) and 1 (0.6%) respectively, led to permanent discontinuation of the study drug.
- In this study, all patients were > 60 years old which is a factor for increased risk for co-morbidities not related to the disease of interest (CDI). In the EPFX arm 5.9% more patients ≥ 75 years old experienced AEs compared with patients < 75 years old. This number was even higher in the standard vancomycin arm were 11.8% more patients ≥ 75 years old experienced AEs compared with patients < 75 years old.
- Patients categorized as having nonsevere CDI, experienced 201 (39.2% EPFX-treated patients) and 240 (43.6% standard vancomycin-treated patients) AEs. For the severe CDI arm, 50 (27.6%) EPFX

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Name of Finished Product: DIFICLIR™		
Name of Active Ingredient: Fidaxomicin		

treated patients experienced 162 AEs and 49 (27.1%) standard vancomycin treated patients experienced 191 AEs.

- Most patients in both treatment arms with no recurrence of CDI experienced AEs. A total of 51.9% of patients in the EPFX arm experienced 280 AEs and 55.8% of patients in the standard vancomycin arm experienced 349 AEs. In non-recurrent patients, a total of 17.7% and 13.8% of patients died in the standard vancomycin and EPFX arm respectively, and was higher compared with patients that had 1 recurrence of CDI (EPFX: 0.6% vs standard vancomycin 1.7%).
- During follow-up a higher number of AEs were reported by patients treated with standard vancomycin (52.5%) vs EPFX-treated patients (34.3%) of which 3 AEs in 3 (1.7%) patients in the EPFX arm and 5 AEs in 3 (1.7%) patients in the standard vancomycin arm were assessed as study drug related. In the EPFX arm, 34 of 181 (18.8%) patients experienced 62 SAEs; in the standard vancomycin arm 60 of 181 (33.1%) patients experienced 131 SAEs.
- One vancomycin-treated patient permanently discontinued the study drug because of an AE.
- No apparent differences were observed between the treatment arms for AEs of interest which were collected at baseline or at an unscheduled visit. A total of 23 patients (9 patients on EPFX and 14 patients on standard vancomycin) attended an unscheduled visit for suspected recurrence of CDI and had additional blood collections for AEs of interest. Of these AEs of interest 14 patients experienced an SAE of which 8 patients were on EPFX and 6 were on standard vancomycin. Hepatic laboratory abnormalities (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase) were found in a higher number of patients on standard vancomycin.

CONCLUSIONS:

- The interim analysis revealed a significant treatment difference in the rates of sustained clinical cure in favor for EPFX-treated patients (14.4% [95% CI: 4.8%, 24.0%], [P = 0.011]). In addition, the recurrence rate of CDI in the EPFX arm was greater than 3.8%.
- Sustained clinical cure of CDI at 30 days after EoT was reached at a significantly higher rate in patients treated with EPFX compared with patients treated with vancomycin (P = 0.030), with a treatment difference of 10.8% (95% CI: 1.0%, 27.0%).
- The odds of achieving sustained clinical cure of CDI at 30 day after EoT in the EPFX arm was 1.6 times the odds in the standard vancomycin arm (OR = 1.62 [95% CI: 1.04, 2.54]).
- Results from multivariate analysis (logistic regression) for sustained clinical cure of CDI adjusted to the stratification factors (CDI severity, presence/absence of cancer, age group and number of previous recurrences) showed that patients with severe CDI were significantly less likely to achieve sustained

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

clinical cure compared with patients who had non-severe CDI (P = 0.019), (OR = 0.57 [95% CI: 0.36, 0.91]).

- The rate of sustained clinical cure at day 40, 55 and 90 (main secondary efficacy endpoints) was significantly higher in the EPFX treatment arm compared with standard vancomycin treatment arm (each with a $P < 0.01$).
- The rate of clinical response of CDI at day 12 (main secondary efficacy endpoints), and at 2 days after EoT was comparable between the 2 treatment arms.
- The rate of CDI recurrence at day 55 was significantly lower when patients were treated with EPFX compared with the rate of patients treated with standard vancomycin: (4.0% vs 17.9% [$P < 0.001$]). Similar results were obtained for CDI recurrence rate at day 40 and day 90.
- The current dataset did not show accumulation of fidaxomicin or OP-1118 plasma levels over 27 days. The MPR in plasma did not seem to be affected by the extended dosing scheme.
- The current dataset did not show accumulation of fidaxomicin or OP-1118 fecal levels over 27 days. The MPR in feces did not seem to be affected by the extended dosing scheme.
- The levels of fidaxomicin observed in plasma were very low.
- The 2 treatments investigated in this study had similar safety profiles.

Date of Report:

16 Feb 2017

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Table 2 Patient Disposition and Analysis Sets

Analysis Set	EPFX (n = 183)	Standard Vancomycin (n = 181)	Total (n = 364)
Randomized	183 (100.0%)	181 (100.0%)	364 (100.0%)
Safety analysis set †	181 (98.8%)	181 (100.0%)	362 (99.5%)
Modified full analysis set ‡	177 (96.7%)	179 (98.9%)	356 (97.8%)
Per protocol set §	124 (67.8%)	125 (69.1%)	249 (68.4%)
Pharmacokinetic analysis set ¶	14 (7.7%)	0	14 (3.8%)
Microbiologically evaluable analysis set	27 (14.8%)	22 (12.2%)	49 (13.5%)
Primary Reason for Treatment Discontinuation			
Randomized but never received/dispensed study drug	2 (1.1%)	0	2 (0.5%)
Adverse event	8 (4.4%)	2 (1.1%)	10 (2.7%)
Death	13 (7.1%)	4 (2.2%)	17 (4.7%)
Lack of efficacy	4 (2.2%)	4 (2.2%)	8 (2.2%)
Lost to follow-up	4 (2.2%)	0	4 (1.1 %)
Withdrawal by patient	6 (3.3%)	4 (2.2%)	10 (2.7%)
Physician decision	2 (1.1%)	0	2 (0.5%)
Non-compliance with study drug	1 (0.6%)	0	1 (0.3%)
Other	0	1 (0.6%)	1 (0.3%)
Primary Reason For Study Discontinuation			
Randomized but never received/dispensed study drug	2 (1.1 %)	0	2 (0.5%)
Death	29 (15.8%)	36 (19.7%)	65 (17.9%)
Lost to follow-up	6 (3.3%)	9 (5.0%)	15 (4.1%)
Withdrawal by patient	6 (3.3%)	7 (3.9%)	13 (3.6%)
Study terminated by sponsor	0	0	0
Physician decision	7 (3.8%)	2 (1.1%)	9 (2.5%)
Other	1 (0.5%)	2 (1.1%)	3 (0.8%)

EPFX: extended pulsed fidaxomicin; n (%): number (percentage) of patients. All randomized patients.

† All patients randomized who took at least 1 dose of study drug.

‡ All patients randomized who received at least 1 dose of study drug, had confirmed CDI and had valid assessment of TOC.

§ All patients who completed study treatment (EPFX) and had at least 2 plasma pharmacokinetic samples' taken within the specified windows.

¶ All patients who received at least 1 dose of the study treatment and provided at least 2 complete microbiome profiles within the specified windows.

Source: Tables 12.1.1.2, 12.1.1.3, 12.1.1.4

Table 3 Summary of Demographics and Baseline Characteristics for Patients, mFAS

Parameter Category/Statistics	EPFX (n = 177)	Standard Vancomycin (n = 179)	Total (n = 356)
Sex, n (%)			
Male	70 (39.5)	79 (44.1)	149 (41.9)
Female	107 (60.5)	100 (55.9)	207 (58.1)
Race, n (%) †			
White	149 (100.0)	153 (100.0)	302 (100.0)
Black or African American	0	0	0
Asian	0	0	0
Other	0	0	0
Age (y)			
Mean (SD)	75.3 (8.4)	74.8 (8.9)	75.1 (8.7)
Median	75.0	75.0	75.0
Min – Max	60 – 94	60 – 95	60 – 95
< 75 y, n (%)	80 (45.2)	82 (45.8)	162 (45.5)
≥ 75 y, n (%)	97 (54.8)	97 (54.2)	194 (54.5)
Weight (kg)			
Mean (SD)	68.70 (12.86)	68.98 (16.36)	68.84 (14.72)
Median	68.75	67.00	68.00
Min – Max	39.0 – 102.0	38.5 – 140.0	38.5 – 140.0
Height (cm)			
Mean (SD)	164.87 (9.05)	166.21 (8.64)	165.55 (8.86)
Median	165.00	167.00	1.66.00
Min – Max	145.0 – 198.0	147.0 – 187.0	145.0 – 198.0
BMI (kg/m2)			
Mean (SD)	25.21 (4.21)	24.90 (5.29)	25.05 (4.78)
Median	24.70	24.40	24.50
Min –Max	15.7 – 35.3	16.3 – 51.4	15.7 – 51.4

CDI: *C. difficile* infection; BMI: body mass index (weight [kg]/height [m^2]); EPFX: extended pulsed fidaxomicin; mFAS: Modified full analysis set; Max: maximum; Min: minimum; n (%): number (percentage) of patients.

mFAS: all enrolled patients who received at least 1 study drug and had confirmed CDI.

† 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 54 patients were classified as 'missing')

Source: Table 12.1.2.1.2

Table 4 Interim Analysis Results of Sustained Clinical Cure at 30 Days after EoT, mFAS

Statistic	EPFX (n = 88)	Standard Vancomycin (n = 99)	P value ‡
Sustained clinical cure (%)	82/88 (93.2)	78/99 (78.8)	
95% CI	(87.9, 98.4)	(70.7, 86.8)	
Treatment difference in % (95% CI) †	14.4 (4.8, 24.0)		0.011
OR vs vancomycin and 95% CI §	0.29 (0.11, 0.80)		

EoT: end of study; EPFX: extended pulsed fidaxomicin; mFAS: Modified full analysis set; n: number of patients: OR: odds ratio.

† Difference between the rates (EPFX - standard vancomycin) and the associated 95% CI around the difference.

‡ P value from the Cochran-Mantel-Haenszel test (general association) adjusted for the stratification factors used for the randomization.

§ Estimate of the common OR and 95% CI

Source: See Table 12.3.1.1.1 Interim Analysis Report Appendix 13.1.9.1

Table 5 Sustained Clinical Cure of CDI at 30 Days After End of Treatment, mFAS

Parameter/Statistic	EPFX (n = 177)	Standard Vancomycin (n = 179)
Sustained clinical cure (%)	124/177 (70.1)	106/179 (59.2)
95% CI	(63.3, 76.8)	(52.0, 66.4)
Treatment difference (95% CI) †	10.8 (1.0, 20.7)	-
P value ‡	0.030	-
OR vs vancomycin and 95% CI §	1.62 (1.04, 2.54)	-
Breslow-Day test ¶	0.034	-

CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; mFAS: modified full analysis set: n (%): number (percentage) of patients; OR: odds ratio.

- : not applicable.

† Difference between the rates (EPFX – standard vancomycin) and the associated 95% CI around the difference.

‡ P value from the Cochran-Mantel-Haenszel test (general association) adjusted for the randomization factors (CDI severity (severe or non-severe), presence or absence of cancer, age (≥ 75 years or < 75 years) and number of previous recurrences (0, 1, and 2).

§ Estimate of the common OR and 95% CI.

¶ P value from Breslow-Day test for homogeneity of the ORs across strata.

Source: Table 12.3.1.1.1

Table 6 Sustained Clinical Cure of CDI at 30 Days After End of Treatment, PPS

Parameter/Statistic	EPFX (n = 124)	Standard Vancomycin (n = 125)
Sustained clinical cure (%)	106/124 (85.5)	83/125 (66.4)
95% CI	(79.3, 91.7)	(58.1, 74.7)
Treatment difference (95% CI) †	19.1 (8.7, 29.4)	-
P value ‡	0.001	-
OR vs vancomycin and 95% CI §	2.99 (1.52, 5.90)	-
Breslow-Day test ¶	0.556	-

CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; n (%): number (percentage) of patients; OR: odds ratio; PPS: per protocol set.

- : not applicable.

† Difference between the rates (EPFX – standard vancomycin) and the associated 95% CI around the difference

‡ P value from the Cochran-Mantel-Haenszel test (general association) adjusted for the randomization factors (CDI severity (severe or non-severe), presence or absence of cancer, age (≥ 75 years or < 75 years) and number of previous recurrences (0, 1, and 2).

§ Estimate of the common OR and 95% CI.

¶ P value from Breslow-Day test for homogeneity of the ORs across strata.

Source: Table 12.3.1.1.4

Table 7 Multivariate Analysis for Sustained Clinical Cure of CDI at 30 Days After End of Treatment Logistic Regression Analysis, mFAS

Parameter/Statistic	Odds ratio (95% CI)	P value
mFAS EPFX arm n = 177; standard vancomycin arm, n = 179		
Treatment (EPFX vs standard vancomycin)	1.62 (1.04, 2.53)	0.035
Baseline CDI severity (severe vs non-severe)	0.57 (0.36, 0.91)	0.019
Presence of cancer (yes vs no)	0.59 (0.35, 1.01)	0.053
Age group (≥ 75 vs < 75 years)	0.83 (0.53, 1.30)	0.414
Number of previous recurrences（2 vs 0)	0.69 (0.26, 1.80)	0.444
Number of previous recurrences (1 vs 0)	0.61 (0.33, 1.11)	0.105

CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; mFAS: modified full analysis set; TOC: test of cure.

Sustained clinical cure is defined as clinical response (as determined by the investigator) at TOC and no recurrence of CDI from TOC until time of assessment. Logistic regression with treatment arm, baseline CDI severity, presence or absence of cancer, age (≥ 75 or < 75 years) and number of previous recurrences (0, 1, 2) as covariates.

Source: Table 12.3.1.1.3

Table 8 Multivariate Analysis for Sustained Clinical Cure of CDI at 30 Days After End of Treatment Logistic Regression Analysis, PPS

Parameter/Statistic	Odds ratio (95% CI)	P value
PPS EPFX arm n = 124; standard vancomycin arm n = 125		
Treatment (EPFX vs standard vancomycin)	3.12 (1.64, 5.93)	< 0.001
Baseline CDI severity (severe vs non-severe)	1.49 (0.73, 3.04)	0.273
Presence of cancer (yes vs no)	0.62 (0.29, 1.35)	0.227
Age group (≥ 75 vs < 75 years)	0.54 (0.28, 1.02)	0.059
Number of previous recurrences（2 vs 0)	0.53 (0.18, 1.63)	0.270
Number. of previous recurrences (1 vs 0)	0.43 (0.20, 0.92)	0.030

CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; PPS: per protocol set; TOC: Test of cure.

Sustained clinical cure is defined as clinical response (as determined by the investigator) at TOC and no recurrence of CDI from TOC until time of assessment. Logistic regression with treatment arm, baseline CDI severity, presence or absence of cancer, age (≥ 75 or < 75 years) and number of previous recurrences (0, 1, 2) as covariates.

Source: Table 12.3.1.1.6

Table 9 Sustained Clinical Cure of CDI, Overall, at Visit 4 (Day 40), Visit 5 (Day 55) and Visit 6 (Day 90), mFAS

Parameter/Statistic	EPFX (n = 177)	Standard Vancomycin (n = 179)
Visit 4 (Day 40)		
Sustained clinical cure (%)	133/177 (75.1)	106/179 (59.2)
95% CI	(68.8, 81.5)	(52.0, 66.4)
Treatment difference (95% CI) †	15.9 (6.3, 25.5)	-
P value	0.001	-
OR vs vancomycin and 95% CI §	2.10 (1.32, 3.34)	-
Breslow-Day test ¶	0.084	-
Visit 5 (Day 55)		
Sustained clinical cure (%)	124/177 (70.1)	99/179 (55.3)
95% CI	(63.3, 76.8)	(48.0, 62.6)
Treatment difference (95% CI) †	14.7 (4.8, 24.7)	-
P value	0.004	-
OR vs vancomycin and 95% CI §	1.91 (1.23, 2.98)	-
Breslow-Day test ¶	0.075	-
Visit 6 (Day 90)		
Sustained clinical cure (%)	116/177 (65.5)	92/179 (51.4)
95% CI	(58.5, 72.5)	(44.1, 58.7)
Treatment difference (95% CI) †	14.1 (4.0, 24.3)	-
P value	0.007	-
OR vs vancomycin and 95% CI §	1.80 (1.17, 2.77)	-
Breslow-Day test ¶	0.120	-

CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; mFAS: modified full analysis set; n (%): number (percentage of patients; OR: odds ratio.

- : not applicable

† Difference between the rates (EPFX – standard vancomycin) and the associated 95% CI around the difference.

‡ P value from the Cochran-Mantel-Haenszel test (general association) adjusted for the randomization factors CDI severity (severe or non-severe), presence or absence of cancer, age (≥ 75 years or < 75 years) and number of previous recurrences (0, 1, and 2).

§ Estimate of the common OR and 95% CI.

¶ P value from Breslow-Day test for homogeneity of the ORs across strata.

Source: Tables 12.3.1.2.1, 12.3.1.3.1, and 12.3.1.4.1

Table 10 Sustained Clinical Cure of CDI, Overall, at Visit 4 (Day 40), Visit 5 (Day 55) and Visit 6 (Day 90), PPS

Parameter/Statistic	EPFX (n = 124)	Standard Vancomycin (n = 125)
Visit 4 (Day 40)		
Sustained clinical cure (%)	113/124 (91.1)	83/125 (66.4)
95% CI	(86.1, 96.1)	(58.1, 74.7)
Treatment difference (95% CI) †	24.7 (15.1, 34.4)	-
P value	< 0.001	-
OR vs vancomycin and 95% CI §	5.83 (2.61, 13.05)	-
Breslow-Day test ¶	0.625	-
Visit 5 (Day 55)		
Sustained clinical cure (%)	106/124 (85.5)	78/125 (62.4)
95% CI	(79.3, 91.7)	(53.9, 70.9)
Treatment difference (95% CI) †	23.1 (12.6, 33.6)	-
P value	< 0.001	-
OR vs vancomycin and 95% CI §	3.61 (1.84, 7.07)	-
Breslow-Day test ¶	0.616	-
Visit 6 (Day 90)		
Sustained clinical cure (%)	100/124 (80.6)	75/125 (60.0)
95% CI	(73.7, 87.6)	(51.4, 68.6)
Treatment difference (95% CI) †	20.6 (9.6, 31.7)	-
P value	0.001	-
OR vs vancomycin and 95% CI §	2.71 (1.48, 4.96)	-
Breslow-Day test ¶	0.711	-

CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; n (%): number (percentage) of patients; OR: odds ratio; PPS: Per protocol set.

- : not applicable

† Difference between the rates (EPFX – standard vancomycin) and the associated 95% CI around the difference.

‡ P value from the Cochran-Mantel-Haenszel test (general association) adjusted for the randomization factors (CDI severity (severe or non-severe), presence or absence of cancer, age (≥ 75 years or < 75 years) and number of previous recurrences (0, 1, and 2).

§ Estimate of the common OR and 95% CI.

¶ P value from Breslow-Day test for homogeneity of the ORs across strata.

Source: Tables 12.3.1.2.4, 12.3.1.3.4 and 12.3.1.4.4

Table 11 Clinical Response of CDI at Visit 2 (Day 12) Stratified by Randomization Factors, mFAS and PPS

Parameter/Statistic	Odds ratio (95% CI)	P value
mFAS EPFX n = 177; standard vancomycin n = 179		
Baseline CDI severity (severe vs non-severe)	0.42 (0.24, 0.72)	0.002
Presence of cancer (yes vs no)	0.72 (0.39, 1.35)	0.311
Age group (≥ 75 vs < 75 years)	1.13 (0.65, 1.96)	0.660
Number of previous recurrences （2 vs 0)	1.09 (0.30, 3.96)	0.898
Number of previous recurrences (1 vs 0)	0.88 (0.42, 1.84)	0.733
PPS EPFX n = 124; standard vancomycin n = 125		
Baseline CDI severity (severe vs non-severe)	0.56 (0.25, 1.26)	0.160
Presence of cancer (yes vs no)	0.99 (0.35, 2.78)	0.985
Age group (≥ 75 vs < 75 years)	0.91 (0.40, 2.05)	0.818
Number of previous recurrences （2 vs 0)	0.96 (0.20, 4.60)	0.955
Number of previous recurrences (1 vs 0)	1.20 (0.39, 3.71)	0.754

CDI: *C. difficile* infection; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; EPFX: extended pulsed fidaxomicin; mFAS: modified full analysis set; n: number of patients; PPS: per protocol set.

Clinical response is defined as per the clinical judgment of the investigator based on the ESCMID criteria. Logistic regression with treatment arm, baseline CDI severity, presence or absence of cancer, age (≥ 75 or < 75 years) and number of previous recurrences (0, 1, 2) as covariates.

Source: Tables 12.2.3.2 and 12.3.2.5

Table 12 Clinical Response of CDI at 2 Days after EoT Logistic Regression Analysis, mFAS

Parameter/Statistic	Odds ratio (95% CI)	P value
mFAS EPFX n = 177; standard vancomycin n = 179		
Baseline CDI severity (severe vs non-severe)	0.54 (0.31, 0.92)	0.025
Presence of cancer (yes vs no)	0.49 (0.27, 0.88)	0.016
Age Group (≥ 75 vs < 75 years)	0.94 (0.55, 1.62)	0.825
Number of previous recurrences （2 vs 0)	1.27 (0.35, 4.65)	0.715
Number of previous recurrences (1 vs 0)	0.83 (0.41, 1.72)	0.624

CDI: *C. difficile* infection; EoT: end of treatment; EPFX: extended pulsed fidaxomicin; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; mFAS: modified full analysis set; n: number of patients.

Clinical response is defined as per the clinical judgment of the investigator based on the ESCMID criteria. Logistic regression with treatment arm, baseline CDI severity, presence or absence of cancer, age (≥ 75 or < 75 years) and number of previous recurrences (0, 1, 2) as covariates.

Source: Table 12.3.5.3

Table 13 Sustained Clinical Cure of CDI at Days 40, 55, and 90 and Clinical Response of CDI at Day 12 using Hochberg Procedure for Main Secondary Endpoints, mFAS

Endpoint	Raw P Value[†]	Adjusted P Value[‡]
Sustained clinical cure of CDI at visit 4 (day 40)	0.001	0.004
Sustained clinical cure of CDI at visit 5 (day 55)	0.004	0.012
Sustained clinical cure of CDI at visit 6 (day 90)	0.007	0.014
Clinical response of CDI at visit 2 (day 12)	0.721	0.721

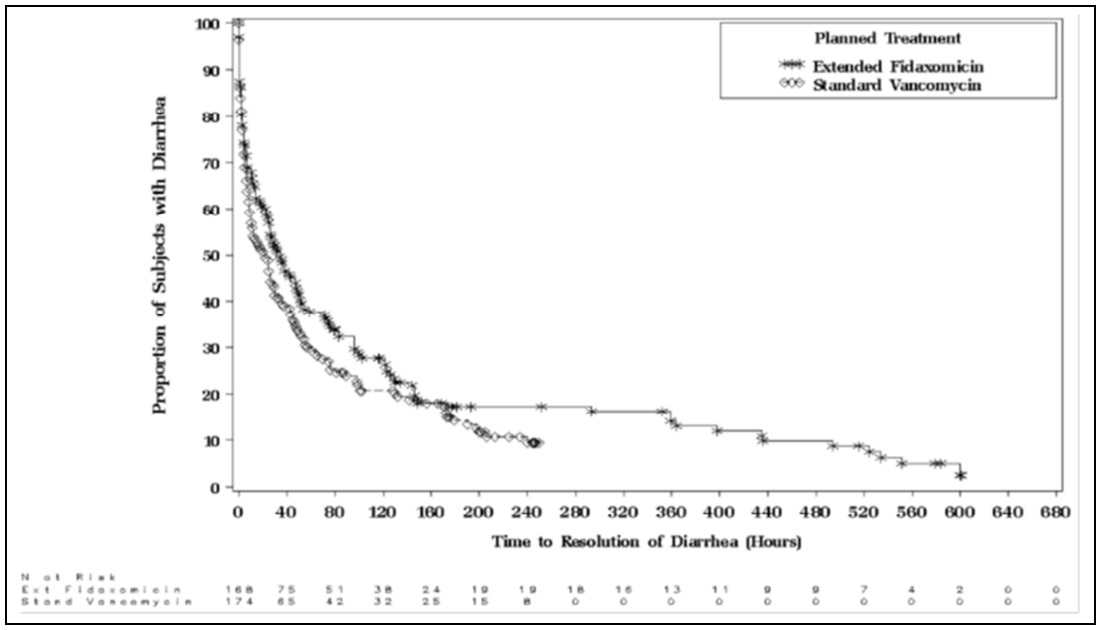
CDI: *C. difficile* infection; mFAS: modified full analysis set.

[†] P values from the Cochran-Mantel-Haenszel tests (general association) adjusted for the stratification variables taken from [Tables 12.3.1.2.3] (Sustained Clinical Cure of CDI at visit 4 [day 40]), [Table 12.3.1.3.3] (Sustained Clinical Cure of CDI at visit 5 [day 55]), [Table 12.3.1.4.3] (Sustained Clinical Cure of CDI at visit 6 [day 90]) and [Table 12.3.2.3] (Clinical Response of CDI at visit 2 [day 12]).

[‡]Adjusted P values obtained using the Hochberg method.

Source Table: 12.3.4

Figure 1 Time to Resolution of Diarrhea, mFAS



EPFX: extended pulsed fidaxomicin; mFAS: modified full analysis set; TOC: test of cure; UBM: unformed bowel movement.

Asterisk label denotes censored observation for the EPFX arm

Diamond label denotes censored observation for the standard vancomycin arm.

Time elapsing (in hours rounded up from minutes > 30) from the start of treatment (time of first dose of study medication) to resolution of diarrhea (time of the last UBM the day prior to the first of 2 consecutive days of ≤ 3 UBMs, > 50% reduction in number of stools or > 75% reduction in volume of liquid stool that are sustained through to TOC).

Source: Figure 12.3.1

Table 14 Recurrence of CDI at Visit 4 (Day 40), Visit 5 (Day 55) and Visit 6 (Day 90), mFAS

Parameter/Statistic	EPFX (n = 177)	Standard Vancomycin (n = 179)
Visit 4 (Day 40)		
Recurrence of CDI (%)	3/177 (1.7)	30/179 (16.8)
95% CI	(0.0, 3.6)	(11.3, 22.2)
Treatment difference (95% CI) †	-15.1 (-20.9, -9.3)	-
P value	< 0.001	-
OR vs vancomycin and 95% CI §	0.09 (0.03, 0.29)	-
Breslow-Day test ¶	0.671	-
Visit 5 (Day 55)		
Recurrence of CDI (%)	7/177 (4.0)	32/179 (17.9)
95% CI	(1.1, 6.8)	(12.3, 23.5)
Treatment difference (95% CI) †	-13.9 (-20.2, -7.6)	-
P value	< 0.001	-
OR vs vancomycin and 95% CI §	0.20 (0.08, 0.46)	-
Breslow-Day test ¶	0.535	-
Visit 6 (Day 90)		
Recurrence of CDI (%)	11/177 (6.2)	34/179 (19.0)
95% CI	(2.7, 9.8)	(13.2, 24.7)
Treatment difference (95% CI) †	-12.8 (-19.5, -6.0)	-
P value	< 0.001	-
OR vs vancomycin and 95% CI §	0.29 (0.14, 0.60)	-
Breslow-Day test ¶	0.593	-

CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; mFAS: modified full analysis set; n: number of patients; OR: Odds ratio; TOC: test of cure.

- : not applicable

† Difference between the rates (EPFX - standard vancomycin) and the associated 95% CI around the difference.

‡ P value from the Cochran-Mantel-Haenszel test (general association) adjusted for the randomization factors (CDI severity (severe or non-severe), presence or absence of cancer, age (≥ 75 years or < 75 years) and number of previous recurrences (0, 1, and 2).

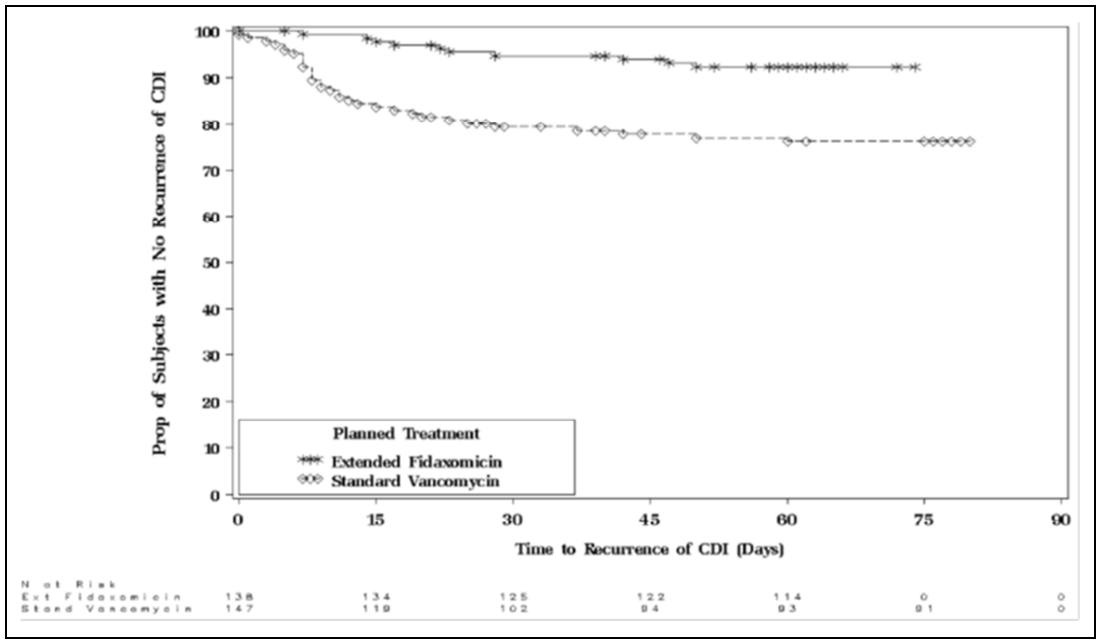
§ Estimate of the common OR and 95% CI.

¶ P value from Breslow-Day test for homogeneity of the ORs across strata.

Recurrence of CDI was defined as patients with a clinical response at TOC, re-establishment of diarrhea after TOC to an extent (judged by the frequency of passed UBMs) that was greater than the frequency recorded on day 10 for the standard vancomycin arm or day 25 for the EPFX arm (2 days prior to TOC), confirmed by a CDI test positive for Toxin A/B and requiring further CDI therapy.

Source: Tables 12.3.7.1.1, 12.3.7.2.1, and 12.3.7.3.1

Figure 2 Time to Recurrence of CDI After End of Treatment, mFAS



CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; mFAS: modified full analysis set; TOC: test of cure; UBM: unformed bowel movement.

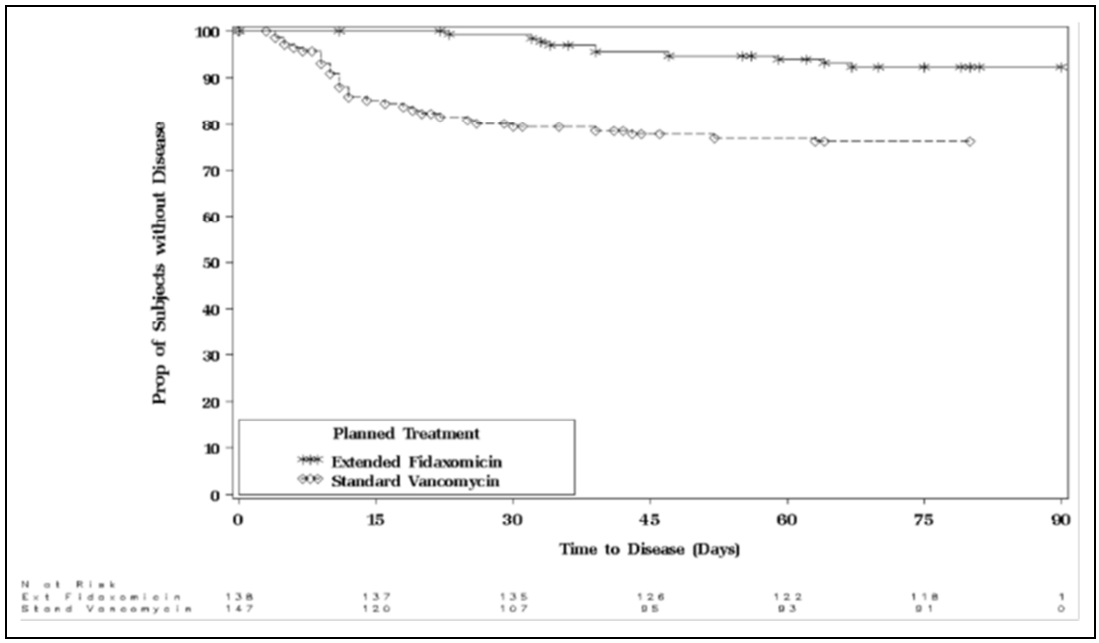
Asterisk label denotes censored observation for the EPFX arm

Diamond label denotes censored observation for the standard vancomycin arm.

Recurrence of CDI was defined as patients with a clinical response at TOC, re-establishment of diarrhea after TOC to an extent (judged by the frequency of passed UBMs) that was greater than the frequency recorded on day 10 for the standard vancomycin arm or day 25 for the EPFX arm (2 days prior to TOC), confirmed by a CDI test positive for toxin A/B and requiring further CDI therapy.

Source: Figure 12.3.2

Figure 3 Disease-Free Survival After Day 10, mFAS



CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; mFAS: modified full analysis set; TOC: test of cure; UBM: unformed bowel movement.

Asterisk label denotes censored observation for the EPFX arm
Diamond label denotes censored observation for the standard vancomycin arm.

Source: Figure 12.3.3

Table 15 Summary of Assessment CDI Toxin in Fecal Stool Samples, SAF

Visit	Statistic/ Category	EPFX (n = 181)	Standard Vancomycin (n = 181)	Total (n = 362)
Screening	n	168	166	334
	Positive	116 (69.0%)	115 (69.3%)	231 (69.2%)
	Negative	52 (31.0%)	51 (30.7%)	103 (30.8%)
Sub-Study visit (day 5)	n †	27	21	48
	Positive	5 (18.5%)	5 (23.8%)	10 (20.8%)
	Negative	22 (81.5%)	16 (76.2%)	38 (79.2%)
Visit 2 (day 12)	n	24	20	44
	Positive	1 (4.2%)	0	1 (2.3%)
	Negative	23 (95.8%)	20 (100.0%)	43 (97.7%)
Visit 3 (day 27)	n	20	17	37
	Positive	1 (5.0%)	3 (17.6%)	4 (10.8%)
	Negative	19 (95.0%)	14 (82.4%)	33 (89.2%)
Visit 4 (day 40)	n	21	16	37
	Positive	1 (4.8%)	3 (18.8%)	4 (10.8%)
	Negative	20 (95.2%)	13 (81.3%)	33 (89.2%)
Visit 5 (day 55)	n	19	14	33
	Positive	3 (15.8%)	2 (14.3%)	5 (15.2%)
	Negative	16 (84.2%)	12 (85.7%)	28 (84.8%)
Treatment failure (unscheduled visit)	n	2	5	7
	Positive	1 (50.0%)	1 (20.0%)	2 (28.6%)
	Negative	1 (50.0%)	4 (80.0%)	5 (71.4%)
Recurrence (unscheduled visit)	n	12	30	42
	Positive	8 (66.7%)	21 (70.0%)	29 (69.0%)
	Negative	4 (33.3%)	9 (30.0%)	13 (31.0%)

CDI: *C. difficile* infection; EPFX: extended pulsed fidaxomicin; n: number of patients; SAF: safety analysis set.

† Denotes the number of patients with treatment failure (at sub-study visit [day 5] or at visit 2 [day 12] or at recurrence).

Source: Table 12.3.14.1

Table 16 Summary of Plasma Concentrations of EPFX (ng/mL), 1 to 5 hours After Dosing, PKAS

Fidaxomicin (ng/mL)	Day 5 (n = 14)	Day 12† (n = 14)	Day 25/26‡ (n = 14)
Mean	33.0	29.4	15.0
SD	33.01	49.60	24.21
Min - Max	3.75 - 122	0 - 175	0 - 88.7
Median	25.15	6.03	6.93

EPFX: extended pulsed fidaxomicin; max: maximum; min: minimum; n: number of patients; PKAS: pharmacokinetic analysis set.

† If patients started in the morning with the EPFX regimen a blood sample was collected on day 11 or 13.

‡ If patients started in the morning with the EPFX regimen a blood sample was collected on day 25. If patients started in the afternoon a blood sample was collected on day 26.

Source: Table 12.4.1

Table 17 Summary of Plasma Concentrations of EPFX (OP 1118) (ng/mL), 1 to 5 hours After Dosing, PKAS

OP 1118 (ng/mL)	Day 5 (n = 14)	Day 12† (n = 14)	Day 25/26‡ (n = 14)
Mean	99.6	84.2	65.8
SD	90.68	110.60	110.52
Min - Max	14.2 - 325	0.936 - 339	0 - 372
Median	64.75	33.75	20.6

EPFX: extended pulsed fidaxomicin; max: maximum; min: minimum; n: number of patients; PKAS: pharmacokinetic analysis set.

† If patients started in the morning with the EPFX regimen a blood sample was collected on day 11 or 13.

‡ If patients started in the morning with the EPFX regimen a blood sample was collected on day 25. If patients started in the afternoon a blood sample was collected on day 26.

Source: Table 12.4.2

Table 18 Molecular Weight Corrected Metabolite to Parent Ratio of EPFX in Plasma, 1 to 5 hours After Dosing, PKAS

MPR (ng/mL)	Day 5 (n = 14)	Day 12† (n = 12)	Day 25/26‡ (n = 11)
Mean	3.7	6.1	6.0
SD	2.25	7.47	7.59
Min - Max	2.006 - 10.853	1.351 - 28.695	2.27 - 28.457
Median	3.1217	3.9428	3.4719

BLOQ: Below Limit of Quantification; EPFX: extended pulsed fidaxomicin; max: maximum; min: minimum; n: number of patients; PKAS: pharmacokinetic analysis set; MPR: metabolite/parent ratio.

Source: Table 12.4.2

Table 19 Summary of Stool Concentrations of EPFX (mcg/g), PKAS

Fidaxomicin (mcg/g)	Day 5 (n = 11)	Day 12 (n = 10)	Day 27 (n = 10)
Mean	998.6	177.4	278.6
SD	764.10	145.27	167.75
Min - Max	0 - 2630	12 - 437	0 - 524
Median	772	141.5	272.5

EPFX: extended pulsed fidaxomicin; max: maximum; min: minimum; n: number of patients; PKAS: pharmacokinetic analysis set.

Source: Table 12.4.3

Table 20 Summary of Stool Concentrations of EPFX Metabolite (OP 1118) (mcg/g), PKAS

OP 1118 (mcg/g)	Day 5 (n = 11)	Day 12 (n = 10)	Day 27 (n = 10)
Mean	709.5	292.7	358.6
SD	530.25	357.92	306.64
Min - Max	0 - 1820	30 - 1240	0 - 1120
Median	599	183.5	280.5

EPFX: extended pulsed fidaxomicin; max: maximum; min: minimum; n: number of patients; PKAS: pharmacokinetic analysis set

Source: Table 12.4.4

Table 21 Molecular Weight Corrected Metabolite to Parent Ratio of EPFX in Stool (mcg/g), PKAS

MPR (mcg/g)	Day 5 (n = 10)	Day 12 (n = 10)	Day 27 (n = 9)
Mean	0.8	1.7	1.9
SD	0.37	0.8	2.13
Min - Max	0.395 - 1.392	1.046 - 1240	0.495 - 7.14
Median	0.7396	1.4349	0.818

BLOQ: Below Limit of Quantification; EPFX: extended pulsed fidaxomicin; max: maximum; min: minimum; n: number of patients; MPR: metabolite/parent ratio.

BLOQ values are replaced with 0 in the summary statistics calculation. Concentration of OP-1118] x [mol.weight of fidaxomicin]/[concentration of fidaxomicin] x [mol.weight of OP-1118], where mol.weight of FDX = 1058.04 g/mol and mol.weight of OP-1118 = 987.949 g/mol.

Source: Table 12.4.5

Table 22 Overview of Treatment-emergent Adverse Events SAF

Parameter	EPFX (n = 181) n (%)	Number AEs	Standard Vancomycin (n = 181) n (%)	Number AEs	P value ¶
AEs	121 (66.9)	363	128 (70.7)	431	
Related† AEs	14 (7.7)	16	9 (5.0)	12	
Deaths	28 (15.5)	28 ‡	36 (19.9)	40 ‡	0.540
SAEs §	68 (37.6)	128	78 (43.1)	172	
Study drug-related† SAEs §	3 (1.7)	3	6 (3.3)	8	
AEs leading to discontinuation of study drug	14 (7.7)	16	5 (2.8)	6	
Study drug-related† AEs leading to permanent discontinuation of study drug	2 (1.1)	2	1 (0.6)	1	

Number of subjects (n), percentage of subjects (%) and number of events (#E)

AE: adverse events; EPFX: extended pulsed fidaxomicin; SAE: serious adverse event; SAF: safety analysis set.

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

An AE was defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

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

‡ Denotes the number of AEs that were reported with fatal outcome.

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

¶ Chi-square test for number of deaths.

Source: Table 12.6.1.1.1

Table 23 Treatment-emergent Adverse Events Occurring in at Least 1% of Patients (SOC), SAF

MedDRA v14.1 **System Organ Class** Preferred Term	**EPFX** **(n = 181)** **n (%)**	**Standard Vancomycin** **(n = 181)** **n (%)**
Overall	121 (66.9)	128 (70.7)
Blood and lymphatic system disorders	**10 (5.5)**	**14 (7.7)**
Anaemia	5 (2.8)	10 (5.5)
Febrile neutropenia	1 (0.6)	3 (1.7)
Cardiac disorders	**21 (11.6)**	**22 (12.2)**
Atrial fibrillation	2 (1.1)	3 (1.7)
Atrial flutter	2 (1.1)	1 (0.6)
Cardiac arrest	3 (1.7)	3 (1.7)
Cardiac failure	4 (2.2)	10 (5.5)
Cardiac failure acute	2 (1.1)	0
Cardiopulmonary failure	2 (1.1)	1 (0.6)
Tachycardia	2 (1.1)	1 (0.6)
Endocrine disorders	**0**	**3 (1.7)**
Hyperthyroidism	0	2 (1.1)
Gastrointestinal disorders	**46 (25.4)**	**47 (26.0)**
Abdominal pain	7 (3.9)	5 (2.8)
Aphthous stomatitis	0	2 (1.1)
Ascites	0	2 (1.1)
Constipation	10 (5.5)	5 (2.8)
Diarrhoea	10 (5.5)	12 (6.6)
Diverticulum intestinal	2 (1.1)	0
Febrile neutropenia	1 (0.6)	3 (1.7)
Gastric ulcer	2 (1.1)	0
Haematemesis	1 (0.6)	2 (1.1)
Nausea	8 (4.4)	7 (3.9)
Rectal haemorrhage	2 (1.1)	1 (0.6)
Vomiting	2 (1.1)	4 (2.2)
General disorders and administration site conditions	**23 (12.7)**	**29 (16.0)**
Death	3 (1.7)	3 (1.7)
Fatigue	3 (1.7)	1 (0.6)
Incorrect product storage	2 (1.1)	1 (0.6)
Non-cardiac chest pain	1 (0.6)	3 (1.7)
Oedema	3 (1.7)	3 (1.7)
Oedema peripheral	4 (2.2)	2 (1.1)
Pyrexia	7 (3.9)	12 (6.6)
Treatment failure	0	2 (1.1)
Hepatobiliary disorders	**6 (3.3)**	**6 (3.3)**
Cholangitis	2 (1.1)	0
Hepatic cirrhosis	0	2 (1.1)
Hepatic failure	0	2 (1.1)
Immune system disorders	**2 (1.1)**	**1 (0.6)**
Infections and infestations	**48 (26.5)**	**74 (40.9)**
Bronchopneumonia	1 (0.6)	2 (1.1)
Clostridial infection	7 (3.9)	24 (13.3)
Escherichia sepsis	0	3 (1.7)
Escherichia urinary tract infection	4 (2.2)	2 (1.1)
Gastroenteritis	2 (1.1)	0
Infected skin ulcer	0	2 (1.1)
Influenza	1 (0.6)	2 (1.1)
Nasopharyngitis	2 (1.1)	2 (1.1)
Oral candidiasis	2 (1.1)	2 (1.1)
Oral fungal infection	0	4 (2.2)
Pneumonia	5 (2.8)	10 (5.5)
Pyelonephritis	2 (1.1)	2 (1.1)

Table continued on next page

MedDRA v14.1 **System Organ Class** Preferred Term	**EPFX** **(n = 181)** **n (%)**	**Standard Vancomycin** **(n = 181)** **n (%)**
Sepsis	1 (0.6)	9 (5.0)
Septic shock	3 (1.7)	2 (1.1)
Upper respiratory tract infection	1 (0.6)	2 (1.1)
Urinary tract infection	6 (3.3)	12 (6.6)
Urinary tract infection bacterial	1 (0.6)	5 (2.8)
Injury, poisoning and procedural complications	**10 (5.5)**	**16 (8.8)**
Fall	4 (2.2)	3 (1.7)
Medication error	0	2 (1.1)
Investigations	**7 (3.9)**	**6 (3.3)**
Blood potassium decreased	0	2 (1.1)
Metabolism and nutrition disorders	**12 (6.6)**	**9 (5.0)**
Hypoalbuminaemia	1 (0.6)	2 (1.1)
Hypoglycaemia	3 (1.7)	1 (0.6)
Hypokalaemia	3 (1.7)	3 (1.7)
Hyponatraemia	0	3 (1.7)
Musculoskeletal and connective tissue disorders	**10 (5.5)**	**11 (6.1)**
Arthralgia	1 (0.6)	2 (1.1)
Back pain	2 (1.1)	4 (2.2)
Neck pain	0	2 (1.1)
Osteoarthritis	0	2 (1.1)
Pain in extremity	1 (0.6)	2 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**8 (4.4)**	**6 (3.3)**
Metastasis	2 (1.1)	0
Nervous system disorders	**7 (3.9)**	**15 (8.3)**
Headache	1 (0.6)	4 (2.2)
Syncope	0	2 (1.1)
Tremor	0	2 (1.1)
VIIth nerve paralysis	0	2 (1.1)
Psychiatric disorders	**11 (6.1)**	**9 (5.0)**
Confusional state	3 (1.7)	1 (0.6)
Depression	1 (0.6)	3 (1.7)
Insomnia	2 (1.1)	2 (1.1)
Sleep disorder	2 (1.1)	1 (0.6)
Renal and urinary disorders	**10 (5.5)**	**8 (4.4)**
Renal failure acute	3 (1.7)	2 (1.1)
Urinary retention	1 (0.6)	2 (1.1)
Reproductive system and breast disorders	**2 (1.1)**	**3 (1.7)**
Scrotal oedema	0	2 (1.1)
Respiratory, thoracic and mediastinal disorders	**23 (12.7)**	**23 (12.7)**
Acute respiratory failure	2 (1.1)	0
Chronic obstructive pulmonary disease	2 (1.1)	2 (1.1)
Cough	3 (1.7)	1 (0.6)
Dyspnoea	5 (2.8)	5 (2.8)
Epistaxis	1 (0.6)	2 (1.1)
Pleural effusion	2 (1.1)	4 (2.2)
Pulmonary embolism	2 (1.1)	1 (0.6)
Pulmonary oedema	1 (0.6)	3 (1.7)
Respiratory distress	1 (0.6)	2 (1.1)
Respiratory failure	2 (1.1)	4 (2.2)
Skin and subcutaneous tissue disorders	**7 (3.9)**	**8 (4.4)**
Pruritus	4 (2.2)	2 (1.1)
Skin lesion	0	2 (1.1)
Vascular disorders	**14 (7.7)**	**13 (7.2)**
Deep vein thrombosis	0	2 (1.1)

Table continued on next page

MedDRA v14.1 **System Organ Class** Preferred Term	**EPFX** **(n = 181)** **n (%)**	**Standard Vancomycin** **(n = 181)** **n (%)**
Haematoma	0	2 (1.1)
Hypertension	3 (1.7)	3 (1.7)
Hypotension	4 (2.2)	3 (1.7)

AE: adverse event; EPFX: extended pulsed fidaxomicin; n (%): number (percentage) of patients; SAE: serious adverse event; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Number of patients and percentage of patients (%) are shown with a cut-off point of 1% per AE.

Sorting order: alphabetical by system organ class and preferred term.

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

Within a system organ class, a patient may have reported more than 1 type of AE.

A TEAE was defined as an AE that started or a condition that existed pre-treatment that worsened after the first study drug intake.

Source: Table 12.6.1.2.

Table 24 Drug-related Treatment-emergent Adverse Events, SAF

MedDRA v14.1 **System Organ Class** Preferred Term	**Extended Pulsed Fidaxomicin (n = 181)** n (%)	**Standard Vancomycin (n = 181)** n (%)
Overall	14 (7.7)	9 (5.0)
Cardiac disorders	**0**	**1 (0.6)**
Cardiac failure	0	1 (0.6)
Gastrointestinal disorders	**5 (2.8)**	**3 (1.7)**
Constipation	4 (2.2)	0
Dyspepsia	0	1 (0.6)
Ileus	0	1 (0.6)
Nausea	1 (0.6)	1 (0.6)
General disorders and administration site conditions	**1 (0.6)**	**1 (0.6)**
Oedema	1 (0.6)	0
Treatment failure	0	1 (0.6)
Hepatobiliary disorders	**1 (0.6)**	**0**
Bile duct stone	1 (0.6)	0
Immune system disorders	**1 (0.6)**	**0**
Drug hypersensitivity	1 (0.6)	0
Infections and infestations	**0**	**3 (1.7)**
Clostridial infection	0	1 (0.6)
Klebsiella infection	0	1 (0.6)
Sepsis	0	1 (0.6)
Injury, poisoning and procedural complications	**0**	**1 (0.6)**
Overdose	0	1 (0.6)
Investigations	**1 (0.6)**	**0**
Gamma-glutamyltransferase increased	1 (0.6)	0
Metabolism and nutrition disorders	**1 (0.6)**	**0**
Hyperuricaemia	1 (0.6)	0
Nervous system disorders	**2 (1.1)**	**1 (0.6)**
Dizziness	1 (0.6)	0
Dysgeusia	1 (0.6)	0
Somnolence	0	1 (0.6)
Reproductive system and breast disorders	**1 (0.6)**	**0**
Vulvovaginal pruritus	1 (0.6)	0
Skin and subcutaneous tissue disorders	**3 (1.7)**	**1 (0.6)**
Eczema	0	1 (0.6)
Pruritus	3 (1.7)	0
Rash maculo-papular	0	1 (0.6)

AE: adverse event; EPFX: extended pulsed fidaxomicin; n (%): number (percentage) of patients; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Number of patients and percentage of patients (%) are shown.

Sorting order: alphabetical by system organ class and preferred term.

A TEAE was defined as an AE that started or a condition that existed pre-treatment that worsened after the first study drug intake.

Source: Table 12.6.1.3

Table 25 Deaths, SAF

Patient Number	Age/Sex	Primary Cause of Death Preferred Term (Investigator's Verbatim Term)	Day of Death	Last Dose Day	Relationship to Study Drug
Standard Vancomycin					
[redacted]	[redacted]	[redacted]	48	12	Not related
			8	8	Not related
			35	11	Not related
			32	11	Not related
			3	3	Not related
			38	11	Not related
			40	11	Not related
			16	11	Not related
			88	11	Not related
			20	10	Not related
			45	11	Not related
			3	3	Not related
			16	10	Not related
			41	11	Not related
			52	11	Not related
			74	11	Not related
			40	10	Not related
			61	12	Not related
			31	11	Not related
			34	11	Not related
			74	11	Not related
			21	5	Not related
			75	10	Not related
			31	10	Not related
			18	10	Not related
			39	10	Not related
			70	10	Not related
			85	11	Not related
			12	11	Probable
			54	11	Not related

Table continued on next page

Patient Number	Age/Sex	Primary Cause of Death Preferred Term (Investigator's Verbatim Term)	Day of Death	Last Dose Day	Relationship to Study Drug
[redacted]	[redacted]	[redacted]	40	10	Not related
[redacted]	[redacted]	[redacted]	51	11	Not related
[redacted]	[redacted]	[redacted]	86	11	Not related
[redacted]	[redacted]	[redacted]	59	11	Not related
[redacted]	[redacted]	[redacted]	54	10	Not related
[redacted]	[redacted]	[redacted]	39	12	Not related
EPFX					
[redacted]	[redacted]	[redacted]	17	12	Not related
[redacted]	[redacted]	[redacted]	42	25	Not related
[redacted]	[redacted]	[redacted]	89	25	Not related
[redacted]	[redacted]	[redacted]	16	9	Not related
[redacted]	[redacted]	[redacted]	65	26	Not related
[redacted]	[redacted]	[redacted]	57	8	Not related
[redacted]	[redacted]	[redacted]	25	23	Not related
[redacted]	[redacted]	[redacted]	6	5	Not related
[redacted]	[redacted]	[redacted]	23	Unknown	Not related
[redacted]	[redacted]	[redacted]	66	26	Not related
[redacted]	[redacted]	[redacted]	10	9	Not related
[redacted]	[redacted]	[redacted]	46	26	Not related
[redacted]	[redacted]	[redacted]	89	26	Not related
[redacted]	[redacted]	[redacted]	3	3	Not related
[redacted]	[redacted]	[redacted]	7	6	Not related
[redacted]	[redacted]	[redacted]	32	26	Not related
[redacted]	[redacted]	[redacted]	28	25	Not related
[redacted]	[redacted]	[redacted]	2	1	Not related
[redacted]	[redacted]	[redacted]	44	25	Not related
[redacted]	[redacted]	[redacted]	26	23	Not related
[redacted]	[redacted]	[redacted]	17	15	Not related

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Patient Number	Age/Sex	Primary Cause of Death Preferred Term (Investigator's Verbatim Term)	Day of Death	Last Dose Day	Relationship to Study Drug
[redacted]	[redacted]	[redacted]	10	9	Not related
[redacted]	[redacted]	[redacted]	7	3	Not related
[redacted]	[redacted]	[redacted]	41	1	Not related
[redacted]	[redacted]	[redacted]	17	14	Not related
[redacted]	[redacted]	[redacted]	85	26	Not related
[redacted]	[redacted]	[redacted]	72	26	Not related
[redacted]	[redacted]	[redacted]	96	25	Not related
[redacted]	[redacted]	[redacted]	85	26	Not related
[redacted]	[redacted]	[redacted]	3	2	Not related
[redacted]	[redacted]	[redacted]	22	4	Not related
[redacted]	[redacted]	[redacted]	3	1	Not related
[redacted]	[redacted]	[redacted]	12	9	Not related

AE: adverse event; EPFX: extended pulsed fidaxomicin; SAF: safety analysis set.

AEs were according to preferred term and the investigator's verbatim term (MedDRA v14.1) either were identified as serious by the investigator, or upgraded by the sponsor based on review of the sponsor's list of Always Serious terms.

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

† Four patients in the EPFX arm ([redacted]) were not included in Table 12.6.1.1.1 and Appendix 13.2.7.3 (refer to Attachment 1).

Source: Appendix 13.2.7.3 and Attachment 1

Table 26 Serious Treatment-emergent Adverse Events Reported with at Least 2% in SOC or PT, SAF

MedDRA v14.1 **System Organ Class** Preferred Term	**EPFX** **(n = 181)** **n (%)**	**Standard Vancomycin** **(n = 181)** **n (%)**
Overall	68 (37.6)	78 (43.1)
Blood and lymphatic system disorders †	**2 (1.1)**	**6 (3.3)**
Cardiac disorders	**14 (7.7)**	**16 (8.8)**
Cardiac failure	3 (1.7)	8 (4.4)
Gastrointestinal disorders †	**17 (9.4)**	**17 (9.4)**
General disorders and administration site conditions †	**8 (4.4)**	**10 (5.5)**
Hepatobiliary disorders †	**3 (1.7)**	**5 (2.8)**
Infections and infestations	**25 (13.8)**	**41 (22.7)**
Clostridial infection	5 (2.8)	18 (9.9)
Pneumonia	2 (1.1)	7 (3.9)
Sepsis	1 (0.6)	9 (5.0)
Urinary tract infection	1 (0.6)	4 (2.2)
Injury, poisoning and procedural complications †	**1 (0.6)**	**9 (5.0)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps) †	**7 (3.9)**	**6 (3.3)**
Nervous system disorders †	**1 (0.6)**	**6 (3.3)**
Respiratory, thoracic and mediastinal disorders	**12 (6.6)**	**12 (6.6)**
Respiratory failure	2 (1.1)	4 (2.2)
Vascular disorders †	**2 (1.1)**	**5 (2.8)**

AE: adverse event; EPFX: extended pulsed fidaxomicin; n (%): number (percentage) of patients; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
Sorting order: alphabetical by system organ class (with frequency of at least 2%) and preferred term.

† This SOC has no categories of PT with serious TEAEs that were ≥ 2%.
A TEAE was defined as an AE that started or a condition that existed pre-treatment that worsened after the first study drug intake.
Source: Table 12.6.1.6

Table 27 Drug-related Serious Treatment-emergent Adverse Events, SAF

MedDRA v14.1 **System Organ Class** **Preferred Term**	**EPFX** **(n = 181)** **n (%)**	**Standard Vancomycin** **(n = 181)** **n (%)**
Overall	3 (1.7)	6 (3.3)
Cardiac disorders	**0**	**1 (0.6)**
Cardiac failure	0	1 (0.6)
Gastrointestinal disorders	**0**	**1 (0.6)**
Ileus	0	1 (0.6)
General disorders and administration site conditions	**0**	**1 (0.6)**
Treatment failure	0	1 (0.6)
Hepatobiliary disorders	**1 (0.6)**	**0**
Bile duct stone	1 (0.6)	0
Immune system disorders	**1 (0.6)**	**0**
Drug hypersensitivity	1 (0.6)	0
Infections and infestations	**0**	**3 (1.7)**
Clostridial infection	0	1 (0.6)
Klebsiella infection	0	1 (0.6)
Sepsis	0	1 (0.6)
Nervous system disorders	**0**	**1 (0.6)**
Somnolence	0	1 (0.6)
Skin and subcutaneous tissue disorders	**1 (0.6)**	**1 (0.6)**
Eczema	0	1 (0.6)
Pruritus	1 (0.6)	0

AE: adverse event; EPFX: extended pulsed fidaxomicin; n (%): number (percentage) of patients; SAE: serious adverse event; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Number of patients and percentage of patients (%) are shown.

Sorting order: alphabetical by system organ class and preferred term.

A TEAE was defined as an AE that started or a condition that existed pre-treatment that worsened after the first study drug intake.

Source: Table 12.6.1.7

Table 28 Summary of Baseline Hematology and Biochemistry, SAF

Laboratory Test (Units)	EPFX Baseline (n = 181) n (%)	Standard Vancomycin Baseline (n = 181) n (%)
Absolute neutrophil count (10^6/L)		
n	171	166
Mean (SD)	9651.8 (7587.8)	8472.7 (5613.2)
Min	60	20
Median	7280.0	7040.0
Max	51870	30000
Lymphocytes (10^6/L)		
n	140	134
Mean (SD)	2186.8 (6516.1)	2022.8 (6789.9)
Min	1	1
Median	1509.0	1248.5
Max	77000	74594
Lymphocytes/leukocytes (fraction)		
n	144	131
Mean (SD)	0.1805 (0.1359)	0.1603 (0.1441)
Min	0.011	0.010
Median	0.1495	0.1370
Max	0.880	0.988
Neutrophils (10^6/L)		
n	72	79
Mean (SD)	8963.5 (8702.6)	8223.1 (5427.0)
Min	1040	0
Median	5982.0	6410.0
Max	51870	23500
Neutrophil band form (10^6/L)		
n	65	71
Mean (SD)	372.7 (882.0)	289.8 (509.9)
Min	0	0
Median	93.0	10.0
Max	5870	2500
Neutrophil band form/leukocytes (fraction)		
n	73	75
Mean (SD)	0.0366 (0.0575)	0.0291 (0.0417)
Min	0.000	0.000
Median	0.0200	0.0100
Max	0.340	0.200
Neutrophils/leukocytes (fraction)		
n	82	83
Mean (SD)	0.6770 (0.1623)	0.7063 (0.1642)
Min	0.090	0.000
Median	0.6785	0.7190
Max	0.958	0.950
Platelets (10^9/L)		
n	180	179
Mean (SD)	273.3 (113.5)	260.4 (117.8)
Min	17	0

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Laboratory Test (Units)	EPFX Baseline (n = 181) n (%)	Standard Vancomycin Baseline (n = 181) n (%)
Median	259.0	247.0
Max	585	693
Erythrocytes (10^{12}/L)		
n	180	177
Mean (SD)	3.916 (0.627)	3.841 (0.686)
Min	2.54	2.34
Median	3.890	3.780
Max	5.77	6.30
Leukocytes (10^9/L)		
n	180	179
Mean (SD)	12.81 (9.58)	11.59 (8.04)
Min	0.1	0.1
Median	9.97	9.70
Max	87.5	75.5
Albumin (g/L)		
n	157	148
Mean (SD)	31.0 (6.4)	29.9 (6.7)
Min	12	16
Median	31.0	29.9
Max	50	52
Alanine aminotransferase (U/L)		
n	164	150
Mean (SD)	24.5 (22.9)	26.2 (31.5)
Min	0	0
Median	17.5	17.2
Max	161	301
Aspartate aminotransferase (U/L)		
n	159	148
Mean (SD)	26.2 (24.8)	27.3 (24.1)
Min	0	0
Median	21.0	21.0
Max	251	156
Bilirubin (µmol/L)		
n	157	146
Mean (SD)	11.77 (9.53)	13.46 (26.68)
Min	2.5	0.5
Median	10.00	8.95
Max	80.0	318.1
Creatinine (µmol/L)		
n	178	175
Mean (SD)	112.5 (92.4)	108.3 (102.4)
Min	31	20
Median	86.0	76.0
Max	695	999
Gamma glutamyl transferase (U/L)		
n	149	138
Mean (SD)	67.7 (96.3)	48.1 (45.3)
Min	0	0

Table continued on next page

Laboratory Test (Units)	EPFX Baseline (n = 181) n (%)	Standard Vancomycin Baseline (n = 181) n (%)
Median	33.0	35.0
Max	751	256
Urea (mmol/L)		
n	171	168
Mean (SD)	11.40 (47.26)	8.32 (7.89)
Min	0.3	0.4
Median	5.66	6.00
Max	620.0	56.1
Glomerular filtration rate (mL/min per 1.73 m^2)		
n	178	175
Mean (SD)	62.78 (27.32)	67.13 (28.67)
Min	6.4	4.0
Median	64.00	70.90
Max	121.2	133.9

EPFX: extended pulsed fidaxomicin; n (%): number (percentage) of patients; SAF: safety analysis set.

Baseline is defined as the value at screening.

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

Source: Tables 12.6.2.1.1 and 12.6.2.1.2

Table 29 Summary of Clinically Significant Markedly Abnormal Liver Enzyme and Total Bilirubin Test Results, SAF

Parameters	Criteria	EPFX (n = 181) n (%)	Standard Vancomycin (n = 181) n (%)
ALT	> 3 x ULN	3/102 (2.9)	3/98 (3.1)
	> 5 x ULN	0	1/98(1.0)
	> 10 x ULN	0	0
	> 20 x ULN	0	0
AST	> 3 x ULN	1/101 (1.0)	5/98 (5.1)
	> 5 x ULN	1/101 (1.0)	0
	> 10 x ULN	0	0
	> 20 x ULN	0	0
ALT or AST	> 3 x ULN	5/102 (4.9)	9/99 (9.1)
Total bilirubin	> 2 x ULN	3/97 (3.1)	4/93 (4.3)
Alkaline phosphatase	> 1.5 x ULN	0	0
ALT and/or AST And total bilirubin†	ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN	0	2/168 (1.2)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; EPFX: extended pulsed fidaxomicin; n (%): number (percentage) of patients; SAF: safety analysis set; ULN: upper limit of normal range.

Maximum value on treatment is presented for each liver enzyme and total bilirubin.

The denominator was the number of patients who had at least 1 nonmissing value after first dosing.

† Combination of values measured within same sample.

Source: Table 12.6.2.2