Safety and Efficacy of Fidaxomicin and Vancomycin in Children and Adolescents with *Clostridioides (Clostridium) difficile* Infection: A Phase 3, Multicenter, Randomized, Single-blind Clinical Trial (SUNSHINE)

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(See the Editorial Commentary by Kociolek on pages 2589–91.)

Background. Fidaxomicin, a narrow-spectrum antibiotic approved for *Clostridioides (Clostridium) difficile* infection (CDI) in adults, is associated with lower rates of recurrence than vancomycin; however, pediatric data are limited. This multicenter, investigator-blind, phase 3, parallel-group trial assessed the safety and efficacy of fidaxomicin in children.

Methods. Patients aged <18 years with confirmed CDI were randomized 2:1 to 10 days of treatment with fidaxomicin (suspension or tablets, twice daily) or vancomycin (suspension or tablets, 4 times daily). Safety assessments included treatment-emergent adverse events. The primary efficacy end point was confirmed clinical response (CCR), 2 days after the end of treatment (EOT). Secondary end points included global cure (GC; CCR without CDI recurrence) 30 days after EOT (end of study; EOS). Plasma and stool concentrations of fidaxomicin and its active metabolite OP-1118 were measured.

Results. Of 148 patients randomized, 142 were treated (30 <2 years old). The proportion of participants with treatment-emergent adverse events was similar with fidaxomicin (73.5%) and vancomycin (75.0%). Of 3 deaths in the fidaxomicin arm during the study, none were CDI or treatment related. The rate of CCR at 2 days after EOT was 77.6% (76 of 98 patients) with fidaxomicin and 70.5% (31 of 44) with vancomycin, whereas the rate of GC at EOS was significantly higher in participants receiving fidaxomicin (68.4% vs 50.0%; adjusted treatment difference, 18.8%; 95% confidence interval, 1.5%–35.3%). Systemic absorption of fidaxomicin and OP-1118 was minimal, and stool concentrations were high.

Conclusions. Compared with vancomycin, fidaxomicin was well tolerated and demonstrated significantly higher rates of GC in children and adolescents with CDI.

Clinical Trials Registration. NCT02218372

Keywords. *Clostridioides difficile* infection; fidaxomicin; vancomycin; pediatric.

Clostridioides difficile (formerly *Clostridium difficile*) infection (CDI) is caused by an anaerobic, spore-forming, gram-positive bacterium [1], and is the leading cause of nosocomial diarrhea in developed countries [2]. Although CDI is classically considered

a hospital-acquired, antibiotic-associated infection, the incidence of community-acquired CDI is also on the rise [3]. Furthermore, the incidence of pediatric CDI seems to be increasing [4], most notably among patients with comorbid conditions, such as cancer [5] or inflammatory bowel disease [6]. The severity of CDI is variable, ranging from asymptomatic colonization or self-limiting diarrhea to fulminant colitis [7]. In hospitalized children, CDI has been associated with increased length of stay and increased risk of mortality [8]. However, because asymptomatic colonization with toxigenic *C. difficile* is common in children aged <2 years [9, 10], the clinical significance of this organism as a cause of diarrhea in young infants is uncertain [11].

The Infectious Disease Society of America and Society for Healthcare Epidemiology of America guidelines for the treatment of CDI in children recommend vancomycin or

metronidazole for an initial nonsevere episode or first recurrence, and vancomycin (with or without metronidazole) for an initial severe episode [12]. However, although these antibiotics are successful in approximately 80%–90% of initial episodes [13, 14], up to 40% of children with CDI experience a recurrence of infection within 60 days [15–17]. Risk factors for recurrence in children include cancer and chronic comorbid conditions [15]; in adults, recurrence is associated with advanced age and the use of non-CDI antibiotics during or after CDI treatment, among other factors [18–20]. Consequently, efforts have been directed toward the development of new antibiotics that reduce the risk of CDI recurrence.

The macrocyclic antibiotic fidaxomicin was approved in the United States and in the European Union in 2011 for the treatment of CDI in patients aged ≥18 years [21, 22]. Two phase 3 registration trials in adults have shown that fidaxomicin is noninferior to vancomycin for initial clinical cure of CDI and is associated with a significant 10%–15% reduction in the risk of recurrence at 28 days after the end of treatment (EOT) [23, 24]. However, patients aged <16 years were excluded from both studies, and the safety and efficacy of fidaxomicin in children aged <18 years has not been established [25]. This is reflected in the Infectious Disease Society of America/Society for Healthcare Epidemiology of America guidelines, which note that insufficient safety and efficacy data are available to recommend the use of fidaxomicin in children with CDI [12], although occasional off-label use has been reported [26].

In a phase 2a pediatric study, 38 patients aged <18 years with CDI received 16 mg/kg fidaxomicin (up to a maximum of 200 mg) twice daily for 10 days. The initial clinical response rate at EOT was 92.1%, with a recurrence rate of 31.4% within 28 days after EOT [27]. Safety outcomes from the study suggested that fidaxomicin was well tolerated in children [27]. The recurrence rate was higher than the 12.7%–15.4% observed in the phase 3 studies in adults [23, 24]; this difference may be because a majority of patients in the pediatric study had prior CDI and/or comorbid conditions. The present study (SUNSHINE) aimed to evaluate the safety and efficacy of fidaxomicin in children and adolescents with CDI.

PATIENTS AND METHODS

Ethics

The study was conducted in accordance with Good Clinical Practice, the International Council for Harmonization guidelines, and the ethical principles of the Declaration of Helsinki. The study protocol and all amendments were approved by the relevant independent ethics committee or institutional review board at each study site, and by local authorities before study initiation for sites in the European Union. All patients and/or their legally authorized representatives provided written informed consent according to local regulations.

Study Design and Patients

The SUNSHINE study was a prospective, multicenter, randomized, investigator-blind, phase 3 parallel-group trial, enrolling patients from 39 sites across the United States, Canada, and Europe. Participants were <18 years of age at enrollment and had CDI diagnosed according to study criteria (watery diarrhea in patients aged <2 years or ≥3 unformed bowel movements within 24 hours before screening in those aged ≥2 years, plus detection of toxin A/B or toxigenic *C. difficile* in stool within 72 hours before randomization using ≥1 local diagnostic test). Participants <5 years of age were required to have a negative rotavirus test. Exclusion criteria included concurrent use of other antibiotic treatments for CDI (unless administered for <24 hours and ≤4 doses); presence of pseudomembranous colitis, fulminant colitis, toxic megacolon or ileus, or a history of inflammatory bowel disease. At French sites, children with body weight <2.5 kg were excluded; at US sites, infants <6 months of age were excluded.

After screening, patients were randomized 2:1 to 10 days of treatment with either fidaxomicin (16 mg/kg oral suspension twice daily [maximum, 400 mg/d] for patients aged 0 to <6 years, or 200-mg tablets twice daily for patients aged ≥6 to <18 years) or vancomycin (10 mg/kg oral liquid 4 times daily [maximum, 500 mg/d] for patients aged 0 to <6 years, or 125-mg capsules 4 times daily for those aged ≥6 to <18 years) (Figure 1). Randomization was stratified by age group and conducted using interactive response technology. Investigators and site staff involved in the assessment of study outcomes were blinded to treatment allocation, but patients, their guardians and other site staff were not. Treatment adherence was assessed based on the weight of the oral suspension or count of tablets or capsules used during the treatment period.

Assessments and End Points

All patients, including those who discontinued study treatment early, were followed up for safety and efficacy until 30 days after EOT (end of study, EOS), unless consent was withdrawn (Figure 1). The safety analysis set and full analysis set (FAS) comprised all randomized patients who received ≥1 dose of study drug.

Safety assessments included adverse events (AEs; recorded throughout) including AEs of special interest (Supplementary Table 1), plus laboratory tests and vital signs (recorded at screening, EOT, and any unscheduled visit if deemed necessary by the investigator). The primary efficacy end point was confirmed clinical response (CCR), defined as initial clinical response at EOT with no further requirement for CDI therapy at 2 days after EOT (Supplementary Table 1 and Figure 1). Secondary efficacy end points included global cure at EOS (GC), time to resolution of diarrhea, CDI recurrence, and time to CDI recurrence (Supplementary Table 1). Diarrhea symptoms and severity were captured using a standardized questionnaire.
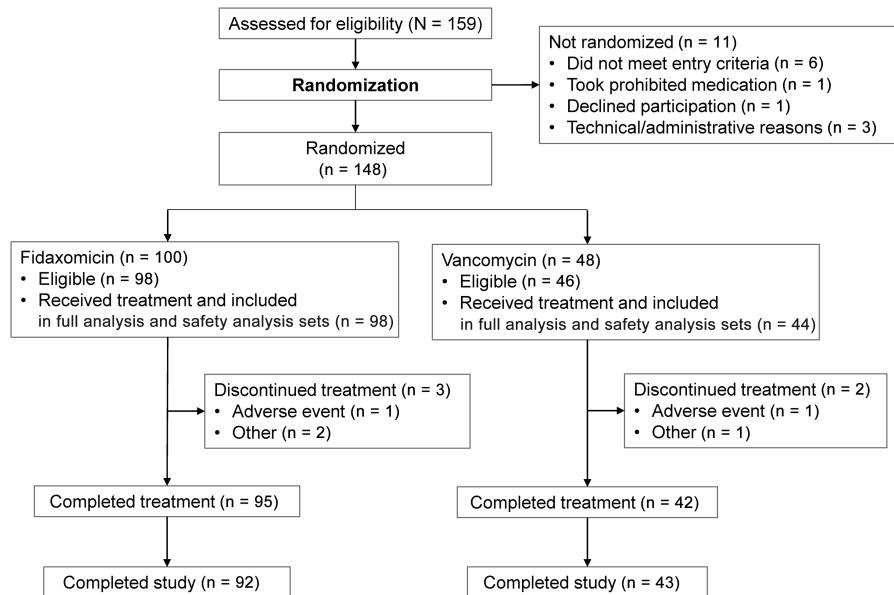
Figure 1. Study design. The choice between oral suspension and tablets depended on the patient's ability to swallow tablets. Abbreviations: CCR, confirmed clinical response (initial clinical response at end of treatment (EOT) with no further requirement for CDI therapy at 2 days after EOT); CDI, *Clostridioides* (*Clostridium*) *difficile* infection; EOS, end of study; GC, global cure (confirmed clinical response without CDI recurrence until the time of assessment, calculated as a proportion of all patients in the full analysis set); ICR, initial clinical response.

Blood samples for the measurement of plasma concentrations of fidaxomicin and its main metabolite OP-1118 were taken within 30 minutes before and 1–5 hours after the dose, on any of days 5–10. Stool samples for the measurement of fidaxomicin and OP-1118 concentrations were taken within 24 hours of any dose from day 5 to day 10. Pharmacokinetic data were summarized for all patients who received ≥1 dose of fidaxomicin and had ≥1 valid measurement of fidaxomicin or OP-1118 concentrations in plasma or stool (pharmacokinetic analysis set).

Prior and Concomitant Medication

Receipt of any investigational therapy for 28 days before screening, with the exception of cancer treatments that do not affect assessment of diarrhea, was prohibited. Concurrent use of other CDI treatments, antidiarrheal drugs, or fecal transplantation was prohibited during the study period, unless given for primary treatment failure or suspected CDI recurrence after initial clinical response at EOT (Supplementary Table 1). Pretreatment for CDI before randomization was discouraged. Drugs that affect peristalsis and potent P-glycoprotein inhibitors (eg, cyclosporine) were withheld during the study period if possible.

Sample Size and Analysis

The target sample size, based on clinical and practical considerations, was 144 eligible patients, with ≥24 patients in each of the following age groups: 0 to <24 months (≥6 to <24 months in the United States), ≥2 to <6 years, ≥6 to <12 years, and ≥12 to <18 years. The study was not designed as a superiority trial and was not powered for this purpose. Post hoc analyses of efficacy

outcomes were conducted in subgroups of patients with compromised immunity and those ≥2 years of age with CDI diagnosed by means of direct toxin detection. Further statistical methods are detailed in the Supplementary Methods.

RESULTS

Patient Characteristics

Of 159 patients screened, 148 patients were randomized: 100 to fidaxomicin and 48 to vancomycin (Figure 2). A total of 142 patients received study treatment as allocated and were included in the safety analysis set and the FAS. In the fidaxomicin arm, the median age of patients was higher (60.0 months) than in the vancomycin arm (48.0 months), and a greater proportion of patients had confirmed CDI in the 3 months before screening (28.6% vs 22.7%) (Table 1). In most patients, CDI was diagnosed using either polymerase chain reaction or direct toxin test (Table 1). A substantial proportion of patients in both treatment groups had ≥1 chronic comorbid condition, including infections, gastroesophageal reflux disease, and neoplasms (Table 1); the number of patients who received medications for constipation in the 30 days before the study was similar across treatment arms (fidaxomicin, 11 of 98 [11.2%]; vancomycin, 5 of 44 [11.4%]). The majority of patients (122 of 142 [85.9%]) had no protocol deviations during the study Supplementary Results. Thirty patients <2 years of age were enrolled in the study, all of whom had a positive toxigenic *C. difficile* result and a negative rotavirus result before screening (Supplementary Table 2).

Figure 2. Patient flow through the study. Of the 2 patients randomized to fidaxomicin who did not receive treatment, 1 did not meet the diagnostic criteria for *Clostridioides* (*Clostridium*) *difficile* infection (CDI), and 1 did not meet the diagnostic criteria for CDI and had received an investigational therapy ≤28 days before screening. Of the 4 patients randomized to vancomycin who did not receive treatment, 2 entered the study although they did not satisfy entry criteria owing to a history of inflammatory bowel disease, 1 eligible patient withdrew consent, and 1 eligible patient did not receive the study drug. Five patients in the fidaxomicin arm completed treatment but did not complete the study. Two patients in the fidaxomicin arm and 1 in the vancomycin arm did not complete treatment but completed the study.

Safety

Adverse Events

The proportions of patients with treatment-emergent AEs (TEAEs) were similar in the treatment arms, as were the proportions experiencing serious TEAEs (Table 2). The incidence of TEAEs was similar between age groups (Table 2). Drug-related TEAEs were experienced by 7.1% of fidaxomicin and 11.4% of vancomycin recipients (Table 2). No serious TEAE was attributed to study treatment by the blinded investigators. The 2 TEAEs that led to study discontinuation were moderate colitis in a fidaxomicin-treated patient and severe vomiting in a vancomycin-treated patient. Three deaths occurred in the fidaxomicin arm during the study period and 2 deaths in the vancomycin arm shortly after the end of the study period; none of these deaths were CDI or treatment related (Supplementary Results). The microbial susceptibility of *C. difficile* isolates to fidaxomicin and vancomycin seemed to be unchanged during treatment (Supplementary Results).

Laboratory Abnormalities and Hypersensitivity

During the study, 80 AEs of special interest occurred (Table 2), 1 of which (an elevated alanine aminotransferase level) was assessed by the investigator as possibly related to fidaxomicin treatment. Hematological AEs seemed to be slightly more common in fidaxomicin recipients (Table 2), most of which were attributed to chemotherapy for cancer.

Efficacy Outcomes

The proportion of participants with CCR at 2 days after EOT was 77.6% (76 of 98) in the fidaxomicin and 70.5% (31 of 44) in the vancomycin group (adjusted treatment difference 7.5%; 95% confidence interval [CI], −7.4% to 23.9%) (Supplementary Figure 1 and Figure 3). Resolution of diarrhea was achieved and sustained through EOT in 74 of 98 patients (75.5%) in the fidaxomicin and 32 of 44 (72.7%) in the vancomycin arm. The median time to resolution of diarrhea was shorter in the fidaxomicin arm (58 hours; 95% CI, 29–122 hours) than in with vancomycin arm (97 hours; 42–146 hours) (Supplementary Table 3), but the difference between the Kaplan-Meier survival functions was not statistically significant (Supplementary Figure 2).

Of patients in whom CCR was achieved, CDI recurrence before EOS occurred in 11.8% (9 of 76) in the fidaxomicin and 29.0% (9 of 31) in the vancomycin arm (adjusted treatment difference, −15.8%; 95% CI, −34.5% to .5%) (Figure 3). As shown in Supplementary Figure 3, the cumulative incidence of recurrence was significantly higher in participants who received vancomycin compared with fidaxomicin (log-rank P = .02). The overall rate of GC at EOS was statistically significantly higher in participants treated with fidaxomicin (68.4% [67 of 98]) versus vancomycin (50.0% [22 of 44]) (adjusted treatment difference, 18.8%; 95% CI, 1.5%–35.3%) (Figure 3).

Subgroup analyses for participants aged ≥2 years showed increased treatment differences in favor of fidaxomicin for CCR at 2 days after EOT, recurrence, and GC (Figure 3). Among immunocompromised patients, the rates of CCR 2 days after EOT were similar with fidaxomicin and vancomycin, and although the rate of GC seemed higher with fidaxomicin, the difference

Table 1. Patient Demographics, Baseline Characteristics, and Treatment Adherence (Full Analysis Set)

Characteristic	Patients, No. (%)	
	Fidaxomicin (n = 98)	Vancomycin (n = 44)
Patient demographics		
Female sex	41 (41.8)	19 (43.2)
White race	81 (82.7)	35 (79.5)
Age, median (IQR), mo	60.0 (24–132)	48.0 (24–111)
Age group		
<6 mo	1 (1.0)	0
≥6 mo to <2 y	19 (19.4)	10 (22.7)
≥2 to <6 y	32 (32.7)	16 (36.4)
≥6 to <12 y	26 (26.5)	10 (22.7)
≥12 to <18 y	20 (20.4)	8 (18.2)
Relevant medical history[a]		
Infections	51 (52.0)	30 (68.2)
Gastrointestinal disorders	53 (54.1)	25 (56.8)
Abdominal pain	17 (17.3)	8 (18.2)
Constipation	19 (19.4)	5 (11.4)
Gastroesophageal reflux disease	15 (15.3)	6 (13.6)
Nausea	25 (25.5)	8 (18.2)
Vomiting	32 (32.7)	11 (25.0)
Neoplasms	44 (44.9)	19 (43.2)
Acute lymphocytic leukemia	14 (14.3)	5 (11.4)
Blood and lymphatic system disorders	40 (40.8)	13 (29.5)
Anemia	15 (15.3)	5 (11.4)
Neutropenia	13 (13.3)	8 (18.2)
Thrombocytopenia	12 (12.2)	3 (6.8)
History of diarrhea		
Diarrhea episodes in 3 mo before screening	42 (42.9)	15 (34.1)
With confirmed CDI	28 (28.6%)	10 (22.7%)
Without confirmed CDI	11 (11.2%)	2 (4.5%)
Unknown CDI confirmation	3 (3.1%)	3 (6.8%)
Watery diarrhea or ≥3 UBMs in 24 h before screening	98 (100.0)	43 (97.7)
Unknown	0	1 (2.3)
Toxigenic *C. difficile* test result		
Positive	98 (100)	43 (97.7)
Not done	0	1 (2.3)
Toxigenic *C. difficile* local test method		
PCR	44 (44.9)	15 (34.1)
Direct detection of toxin	44 (44.9)	22 (50.0)
Culture	9 (9.2)	4 (9.1)
Other	1 (1.0)	2 (4.5)
Rotavirus test result at screening		
Positive	0	0
Negative	65 (66.3)	31 (70.5)
Not done	0	1 (2.3)
NA[b]	33 (33.7)	12 (27.3)

Abbreviations: *C. difficile*, *Clostridioides* (*Clostridium*) *difficile*; CDI, *C. difficile* infection; IQR, interquartile range; NA, not applicable; PCR, polymerase chain reaction; UBMs, unformed bowel movements.

[a]History by preferred terms and system organ class, as deemed relevant by the investigator. Preferred terms presented are those experienced by ≥10% of patients in each treatment arm.

[b]Because the rotavirus test was required only for patients <5 years of age, those aged ≥5 years who were not tested for rotavirus at screening are included in the NA category.

was smaller than in the overall population and was not statistically significant (Figure 3).

Pharmacokinetic Outcomes

Of 98 patients treated with fidaxomicin, 95 had available plasma and stool concentrations of fidaxomicin and its active metabolite OP-1118. Postdose mean (standard deviation) plasma concentrations were approximately double predose concentrations, at 39.4 (62.2) ng/mL for fidaxomicin and 116.6 (259.1) ng/mL for OP-1118 (Supplementary Table 4), and they were lower with the oral suspension than with tablets (Supplementary Table 4). The mean stool concentration of fidaxomicin was higher with the oral suspension, but the mean stool concentration of OP-1118 was higher with tablets (Supplementary Table 4).

DISCUSSION

This is the first phase 3 clinical trial of fidaxomicin treatment for CDI in patients <18 years of age. Fidaxomicin was well tolerated in this age group: the proportions of patients with TEAEs were similar in the fidaxomicin and vancomycin arms, whereas some TEAEs (such as pyrexia, abdominal pain, and diarrhea) seemed less frequent with fidaxomicin than vancomycin. The overall TEAE incidence with fidaxomicin (73.5%) was higher than in the study by Louie et al (62.3%) [23], but similar to that reported by Cornely et al (75.0%) [24], both of which were phase 3 studies in patients >16 years old. The difference in incidence may be related to the longer follow-up period of 30 days after EOT in both the study by Cornely et al and the present study, compared with a shorter reporting period of 7 days after EOT in the study by Louie et al. Our safety results are particularly favorable given the young patient population enrolled, the higher percentage of patients with prior CDI in the fidaxomicin arm, and the large proportion of patients with coinfections and hematological cancers. These comorbid conditions accounted for the 3 deaths in the fidaxomicin arm during the study period and the 2 deaths in the vancomycin arm shortly after the end of the study period.

For the overall FAS, differences in CCR at 2 days after EOT did not differ significantly between the treatment arms. However, owing to a numerically higher CCR and a lower rate of recurrence, fidaxomicin-treated patients had a significantly higher rate of GC. The number needed to treat to prevent 1 additional treatment failure or recurrence was 5.3 (95% CI, 2.8–66.7). This outcome is consistent with findings from studies in adults with CDI, which showed that rates of clinical response without recurrence were significantly higher with fidaxomicin than with vancomycin. The subgroup of immunocompromised patients also showed improved clinical outcomes with fidaxomicin compared with vancomycin, although treatment differences were not significant; this result is encouraging, because this patient

Table 2. Treatment-emergent Adverse Events by Preferred Term (Safety Analysis Set)

TEAE[a]	Fidaxomicin (n = 98)		Vancomycin (n = 44)	
	Patients, No. (%)	Events, No.	Patients, No. (%)	Events, No.
Any TEAE, all patients	72 (73.5)	303	33 (75.0)	126
Pyrexia	13 (13.3)	20	10 (22.7)	13
Abdominal pain	5 (5.1)	6	9 (20.5)	11
Vomiting	7 (7.1)	8	6 (13.6)	8
Diarrhea	7 (7.1)	7	5 (11.4)	6
Headache	8 (8.2)	12	0	0
Constipation	5 (5.1)	6	1 (2.3)	1
Oral candidiasis	3 (3.1)	3	3 (6.8)	3
Pruritus	3 (3.1)	3	3 (6.8)	3
Any TEAE by age group				
≥2 to <18 y	59 (75.6)	225	27 (79.4)	113
<2 y	13 (65.0)	78	6 (60.0)	13
≥2 to <6 y	23 (71.9)	103	13 (81.3)	44
≥6 to <12 y	21 (80.8)	60	7 (70.0)	33
≥12 to <18 y	15 (75.0)	62	7 (87.5)	36
Drug-related TEAE	7 (7.1)	7	5 (11.4)	5
Constipation	2 (2.0)	2	0	0
Abdominal pain	0	0	1 (2.3)	1
Diarrhea	1 (1.0)	1	0	0
Vomiting	0	0	1 (2.3)	1
Pyrexia	1 (1)	1	0	0
Oral candidiasis	1 (1)	1	1 (2.3)	1
Vulvovaginal mycotic infection	0	0	1 (2.3)	1
Elevated ALT level	1 (1.0)	1	0	0
Irritability	1 (1.0)	1	0	0
Hypotension	0	0	1 (2.3)	1
Serious TEAE	24 (24.5)	43	12 (27.3)	16
Drug-related serious TEAE	0	0	0	0
TEAE leading to death	3 (3.1)	5	0[b]	0
TEAE leading to withdrawal of treatment	1 (1.0)	1	1 (2.3)	1
TEAE of special interest				
Hypersensitivity	9 (9.2)	12	4 (9.1)	4
Hematological AE (decrease in WBC, neutrophil, and lymphocyte counts)	12 (12.2)	43	4 (9.1)	6
Renal AE (renal laboratory value abnormalities)	5 (5.1)	5	1 (2.3)	1
Gastrointestinal hemorrhage	1 (1.0)	1	0	0
QT prolongation	0	0	0	0
Hepatic laboratory value abnormalities/potential drug-induced liver injury[c]	5 (5.1)	7	1 (2.3)	1

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; QT, Q wave to the end of the T wave; TEAE, treatment-emergent AE; WBC, white blood cell.

[a]Individual TEAEs presented are those experienced by ≥5% patients in either treatment arm.

[b]Two patients in the vancomycin arm died after the end of the study, on days 43 and 47, from causes unrelated to treatment.

[c]Drug-induced liver injury was defined as moderate (ALT or aspartate aminotransferase [AST] >3 times the upper limit of normal [ULN] or total bilirubin >2 times ULN) or severe (ALT or AST >3 times ULN and total bilirubin >2 times ULN). In addition, the patient was considered to have severe hepatic abnormalities if any of the following was observed: ALT or AST >8 times ULN; ALT or AST >5 times ULN for >2 weeks; ALT or AST >3 times ULN and international normalized ratio (INR) >1.5 (if INR testing was applicable/evaluated); or ALT or AST >3 times ULN with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

population is at particularly high risk of CDI incidence and recurrence [28, 29]. The apparently lower treatment effect in this population, compared with the overall FAS, may reflect a greater likelihood for these patients to have an alternative [30] or a multifactorial cause for diarrhea [31], and/or to require additional antibiotics during treatment or follow-up.

Improved treatment outcomes with fidaxomicin were most pronounced in patients aged ≥2 years of age and those whose CDI was diagnosed by means of direct toxin detection. This observation may be related to the high rate of asymptomatic colonization, and the consequential challenge of CDI diagnosis, in children <2 years old [9, 10]. Consequently, *C. difficile* testing in children <2 years old with diarrhea is discouraged in clinical practice, unless other potential causes have been excluded [12]. Although all patients <2 years old had a positive toxigenic *C. difficile* test result and a negative rotavirus result for the purposes of this study, it is possible that some children in this age group had an alternative cause of diarrhea that would not be expected to respond to the CDI treatments used here. The trend toward improved clinical response with vancomycin in children
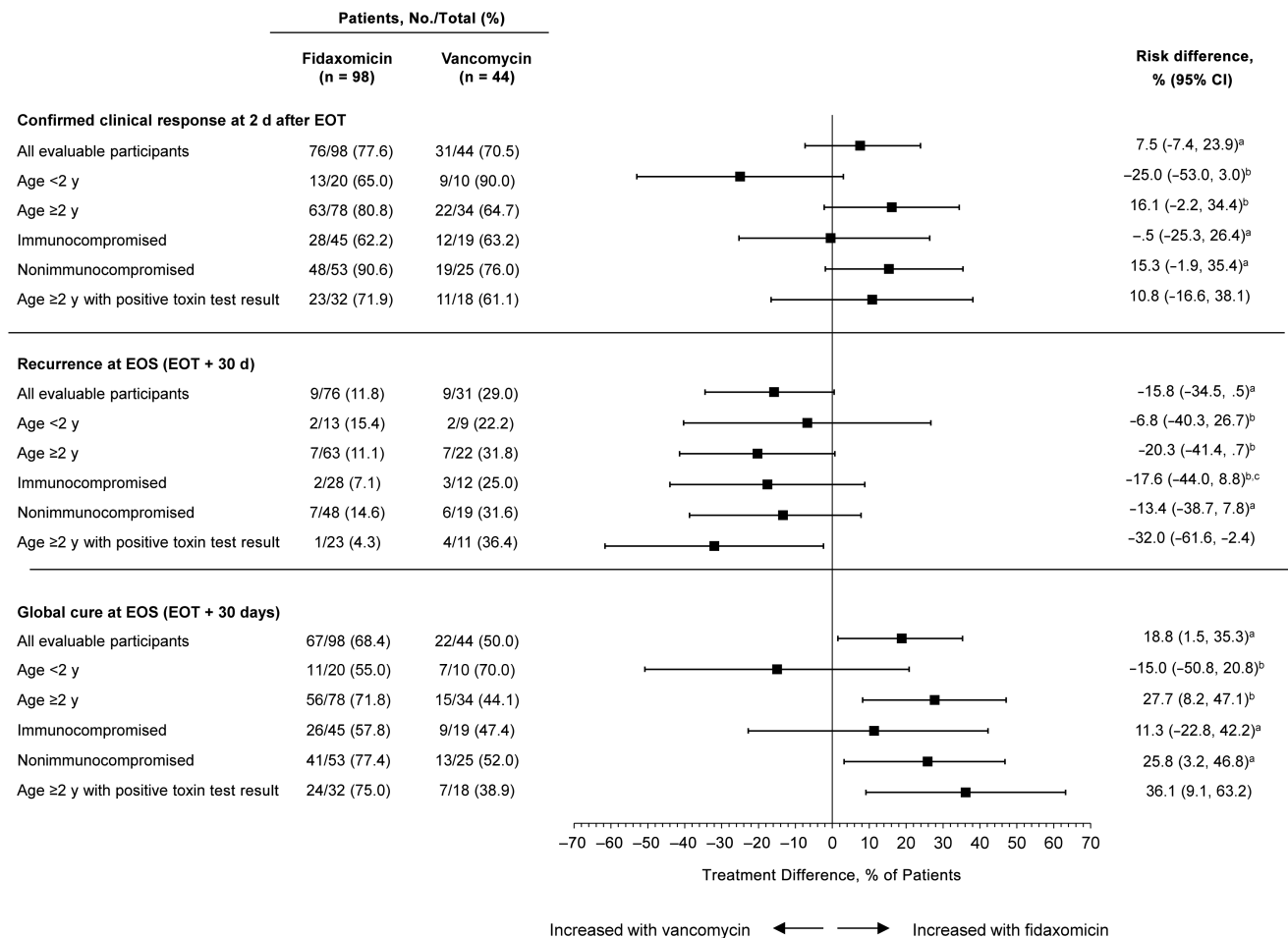
	Patients, No./Total (%)			Risk difference,
	Fidaxomicin (n = 98)	Vancomycin (n = 44)		% (95% CI)
Confirmed clinical response at 2 d after EOT				
All evaluable participants	76/98 (77.6)	31/44 (70.5)		7.5 (−7.4, 23.9)[a]
Age <2 y	13/20 (65.0)	9/10 (90.0)		−25.0 (−53.0, 3.0)[b]
Age ≥2 y	63/78 (80.8)	22/34 (64.7)		16.1 (−2.2, 34.4)[b]
Immunocompromised	28/45 (62.2)	12/19 (63.2)		−.5 (−25.3, 26.4)[a]
Nonimmunocompromised	48/53 (90.6)	19/25 (76.0)		15.3 (−1.9, 35.4)[a]
Age ≥2 y with positive toxin test result	23/32 (71.9)	11/18 (61.1)		10.8 (−16.6, 38.1)
Recurrence at EOS (EOT + 30 d)				
All evaluable participants	9/76 (11.8)	9/31 (29.0)		−15.8 (−34.5, .5)[a]
Age <2 y	2/13 (15.4)	2/9 (22.2)		−6.8 (−40.3, 26.7)[b]
Age ≥2 y	7/63 (11.1)	7/22 (31.8)		−20.3 (−41.4, .7)[b]
Immunocompromised	2/28 (7.1)	3/12 (25.0)		−17.6 (−44.0, 8.8)[b,c]
Nonimmunocompromised	7/48 (14.6)	6/19 (31.6)		−13.4 (−38.7, 7.8)[a]
Age ≥2 y with positive toxin test result	1/23 (4.3)	4/11 (36.4)		−32.0 (−61.6, −2.4)
Global cure at EOS (EOT + 30 days)				
All evaluable participants	67/98 (68.4)	22/44 (50.0)		18.8 (1.5, 35.3)[a]
Age <2 y	11/20 (55.0)	7/10 (70.0)		−15.0 (−50.8, 20.8)[b]
Age ≥2 y	56/78 (71.8)	15/34 (44.1)		27.7 (8.2, 47.1)[b]
Immunocompromised	26/45 (57.8)	9/19 (47.4)		11.3 (−22.8, 42.2)[a]
Nonimmunocompromised	41/53 (77.4)	13/25 (52.0)		25.8 (3.2, 46.8)[a]
Age ≥2 y with positive toxin test result	24/32 (75.0)	7/18 (38.9)		36.1 (9.1, 63.2)

−70 −60 −50 −40 −30 −20 −10 0 10 20 30 40 50 60 70
Treatment Difference, % of Patients

Increased with vancomycin ← → Increased with fidaxomicin

Figure 3. Treatment differences between fidaxomicin and vancomycin for rates of confirmed clinical response, recurrence, and global cure (full analysis set). [a]Adjusted treatment difference (calculated using age-stratified Cochran-Mantel-Haenszel test, for which 95% confidence intervals [CIs] were calculated using a Newcombe method). [b]Unadjusted treatment differences (with exact 95% CIs calculated using a binomial distribution). [c]Adjusted difference not estimable. Abbreviations: CI, confidence interval; EOS, end of study; EOT, end of treatment.

aged <2 years may therefore be due to random variation, because the CIs were particularly wide in this small subpopulation. Similarly, the higher relative efficacy of fidaxomicin in patients whose CDI was diagnosed through direct toxin detection, compared with those diagnosis by means of polymerase chain reaction, is in keeping with finding in a study in adults that found greater benefit of adjunctive bezlotoxumab in patients with CDI diagnosed by this method [32].

The mean plasma concentrations of fidaxomicin and OP-1118 observed 1–5 hours after the dose were 39.41 and 116.64 ng/mL, respectively. Although higher than the mean concentrations 3–5-hours after the dose in the phase 2 study in children [27] and the study by Louie et al in adults [23], these results indicate that systemic absorption is minimal in children, consistent with findings in adults. The mean end-of-therapy stool concentration of fidaxomicin of 2.7 mg/g was well in excess of the 90% minimum inhibitory concentration of 0.125 mg/L for *C. difficile* determined in the *Clos*ER surveillance study [33].

The strengths of the current study include its multicenter, multicountry design; a relatively even geographic distribution of patients between sites; and a relatively even distribution of patients enrolled across age groups from ≥6 months to <18 years, although only 1 patient <6 months old was enrolled. Limitations include the single-blinded (rather than double-blinded) design, which was for practical reasons due to differences in formulations and dosing regimens between fidaxomicin and vancomycin. Second, CDI was diagnosed based on symptoms of watery diarrhea or unformed bowel movements plus a local laboratory test. However, local diagnostic methods varied between centers, and tests have differing levels of sensitivity and specificity [12]. In addition, colonization with toxigenic *C. difficile* and active toxin production may occur in the absence of disease, particularly in infants, and no test for CDI reliably distinguishes between asymptomatic colonization and true infection [34, 35]. It is therefore possible that some enrolled patients, particularly those aged <2 years, were *C. difficile* carriers. Third,

because recruitment numbers were limited owing to the specific patient population targeted, the study was not powered for efficacy or safety and conclusions regarding differences between age groups are limited due to low sample sizes. In conclusion, fidaxomicin for the treatment of CDI in children and adolescents was well tolerated, and fidaxomicin was associated with a lower risk of treatment failure or recurrence than vancomycin.

Supplementary Data

Notes

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