Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Fidaxomicin		
Name of Active Ingredient: ASP2819		

SYNOPSIS

Title of Study: A Phase 3, Multicenter, Investigator-blind, Randomized, Parallel Group Study to Investigate the Safety and Efficacy of Fidaxomicin Oral Suspension or Tablets Taken q12h, and Vancomycin Oral Liquid or Capsules Taken q6h, for 10 Days in Pediatric Subjects with *Clostridium difficile*-associated Diarrhea (The SUNSHINE Study)

Investigators/Coordinating Investigator: [redacted], FRACP, [redacted] USA

Study Centers: 74 sites in North America and Europe, in 11 countries including the US (23 sites), Poland (9 sites), France (7 sites), Germany (7 sites), Romania (6 sites), Hungary (5 sites), Spain (5 sites), Italy (4 sites), Belgium (3 sites), Canada (3 sites) and Slovakia (2 sites).

Publication Based on the Study: None at the time of reporting

Study Period:

Study Initiation Date (Date of First Evaluation): 09 Jan 2015

Study Completion Date (Date of Last Evaluation): 07 Mar 2018

Phase of Development: Phase 3

Objectives:

Primary Objective

- To investigate the clinical response to fidaxomicin oral suspension or tablets and vancomycin oral liquid or capsules of pediatric subjects with *C. difficile*-associated diarrhea (CDAD) from birth to < 18 years of age

Secondary Objectives

- To investigate the recurrence/sustained clinical response (SCR) to and safety of fidaxomicin and vancomycin in pediatric subjects with CDAD from birth to < 18 years of age
- To investigate the palatability (acceptance) of the fidaxomicin oral suspension formulation.

Methodology: This was a multicenter, investigator-blind, randomized, parallel-group study to investigate the safety and efficacy of a 10-day course of fidaxomicin oral suspension or tablets and a 10 day course of vancomycin oral liquid or capsules in subjects from birth to < 18 years of age with confirmed CDAD. Subjects were randomized to either fidaxomicin or vancomycin arm in a 2:1 ratio, stratified by age group. A Data and Safety Monitoring Board (DSMB) was established for this study.

Number of Patients (Planned, Enrolled and Analyzed): A total of 144 eligible subjects were planned to be randomized; 159 patients signed informed consent and 148 patients were randomized; 144 of 148 randomized patients met the eligibility criteria and 142 patients received at least one dose of treatment [Figure 1].

Diagnosis and Main Criteria for Inclusion: Male and female subjects from birth (US only: ≥ 6 months) to < 18 years of age, diagnosed with CDAD according to local diagnostic criteria. As a minimum there was to be positive detection, within 72 hours prior to randomization, of either toxin A and/or toxin B in stool or positive detection of toxigenic *C. difficile* in stool and: a) from birth to < 2 years of age: watery diarrhea in the 24 hours prior to screening; b) ≥ 2 years to < 18 years of age: ≥ 3 unformed bowel movements (UBMs) in the 24 hours prior to screening; c) < 5 years of age: negative rotavirus test. Subjects were excluded if metronidazole, oral vancomycin or any other antibiotic treatments for CDAD was concurrently used. If the investigator felt the clinical imperative to begin treatment before knowing the laboratory result for toxigenic *C. difficile*, up to 4 doses but no more than 24 hours of treatment with metronidazole, oral vancomycin or any other effective treatment for CDAD were allowed.

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

Fidaxomicin granules for oral suspension were supplied as granules in a bottle. Fidaxomicin tablets provided to the sites were identical to the commercially available Dificlir 200-mg film-coated tablets (SmPC Dificlir); each tablet contained 200 mg of fidaxomicin.

Subjects from birth (US only: ≥ 6 months) to 6 years of age took fidaxomicin oral suspension, 32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses/day, for 10 days.

Subjects aged ≥ 6 years to < 18 years took fidaxomicin 200-mg tablets, 2 times daily, for 10 days.

Increases and reductions of dose were not permitted.

Batch numbers: fidaxomicin film coated tablets 200 mg: [redacted]; fidaxomicin granules for oral suspension 7.7 g: [redacted].

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

Subjects were scheduled to take the study drug for 10 days. The end of study (EOS) telephone call (TC)/visit took place 30 days after end of treatment (EOT).

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

Vancomycin oral liquid was supplied as powder for oral solution. Vancomycin capsules provided to the sites were commercially available 125-mg vancomycin capsules containing 125 mg vancomycin.

Subjects from birth (US only: ≥ 6 months) to 6 years of age took vancomycin oral liquid, 40 mg/kg/day with a maximum dose of 500 mg/day, divided in 4 doses/day, for 10 days.

Subjects aged ≥ 6 years to < 18 years took vancomycin 125-mg capsules, 4 times daily, for 10 days.

Increases and reductions of dose were not permitted.

Batch numbers: vancomycin capsules 125 mg: [redacted]; vancomycin powder for oral suspension 1 g: [redacted].

Criteria for Evaluation:

Efficacy

- Confirmed clinical response (CCR) based on the assessment by the investigator at EOT + 2 days TC/visit (primary endpoint),
- SCR at EOT + 30 days,
- SCR 14 days after CCR TC/visit (EOT + 16 days),
- Time to resolution of diarrhea (TTROD),
- Recurrence of CDAD during or at the end of the follow-up period, and
- Time to recurrence of CDAD during or at the end of the follow-up period.

Pharmacokinetics

- Plasma concentrations of fidaxomicin and its main metabolite (OP-1118) within 30 minutes predose and 1 to 5 hours postdose (the morning or evening dose) taken on any day from day 5 through day 10, and
- Fecal concentration of fidaxomicin and its main metabolite (OP-1118) within 24 hours of a dose taken on any day from day 5 through day 10.

Safety

- Adverse events (AEs; frequency, severity, seriousness, and relationship to study drug),
- Laboratory tests (hematology, biochemistry including liver function tests, urinalysis),
- Vital signs (systolic and diastolic blood pressure, pulse rate and body temperature), and
- 12-lead electrocardiogram (ECG).

Statistical Methods:

The Statistical Analysis Plan (SAP), Final Version 3.0 dated 20 Apr 2018, was finalized and signed prior to any of the following: study unblinding, database hard lock, interim analysis, or accumulation of substantial amount of data in an open-label study to ensure lack of bias.

The primary efficacy endpoint of CCR at EOT + 2 days as assessed by the investigator was analyzed using the primary analysis set of full analysis set (FAS). Within each treatment arm, the proportion of patients with CCR at EOT + 2 days was calculated based on the total number of patients in the FAS regardless of ICR status, and also over patients with nonmissing CCR (Yes/No). The corresponding 2-sided 95% CI was calculated based on an exact binomial distribution for each treatment group. The unadjusted difference of proportions (fidaxomicin - vancomycin) was also calculated. The proportion of patients with CCR and the unadjusted difference of proportions were also presented using the multiple imputation (MI) method (using exact binomial distribution for 95% CI). The same analyses were performed on the intent-to-treat (ITT) analysis set.

In addition, the adjusted treatment difference of proportions (fidaxomicin - vancomycin) by age group was calculated using a stratified Cochran-Mantel-Haenszel method, where the 95% CI was calculated using the Newcombe method. The strata consisted of the age grouping levels used during the stratified allocation of

patients at screening (birth to < 24 months of age, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years of age).

Completers were defined as patients who had completed the 10-day treatment period. Missing primary and selected secondary efficacy endpoints were handled by using logical derivations and thereafter a MI approach. Missing data were either derived or imputed via MI.

The following analyses were conducted as sensitivity analysis for the primary efficacy endpoint of CCR at EOT + 2 days using the FAS: Patients with observed and nonmissing CCR data at EOT + 2 days were analyzed as above. A patient with a missing CCR outcome or a CCR assessment marked as "Not done" was considered as nonresponder. In addition, the above statistical methods were applied to completers. Patients with a missing CCR outcome or a CCR assessment marked as "Not done" were considered as nonresponders. In this case, the proportion of patients with CCR at EOT + 2 days in each treatment group was calculated based on completers and not on the entire population (FAS). In a further sensitivity analysis, 2 patients were excluded from the fidaxomicin group because the hospital's Institutional Review Board (IRB) early terminated its approval of the study conduct at the site.

Analysis of the secondary efficacy endpoints were based on both the FAS and the ITT analysis set, except for SCR, recurrence of CDAD and palatability.

The number and percentage of patients with treatment-emergent adverse events (TEAEs) as classified by SOC and PT were summarized for each treatment group and for each age group category, also for: TEAEs of special interest, drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to permanent discontinuation of study drug, drug-related TEAEs leading to permanent discontinuation of study drug, and TEAEs excluding SAEs that equaled to or exceeded a threshold of 5.0% in either treatment group. The number of TEAEs and the number and percentage of patients with TEAEs, as classified by SOC and preferred term (PT), were summarized by severity and by relationship to study drug.

Quantitative clinical laboratory variables, i.e., hematology, biochemistry and urinalysis were summarized using descriptive statistics for each treatment group at each visit by age group. In addition, a within-patient change was calculated as the postbaseline measurement minus the baseline measurement and summarized in the same way. Vital signs were analyzed following the same approach. Potentially clinically significant criteria in liver function tests for alkaline phosphatase (ALP), alanine aminotransferase (ALT), total bilirubin (TBL), aspartate transaminase (AST) and their combination were defined.

ECG variables were summarized using descriptive statistics for each treatment group at each treatment visit and time point for each age group, including changes from baseline. The number and percent of patients with normal, not clinically significant abnormal and clinically significant abnormal results as assessed by investigator for the 12-lead ECG as well as the number and percent of patients with 12-lead ECG abnormalities (local and central review) were tabulated by treatment group at each treatment visit and time point by age group.

Summary of Results/Conclusions:

Study Population:

Treatment groups were balanced with respect to demographic Table 1 and diagnostic Table 2 characteristics, apart from the fact that patients receiving fidaxomicin appeared to be slightly older (mean 6.7 vs 6.2 years) and to have more prior episodes of diarrhea than those treated with vancomycin (42.9% vs 34.1%). More prevalent

in the medical history of the fidaxomicin group compared with the vancomycin group were metabolism and nutrition disorders (43.9% vs 25.0%), blood and lymphatic system disorders (40.8% vs 29.5%) (febrile neutropenia [18.4% vs 6.8%], thrombocytopenia [12.2% vs 6.8%]), immune system disorders (24.5% vs 4.5%) and respiratory, thoracic and mediastinal disorders (19.4% vs 4.5%) as well as constipation (19.4% vs 11.4%). Infections and infestations (52.0% vs 68.2%) were less common in the medical history of the fidaxomicin group.

Prior diarrhea episodes had been treated with antibacterial medication in 25.4% of patients overall (fidaxomicin: 28.6%, vancomycin: 18.2%) and with antibiotics in 21.8% of patients (fidaxomicin: 24.5%, vancomycin: 15.9%). Antiinfectives for systemic use had previously been taken by 88.7% of patients overall (fidaxomicin: 89.9%, vancomycin: 86.4%).

The proportion of patients who concomitantly took antiinfectives for systemic use was similar between fidaxomicin (74.5%) and vancomycin (72.7%). Of note, a greater proportion of patients in the fidaxomicin group compared with the vancomycin group were taking concomitant antidiarrheals, intestinal antiinflammatory/antiinfective agents (67.3% vs 50.0%), drugs for constipation (34.7% vs 22.7%) and mineral supplements (31.6% vs 22.7%).

Treatment compliance was high, with a mean of 98.0% in the fidaxomicin group and 95.8% in the vancomycin group. In none of the patients was study drug interrupted and restarted. Treatment compliance < 80% was recorded for slightly more patients in the vancomycin group than the fidaxomicin group (5 [11.4%] vs 4 [4.1%] patients).

Efficacy/Pharmacokinetic Results:

Primary Efficacy

In the primary analysis, the proportion of patients in the FAS with investigator-assessed CCR at EOT + 2 days was 77.6% (76 of 98 patients) in the fidaxomicin group and 70.5% (31 of 44 patients) in the vancomycin group, the adjusted difference being 7.5% (95% CI: -7.4%, 23.9%) [Table 3].

These results are supported by data from sensitivity analyses. In an analysis of completers (95 and 42 patients), the proportion of patients with CCR were 78.9 % for fidaxomicin and 73.8% for vancomycin (adjusted difference = 5.6%; 95% CI: -8.9%, 22.2%). In an analysis excluding 2 patients from the fidaxomicin group because the hospital's IRB early terminated its approval of the study conduct at the site, the proportion of patients with CCR was 77.1% for fidaxomicin and 70.5% for vancomycin (adjusted difference = 7.2%; 95% CI: -7.8%, 23.7%).

In the age group younger than 2 years, the proportion of patients with CCR was numerically lower for fidaxomicin than for vancomycin (65.0% vs 90.0%) but the difference was not statistically significant. This result should be viewed with caution due to the very small sample size (20 and 10 patients) and the possibility for random fluctuation in subgroups.

In the age group between 6 to 12 years, the proportion of patients with CCR was higher for fidaxomicin than for vancomycin (88.5% vs 50.0%), the difference being statistically significant (38.5%; 95% CI: 5.1%, 71.8%). The proportions of patients with CCR were similar between treatments for the other age groups, i.e., from 2 to 6 years and from 12 to 18 years.

In ITT analysis, with a proportion of patients with CCR at EOT + 2 days of 76.0% (76 of 100 patients) for fidaxomicin and 64.6% (31 of 48 patients) for vancomycin, the adjusted difference between treatments was 11.3% (95% CI: -4.0%, 27.3%), which is consistent with the results from the FAS.

Secondary Efficacy

The proportions of patients in the FAS with global cure at EOS (EOT + 30 days) were higher for fidaxomicin than for vancomycin (68.4% vs 50.0%), the adjusted difference being statistically significant (18.8%; 95% CI: 1.5%, 35.3%) Table 4. Similar results were observed for the ITT analysis set. Global cure rates at EOS in the age groups were numerically higher for fidaxomicin compared to vancomycin except for the youngest patient group (< 2 years). The differences between treatments in global cure rates were statistically significant only for patients from 6 to 12 years of age (difference = 52.3%; 95% CI: 20.3%, 84.4%).

The proportion of patients with recurrence at EOS (EOT + 30 days) was 11.8% for fidaxomicin and 29.0% for vancomycin, but the difference was not statistically significant Table 4. Similar results were observed in the different age groups. The estimated time until 20% of patients developed recurrence of CDAD was 25 and 8 days for fidaxomicin and vancomycin, respectively. The estimated median time to recurrence was 25 and 26 days, respectively. The difference between the time-to-recurrence functions was statistically significant (P = 0.023) Table 5.

The proportion of patients with SCR at EOS (EOT + 30 days) was 85.5% for fidaxomicin and 71.0% for vancomycin, but again the difference was not statistically significant Table 4. Similar results were observed in the different age groups.

The estimated median TTROD was 58 hours (2.4 days) and 97 hours (4.0 days) for fidaxomicin and vancomycin, respectively. The estimated time until 90% of patients achieved resolution of diarrhea was 222 hours (9.3 days) and 172 hours (7.2 days), respectively. The difference between the TTROD functions was not statistically significant Table 5.

Overall, among the secondary endpoints, global cure rate at EOS was statistically significantly higher for fidaxomicin than for vancomycin (68.4% vs 50.0%), and time to recurrence was statistically significantly longer. The other secondary endpoints, the proportion of patients with SCR, recurrence rate and TTROD indicated more favorable results for fidaxomicin but did not reach statistical significance. More patients in the vancomycin group had compliance < 80%, which needs to be taken into consideration when evaluating these results.

The palatability of formulation on day 1 was assessed as "good" and "excellent" for 34.5% and 23.6% of patients receiving fidaxomicin granules for oral suspension, respectively, and for 28.0% and 16.0% of those receiving vancomycin oral liquid. On day 7, "good" and "excellent" assessments were documented for 40.4% and 30.8% of patients treated with fidaxomicin granules for oral suspension and for 36.0% and 12.0% of patients treated with vancomycin oral liquid, respectively. While the acceptance rates increased with repeated use in both treatment groups, the level of acceptance of fidaxomicin granules for oral suspension appeared slightly higher than that of vancomycin oral liquid.

Pharmacokinetics

Out of the 98 patients treated with fidaxomicin, 95 were included in the pharmacokinetics analysis set.

For fidaxomicin, pre and postdose plasma concentration values were higher for tablets as compared to oral suspension (geometric mean [%CV], predose: tablets 12.52 [209.8] ng/mL vs oral suspension 9.19 [133.8] ng/mL, postdose: tablets 27.33 [143.9] ng/mL vs oral suspension 18.68 [167.0] ng/mL).

For OP-1118, its main metabolite, pre and postdose plasma concentration values were higher for tablets as compared to oral suspension (predose: tablets 32.58 [263.1] ng/mL vs oral suspension 25.32 [182.0] ng/mL, postdose: tablets 63.84 [199.3] ng/mL vs oral suspension 47.65 [239.5] ng/mL).

Postdose fecal concentrations for oral suspension were higher compared to tablets (2242.89 [91.4] µg/g vs 1438.81 [89.0] µg/g); however, for its metabolite OP-1118, postdose fecal concentrations for oral suspension were lower as compared to tablets (584.13 [92.3] µg/g vs 701.43 [88.8] µg/g).

For plasma concentration, the MPR was nearly similar between oral suspension and tablets (predose: 2.95 [45.1] and 2.79 (44.2), postdose: 2.73 [41.8] and 2.50 [39.4]). For fecal concentration, this ratio was nearly double for tablets as compared to oral suspension (0.52 [60.3] vs 0.28 [59.6]).

Safety Results:

The median duration of treatment was 11.0 days in both treatment groups; the mean duration was 10.7 days for patients on fidaxomicin and 10.5 days for those on vancomycin. The average daily dose was 345.6 mg and 431.5 mg for fidaxomicin and vancomycin, respectively.

TEAEs were recorded in 105 (73.9%) patients overall. The proportion of patients with TEAEs was comparable between both treatment groups (fidaxomicin: 73.5%, vancomycin: 75.0%) [Table 6]. A summary of common TEAEs, regardless of their relationship to study drug, is provided in [Table 7].

TEAEs were assessed by the investigator as drug-related in 12 (8.5%) patients overall, 7 (7.1%) in the fidaxomicin group and 5 (11.4%) in the vancomycin group, most frequently in the SOC of gastrointestinal (GI) disorders (fidaxomicin: 3.1%, vancomycin: 4.5%) and were generally mild and none was severe. The TEAEs considered drug-related in the fidaxomicin group were constipation (2.0%), diarrhea, oral candidiasis, pyrexia, ALT increased and irritability (1.0% each); in the vancomycin group, these were abdominal pain, vomiting, oral candidiasis, vulvovaginal mycotic infection and hypotension (2.3% each).

During formal study conduct, 3 deaths were reported in the fidaxomicin treatment arm in the youngest age group (< 2 years of age); none of those was assessed by the investigator as related to the study drug. Two deaths occurring shortly after the formal EOS observation were reported in the vancomycin treatment arm, also considered unrelated to study drug by the investigator [Table 6].

Serious TEAEs were most commonly reported in the SOCs of infections and infestations (9.2%), GI disorders (5.6%) and blood and lymphatic system disorders (4.2%) [Table 8]. Reports of serious TEAEs were more frequent for fidaxomicin compared with vancomycin for infections and infestations (10.2% vs 6.8%) and blood and lymphatic system disorders (5.1% vs 2.3%), while GI disorders were less frequently reported (4.1% vs 9.1%). The most frequently reported serious TEAEs by PT were pyrexia and febrile neutropenia (2.8% overall). None of the serious TEAEs were considered drug-related by the investigator.

TEAEs leading to permanent discontinuation of study drug were reported for 2 (1.4%) patients overall [Table 6], notably moderate colitis in a patient treated with fidaxomicin and severe vomiting in a patient receiving vancomycin. Both TEAEs were assessed by the investigator as not related to study drug.

The TEAEs of special interest most commonly recorded in the fidaxomicin group were hematological events including decreases in white blood cell (WBC), neutrophil and lymphocyte counts (12.2%), followed by hypersensitivity (9.2%) and hepatic and renal laboratory value abnormalities (5.1% each). Less common was GI hemorrhage (1.0%). QT prolongation as defined by broad standardized MedDRA query (SMQ) was not observed [Table 9].

One patient in the fidaxomicin group experienced a TEAE of anaphylactic reaction. This serious TEAE occurred on day 28 and was resolved on the following day. In the investigator's opinion, the event was assessed as not related to study drug.

ALT increased was experienced by 4 patients; AST increased and liver function test abnormal were experienced by 3 patients each. All these TEAEs occurred in the fidaxomicin group. Whereas TEAE frequency of liver enzyme abnormalities was higher for fidaxomicin than for vancomycin, such a pattern was not observed in the shift analyses [Table 10]. None of the renal events recorded in 6 patients were related to study drug, according to the investigator.

One case in the fidaxomicin group met the laboratory criteria of Hy's law with simultaneous elevations of "ALT > 3 x upper limit of normal (ULN) and TBL > 2 x ULN" and "AST > 3 x ULN and TBL > 2 x ULN". This was a [redacted]

No clinically significant changes or findings were noted from vital sign measurements including blood pressure, pulse rate and body temperature.

The most common 12-lead ECG abnormalities and findings from central review were related to rhythm (mainly sinus tachycardia) and QRS complex. Prolonged QTc interval was less common and observed at equal frequencies in both treatment groups (fidaxomicin: 11 patients, vancomycin: 6 patients) and was present at baseline. Except for 1 case related to underlying Leigh syndrome, none of the ECG findings were clinically significant abnormal.

Overall, the safety profile appears to be similar for fidaxomicin and vancomycin, except for a tendency towards fewer GI events and a slightly higher frequency of renal abnormalities and elevated liver enzymes in patients treated with fidaxomicin.

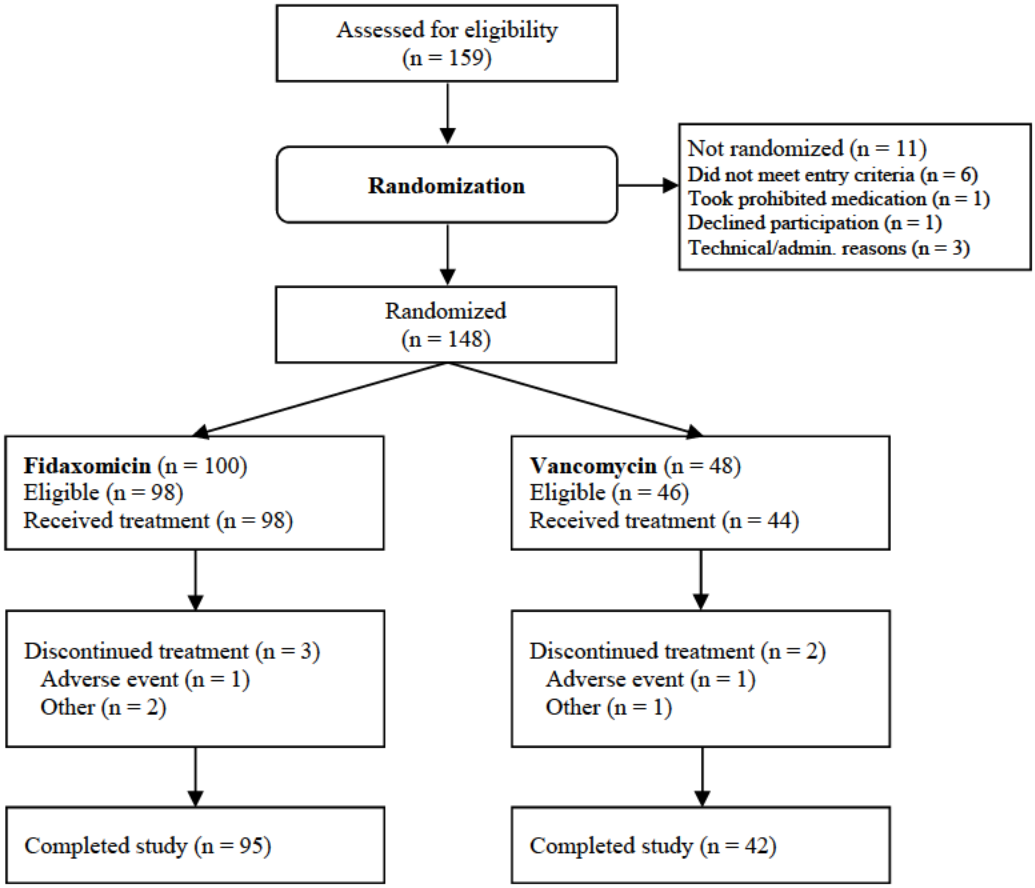
CONCLUSIONS:

Regarding the primary endpoint, the proportion patients with CCR at EOT + 2 days was 77.6% for fidaxomicin and 70.5% for vancomycin with an adjusted difference of 7.5% (95% CI: -7.4%, 23.9%). Among the secondary endpoints, global cure rate at EOS was statistically significantly higher for fidaxomicin than for vancomycin (68.4% vs 50.0%) and time to recurrence was statistically significantly longer. The other secondary endpoints, the proportion of patients with SCR, recurrence rate and TTROD indicated more favorable results for fidaxomicin but did not reach statistical significance.

The safety profile appears to be similar between both treatment groups, except for a tendency towards fewer GI events and a slightly higher frequency of renal abnormalities in the fidaxomicin group. The AE profile of fidaxomicin seen in the pediatric population matches that in the adult population; no suspected unexpected serious adverse reactions were reported. Overall, fidaxomicin granules for oral suspension and tablets administered with age-dependent dosing over 10 days was shown to be safe and well tolerated in the pediatric population.

Date of Report: 23 Aug 2018

Figure 1 Disposition of Subjects



Source: Tables 12.1.1.1, 12.1.1.2, 12.1.1.3.1, Appendices 13.1.7.1 and 13.2.2.2

Among the 48 patients randomized to vancomycin and did not receive treatment, 2 patients entered into the study even though they did not satisfy entry criteria (patients had a history of inflammatory bowel disease), 1 patient (who was eligible) parent withdraw consent and 1 patient (who was eligible) never received/dispensed study drug.

Table 1 Demographic Characteristics – FAS

Characteristic Statistic	Fidaxomicin (n = 98)	Vancomycin (n = 44)	Total (n = 142)
Sex			
Male	57 (58.2)	25 (56.8)	82 (57.7)
Female	41 (41.8)	19 (43.2)	60 (42.3)
Ethnicity			
Hispanic or Latino	12 (12.2)	5 (11.4)	17 (12.0)
Not Hispanic or Latino	80 (81.6)	33 (75.0)	113 (79.6)
Missing	6 (6.1)	6 (13.6)	12 (8.5)
Race†			
White	81 (82.7)	35 (79.5)	116 (81.7)
Black or African American	6 (6.1)	2 (4.5)	8 (5.6)
Asian	2 (2.0)	0	2 (1.4)
Other	4 (4.1)	1 (2.3)	5 (3.5)
Missing	5 (5.1)	6 (13.6)	11 (7.7)
Age (months)			
Mean (SD)	80.0 (62.2)	73.9 (60.0)	78.1 (61.3)
Median	60.0	48.0	60.0
Min – Max	1 – 204	8 – 204	1 – 204
Age Group, n (%)			
≥ 6 months to < 18 years	97 (99.0)	44 (100)	141 (99.3)
< 2 years	20 (20.4)	10 (22.7)	30 (21.1)
< 6 months	1 (1.0)	0	1 (0.7)
≥ 6 months to < 2 years	19 (19.4)	10 (22.7)	29 (20.4)
≥ 2 years to < 18 years	78 (79.6)	34 (77.3)	112 (78.9)
≥ 2 years to < 6 years	32 (32.7)	16 (36.4)	48 (33.8)
≥ 6 years to < 12 years	26 (26.5)	10 (22.7)	36 (25.4)
≥ 12 years to < 18 years	20 (20.4)	8 (18.2)	28 (19.7)
EudraCT Age Category, n (%)			
≥ 28 days to ≤ 23 months (infants and toddlers)	20 (20.4)	10 (22.7)	30 (21.1)
≥ 2 to ≤ 11 years (children)	58 (59.2)	26 (59.1)	84 (59.2)
≥ 12 to ≤ 17 years (adolescents)	20 (20.4)	8 (18.2)	28 (19.7)
Weight (kg)			
Mean (SD)	27.2 (20.7)	23.0 (13.6)	25.9 (18.9)
Median	19.2	17.9	18.6
Min – Max	4.3 – 100.0	5.8 – 52.1	4.3 – 100.0
Height (cm)			
n	96	44	140
Mean (SD)	115.9 (32.3)	113.3 (30.5)	115.1 (31.6)
Median	113.0	104.0	109.5
Min – Max	56.0 – 180.0	63.0 – 170.6	56.0 – 180.0
BMI (kg/m^2)			
n	96	44	140
Mean (SD)	17.3 (4.6)	16.4 (2.4)	17.1 (4.0)
Median	16.1	16.2	16.1
Min – Max	12.4 – 38.2	12.4 – 22.9	12.4 – 38.2

BMI: body mass index = weight (kg)/height^2 (m^2); EudraCT: European Clinical Trials Database; FAS: full analysis set; Max: maximum; Min: minimum.

The table gives the number (percentage) of patients, unless specified otherwise.

† Race is not allowed for France.

Source: Table 12.1.2.1.1

Table 2 Diagnosis of the Target Disease: Diarrhea and Bowel Movement History – FAS

Characteristic Statistic	Fidaxomicin (n = 98)	Vancomycin (n = 44)	Total (n = 142)
Diarrhea History in the 3 Months Prior to Screening			
Prior Diarrhea Episodes			
No	56 (57.1)	29 (65.9)	85 (59.9)
Yes	42 (42.9)	15 (34.1)	57 (40.1)
1	29 (29.6)	12 (27.3)	41 (28.9)
2	9 (9.2)	2 (4.5)	11 (7.7)
≥ 3	4 (4.1)	1 (2.3)	5 (3.5)
Prior Diarrhea Episodes with Confirmed CDAD			
Unknown	3 (3.1)	3 (6.8)	6 (4.2)
Not confirmed CDAD	11 (11.2)	2 (4.5)	13 (9.2)
Yes	28 (28.6)	10 (22.7)	38 (26.8)
1	21 (21.4)	7 (15.9)	28 (19.7)
2	5 (5.1)	2 (4.5)	7 (4.9)
≥ 3	2 (2.0)	1 (2.3)	3 (2.1)
Prior Diarrhea Episodes Treated With Antibacterial Medication†			
Not treated with such medication	14 (14.3)	7 (15.9)	21 (14.8)
Yes	28 (28.6)	8 (18.2)	36 (25.4)
1	19 (19.4)	6 (13.6)	25 (17.6)
2	6 (6.1)	1 (2.3)	7 (4.9)
≥ 3	3 (3.1)	1 (2.3)	4 (2.8)
Prior Diarrhea Episodes with Confirmed CDAD, Treated with Antibiotics			
Not treated with such medication	4 (4.1)	3 (6.8)	7 (4.9)
Yes	24 (24.5)	7 (15.9)	31 (21.8)
1	17 (17.3)	5 (11.4)	22 (15.5)
2	5 (5.1)	1 (2.3)	6 (4.2)
≥ 3	2 (2.0)	1 (2.3)	3 (2.1)
Bowel Movement History 24 Hours Prior to Screening			
Watery Diarrhea Present‡			
Yes	20 (20.4)	10 (22.7)	30 (21.1)
No	0	0	0
NA	78 (79.6)	34 (77.3)	112 (78.9)
Number of UBMs§			
n	78	33	111
Mean (SD)	6.4 (6.3)	6.3 (5.8)	6.4 (6.1)
Median	5.0	4.0	4.0
Min – Max	3 – 48	3 – 24	3 – 48
n (%)			
< 3	0	0	0
3 to 5	49 (50.0)	23 (52.3)	72 (50.7)
6 to 10	22 (22.4)	6 (13.6)	28 (19.7)
≥ 11	7 (7.1)	4 (9.1)	11 (7.7)
NA	20 (20.4)	10 (22.7)	30 (21.1)
Watery Diarrhea or ≥ 3 UBMs¶			
Yes	98 (100.0)	43 (97.7)	141 (99.3)
No	0	0	0
Unknown	0	1 (2.3)	1 (0.7)

CDAD: *Clostridium difficile*-associated diarrhea; FAS: full analysis set; Max: maximum; Min: minimum; NA: not applicable; UBM: unformed bowel movement.

Footnotes continued on next page.

The table gives the number (percentage) of patients, unless specified otherwise.

† Prior diarrhea episode treated with antibacterial medication irrespective of CDAD confirmation.

‡ Presence of watery diarrhea 24 h prior to screening (children < 2 years). Patients ≥ 2 years of age were included in the NA category.

§ Number of UBMs in the last 24 h prior to screening (children ≥ 2 years). Patients < 2 years of age were included in the NA category.

¶ Missing UBM in the 24 hours prior to screening was queried for 1 patient, and site answered the exact number was not known.

Source: Tables 12.1.2.2.1.1.1, 12.1.2.2.1.1.2

Table 3 Primary Analysis of Confirmed Clinical Response at EOT + 2 Days – FAS

Outcome Statistic	Fidaxomicin (n = 98)	Vancomycin (n = 44)	Difference (%)	Adjusted Difference (%)
ICR				
Yes	79 (80.6%)	36 (81.8%)	—	—
No	18 (18.4%)	8 (18.2%)	—	—
Missing	1 (1.0%)	0	—	—
CCR				
All patients†	n = 98	n = 44	—	—
Yes – n (%)	76 (77.6%)	31 (70.5%)	7.1%	7.5%
95% CIs (%)	(68.0%, 85.4%)	(54.8%, 83.2%)	—	(-7.4%, 23.9%)
Missing	3 (3.1%)	1 (2.3%)	—	—
Patients with CCR nonmissing	n = 95	n = 43	—	—
Yes – n (%)	76 (80.0%)	31 (72.1%)	7.9%	8.1%
95% CIs (%)	(70.5%, 87.5%)	(56.3%, 84.7%)	—	(-6.6%, 24.5%)
Imputing CCR missing/not done†‡	n = 98	n = 44	—	—
Yes – %	80.4%	72.7%	7.7%	8.2%
95% CIs (%)	(72.5%, 88.3%)	(59.6%, 85.9%)	—	(-7.1%, 23.6%)

CCR: confirmed clinical response; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; EOT: end of treatment; FAS: full analysis set; ICR: initial clinical response; MI: multiple imputation; TC: telephone call; —: not applicable.

† Including all patients regardless of ICR status.

‡ Missing information for CCR or not done at TC/visit (EOT + 2 days) was imputed using logical derivation and MI method.

Adjusted treatment difference of proportions was calculated using a stratified CMH method.

The stratification levels correspond to the age groups defined for randomization purposes.

Binomial exact 95% CIs are presented for treatment proportion and treatment difference, while Newcombe 95% CIs presented for adjusted treatment difference.

Source: Table 12.3.1.1

Table 4 Global Cure, Recurrence of CDAD and Sustained Clinical Response at EOS – FAS

Outcome Statistic	Fidaxomicin (n = 98)	Vancomycin (n = 44)	Difference (%)	Adjusted Difference (%)
Time Point: EOT + 30 days				
CCR Endpoint Derived†				
Yes	78 (79.6%)	32 (72.7%)	—	—
No	19 (19.4%)	12 (27.3%)	—	—
Missing	1 (1.0%)	0	—	—
Global Cure				
All patients‡				
Yes – n (%)	67 (68.4%)	22 (50.0%)	18.4%	18.8%
95% CIs (%)	(58.2%, 77.4%)	(34.6%, 65.4%)	—	(1.5%, 35.3%)
Imputing global cure missing/not done‡§				
Yes – %	70.4%	50.0%	20.4%	20.9%
95% CIs (%)	(61.3%, 79.6%)	(35.2%, 64.8%)	—	(4.0%, 37.8%)
Time Point: EOT + 30 days – Patients With Confirmed *C. Difficile* at Baseline				
CCR Endpoint Derived†				
Yes	35 (74.5%)	22 (78.6%)	—	—
No	12 (25.5%)	6 (21.4%)	—	—
Missing	0	0	—	—
Global Cure				
All patients‡				
Yes – n (%)	30 (63.8%)	14 (50.0%)	13.8%	16.2%
95% CIs (%)	(48.5%, 77.3%)	(30.6%, 69.4%)	—	(-6.7%, 37.6%)
Imputing global cure missing/not done‡§				
Yes – %	63.8%	50.0%	13.8%	16.2%
95% CIs (%)	(50.1%, 77.6%)	(31.5%, 68.5%)	—	(-6.0%, 38.4%)
Time Point: EOT + 30 days				
Patients with CCR at EOT + 2 days¶	76 (77.6%)	31 (70.5%)	—	—
Recurrence of CDAD				
Yes – n (%)	9 (11.8%)	9 (29.0%)	-16.9%	-15.8%
95% CIs (%)	(5.6%, 21.3%)	(14.2%, 48.0%)	—	(-34.5%, 0.5%)
Missing	2 (2.6%)	0	—	—
SCR				
Yes – n (%)	65 (85.5%)	22 (71.0%)	16.9%	15.8%
95% CIs (%)	(75.6%, 92.5%)	(52.0%, 85.8%)	—	(-0.5%, 34.5%)
Missing	2 (2.6%)	0	—	—

CCR: confirmed clinical response; CDAD: Clostridium difficile-associated diarrhea; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; CRF: case report form; EOS: end of study; EOT: end of treatment; FAS: full analysis set; ICR: initial clinical response; SCR: sustained clinical response; —: not applicable.

† CCR endpoint derived using logical derivation.

‡ Including all patients regardless of ICR/CCR status.

§ ICR/CCR and SCR derived endpoint (i.e., after logical derivation) are used to assess global cure. Adjusted treatment difference of proportions is calculated using a stratified CMH method. The stratification levels correspond to the age groups defined for randomization purposes. Binomial exact 95% CIs are presented for treatment proportion, while Newcombe 95% CIs presented for adjusted treatment difference.

¶ Using CCR endpoint as per CRF.

Source: Tables 12.3.2.1, 12.3.2.3, 12.3.4.1

Table 5 Time to Resolution of Diarrhea (Hours) and Time to Recurrence of CDAD (Days) for Patients with CCR at EOT + 2 Days – FAS

Parameter Category/Statistic	Fidaxomicin (n = 98)	Vancomycin (n = 44)	Log-rank Test P value
TTROD by K-M Method†			
n‡	98	44	—
Number of Patients with Events (Censored)	74 (24)	32 (12)	0.579
Q1 time (95% CI)	12 (1.0, 22.0)	29 (1.0, 46.0)	—
Median time (95% CI)	58 (29.0, 122.0)	97 (42.0, 146.0)	—
Q3 time (95% CI)	173 (148.0, NE)	172 (129.0, NE)	—
P80 time (95% CI)	222 (167.0, NE)	172 (148.0, NE)	—
P90 time (95% CI)	222 (NE, NE)	172 (NE , NE)	—
Time (hours)§			
n	74	32	—
Mean (SD)	55.1 (60.0)	63.2 (56.4)	—
Median	25.5	45.5	—
Min – Max	1 – 173	1 – 172	—
Time to recurrence by K-M Method¶			
n††	76	31	—
Number of Patients with Events (Censored)	9 (67)	9 (22)	0.023
P10 time (95% CI)	18 (7.0, NE)	6 (4.0, 8.0)	—
P20 time (95% CI)	25 (18.0, NE)	8 (4.0, NE)	—
Q1 time (95% CI)	25 (NE, NE)	14 (6.0, NE)	—
Median time (95% CI)	25 (NE, NE)	26 (NE, NE)	—
Time (days)			
n‡‡	9	9	—
Mean (SD)	11.9 (6.2)	9.1 (6.6)	—
Median	11.0	7.0	—
Min – Max	3 – 22	4 – 25	—

CCR: confirmed clinical response; CDAD: *Clostridium difficile*-associated diarrhea; CI: confidence interval; EOT: end of treatment; FAS: full analysis set; K-M: Kaplan-Meier; Max: maximum; Min: minimum; NE: not evaluable; P80: 80th percentile; Q1: first quartile (25th percentile) estimate, Q3: third quartile (75th percentile) estimate, TTROD: time to resolution of diarrhea; —: not applicable.

† Patients who completed the 10-day treatment period but did not show resolution of diarrhea until EOT were censored at day 10 (240 hours). Patients who did not complete the 10-day treatment period, discontinued treatment earlier but did not show resolution of diarrhea until day of discontinuation were censored at day of discontinuation (days converted to hours). Patients whose diarrhea did not continue after the first dose of study drug are included with a time to resolution to diarrhea of 1 hour.

‡ Number of patients in total, with valid resolution of diarrhea status.

§ Summary statistics for patients with observed event (resolution of diarrhea).

¶ Patients with CCR at EOT + 2 days, who completed the follow-up period but did not experience a recurrence of CDAD were censored at EOT + 30 days, and those who did not complete the follow-up period and discontinued during this period and did not experience a recurrence of CDAD were censored at day of discontinuation.

†† Number of patients with positive CCR.

‡‡ Summary statistics for patients with observed event (CDAD recurrence).

Source: Tables 12.3.3.1, 12.3.5.1

Table 6 Overview of Treatment-emergent Adverse Events – SAF

Incidence of TEAEs	Fidaxomicin (n = 98)	Vancomycin (n = 44)
TEAE	72 (73.5)	33 (75.0)
Drug-related† TEAE	7 (7.1)	5 (11.4)
Serious TEAE‡	24 (24.5)	12 (27.3)
Drug-related† Serious TEAE‡	0	0
Moderate TEAE‡	39 (39.8)	14 (31.8)
Drug-related† Moderate TEAE‡	4 (4.1)	1 (2.3)
Mild TEAE‡	56 (57.1)	30 (68.2)
Drug-related† Mild TEAE‡	3 (3.1)	4 (9.1)
TEAE Leading to Death	3 (3.1)	0§
Drug-related† TEAE Leading to Death	0	0
TEAE leading to Withdrawal of Treatment	1 (1.0)	1 (2.3)
Drug-related† TEAE Leading to Withdrawal of Treatment	0	0

SAF: safety analysis set; TEAE: treatment-emergent adverse event.

The table gives the number (percentage) of patients.

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

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

§ Two patients from the vancomycin treatment arm died after end of study.

Source: Table 12.6.1.1.1

Table 7 Summary of Common (≥ 5% in Either Treatment Group) Treatment-emergent Adverse Events – SAF

MedDRA V17.0 SOC Preferred Term	Fidaxomicin (n = 98)	Vancomycin (n = 44)
Gastrointestinal Disorders	**31 (31.6)**	**19 (43.2)**
Abdominal pain	5 (5.1)	9 (20.5)
Vomiting	7 (7.1)	6 (13.6)
Diarrhoea	7 (7.1)	5 (11.4)
Constipation	5 (5.1)	1 (2.3)
Infections and Infestations	**31 (31.6)**	**15 (34.1)**
Oral candidiasis	3 (3.1)	3 (6.8)
General Disorders and Administration Site Conditions	**23 (23.5)**	**11 (25.0)**
Pyrexia	13 (13.3)	10 (22.7)
Metabolism and Nutrition Disorders	**14 (14.3)**	**4 (9.1)**
Blood and Lymphatic System Disorders	**11 (11.2)**	**4 (9.1)**
Skin and Subcutaneous Tissue Disorders	**9 (9.2)**	**5 (11.4)**
Pruritus	3 (3.1)	3 (6.8)
Investigations	**12 (12.2)**	**2 (4.5)**
Respiratory, Thoracic and Mediastinal Disorders	**9 (9.2)**	**4 (9.1)**
Nervous System Disorders	**12 (12.2)**	**0**
Headache	8 (8.2)	0
Psychiatric Disorders	**6 (6.1)**	**1 (2.3)**
Injury, Poisoning and Procedural Complications	**5 (5.1)**	**2 (4.5)**
Renal and Urinary Disorders	**4 (4.1)**	**3 (6.8)**
Musculoskeletal and Connective Tissue Disorders	**4 (4.1)**	**3 (6.8)**

SAF: safety analysis set.

The table gives the number (percentage) of patients.

Sorting order: descending order of frequency (total), by system organ class and preferred term.

Source: Table 12.6.1.2.1

Table 8 Summary of Serious Treatment-emergent Adverse Events (≥ 2% in Either Treatment Group) – SAF

MedDRA V17.0 SOC Preferred Term	Fidaxomicin (n = 98)		Vancomycin (n = 44)	
	n (%)	E	n (%)	E
Infections and Infestations	**10 (10.2)**	**11**	**3 (6.8)**	**4**
Sepsis	2 (2.0)	2	0	0
Clostridium difficile colitis	0	0	1 (2.3)	1
Fungal sepsis	0	0	1 (2.3)	1
Influenza	0	0	1 (2.3)	1
Scedosporium infection	0	0	1 (2.3)	1
Gastrointestinal Disorders	**4 (4.1)**	**4**	**4 (9.1)**	**5**
Colitis	0	0	1 (2.3)	1
Diarrhoea	0	0	1 (2.3)	1
Gastrointestinal necrosis	0	0	1 (2.3)	1
Ileus paralytic	0	0	1 (2.3)	1
Intestinal obstruction	0	0	1 (2.3)	1
Blood and Lymphatic System Disorders	**5 (5.1)**	**8**	**1 (2.3)**	**1**
Febrile neutropenia	3 (3.1)	6	**1 (2.3)**	**1**
General Disorders and Administration Site Conditions	**3 (3.1)**	**4**	**2 (4.5)**	**2**
Pyrexia	2 (2.0)	2	2 (4.5)	2
Metabolism and Nutrition Disorders	**3 (3.1)**	**3**	**0**	**0**
Dehydration	2 (2.0)	2	0	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**2 (2.0)**	**2**	**1 (2.3)**	**1**
Malignant ascites	0	0	1 (2.3)	1
Nervous System Disorders	**2 (2.0)**	**3**	**0**	**0**
Renal and Urinary Disorders	**2 (2.0)**	**2**	**1 (2.3)**	**1**
Renal failure acute	2 (2.0)	2	0	0
Renal failure	0	0	1 (2.3)	1
Immune System Disorders	**2 (2.0)**	**2**	**0**	**0**
Respiratory, Thoracic and Mediastinal Disorders	**1 (1.0)**	**1**	**1 (2.3)**	**1**
Respiratory failure	0	0	1 (2.3)	1
Investigations	**0**	**0**	**1 (2.3)**	**1**
Heart rate irregular	0	0	1 (2.3)	1

E: includes each occurrence of an event; SAF: safety analysis set.

Sorting order: descending order of frequency (total), by system organ class and preferred term.

Source: Table 12.6.1.6.1

Table 9 Treatment-emergent Adverse Events of Special Interest – SAF

	Fidaxomicin (n = 98)		**Vancomycin (n = 44)**	
MedDRA V17.0 SMQ	n (%)	E	n (%)	E
Decreases in WBC, neutrophil and lymphocyte counts (hematological events)†	12 (12.2)	43	4 (9.1)	6
Hypersensitivity‡	9 (9.2)	12	4 (9.1)	4
Hepatic laboratory value abnormalities (potential DILI)	5 (5.1)	7	1 (2.3)	1
Renal laboratory value abnormalities (renal events)§	5 (5.1)	5	1 (2.3)	1
Gastrointestinal hemorrhage‡	1 (1.0)	1	0	0
QT prolongation§	0	0	0	0

DILI: drug-induced liver injury; E: includes each occurrence of an event; SAF: safety analysis set; SMQ: standardized MedDRA query; WBC: white blood cell.

Sorting order: descending order of frequency (total).

† Identified via medical review

‡ SMQ narrow

§ SMQ broad

Source: Table 12.6.1.12.1

Table 10 Summary Shifts in Laboratory Test Results: Liver Enzymes and Creatinine – SAF

Parameter	Fidaxomicin (n = 98)	Vancomycin (n = 44)
Alanine aminotransferase (U/L)		
Shift to Low†	2/94 (2.1)	1/41 (2.4)
Shift to High‡	13/76 (17.1)	6/29 (20.7)
Categorized Increase§	12/76 (15.8)	7/29 (24.1)
Categorized No Change¶	73/96 (76.0)	30/43 (69.8)
Categorized Decrease††	9/94 (9.6)	6/41 (14.6)
Aspartate aminotransferase (U/L)		
Shift to Low†	1/89 (1.1)	0/40
Shift to High‡	9/84 (10.7)	5/32 (15.6)
Categorized Increase§	12/84 (14.3)	7/32 (21.9)
Categorized No Change¶	78/96 (81.3)	32/42 (76.2)
Categorized Decrease††	4/89 (4.5)	3/40 (7.5)
Gamma-glutamyl transferase (U/L)		
Shift to Low†	4/69 (5.8)	1/36 (2.8)
Shift to High‡	12/65 (18.5)	3/22 (13.6)
Categorized Increase§	16/65 (24.6)	3/22 (13.6)
Categorized No Change¶	61/86 (70.9)	31/40 (77.5)
Categorized Decrease††	4/69 (5.8)	5/36 (13.9)
Bilirubin (µmol/L)		
Shift to Low†	8/54 (14.8)	9/23 (39.1)
Shift to High‡	0/93	0/40
Categorized Increase§	15/93 (16.1)	6/40 (15.0)
Categorized No Change¶	66/96 (68.8)	28/41 (68.3)
Categorized Decrease††	10/54 (18.5)	7/23 (30.4)
Creatinine (µmol/L)		
Shift to Low†	3/97 (3.1)	0/43
Shift to High‡	5/96 (5.2)	0/43
Categorized Increase§	5/96 (5.2)	1/43 (2.3)
Categorized No Change¶	87/97 (89.7)	42/44 (95.5)
Categorized Decrease††	3/97 (3.1)	1/43 (2.3)

EOT: end of treatment; SAF: safety analysis set.

The table displays shifts from baseline to EOT, as number (percentage) of patients.

† High → low, normal → low, or missing at baseline to low at postbaseline. The denominator for shift to low is the number of patients who had any postbaseline value and did not have low at baseline.

‡ Low → high, normal → high, or missing at baseline to high at postbaseline. The denominator for shift to high is the number of patients who had any postbaseline value and did not have high at baseline.

§ Low → high, normal → high, or low → normal. The denominator for categorized increase is the number of patients who had any postbaseline value and did not have high at baseline.

¶ High → high, normal → normal, or low → low. The denominator for categorized no change is the number of patients with a nonmissing baseline and postbaseline value.

†† High → low, normal → low, or high → normal. The denominator for categorized decrease is the number of patients who had any postbaseline value and did not have low at baseline.

Source: Table 12.6.2.4.2.2