# NDA Multi-Disciplinary Review and Evaluation

<table>
<tr><td>Applications Types</td><td>Supplemental NDA (sNDA) – Efficacy Supplement (SE5)<br>505(b)(1) NDA</td></tr>
<tr><td>Applications Numbers</td><td>sNDA 201699/S-012, DIFICID (fidaxomicin) tablets<br>NDA 213138, DIFICID (fidaxomicin) oral suspension</td></tr>
<tr><td>Priority or Standard</td><td>Priority</td></tr>
<tr><td>Submit Date</td><td>07/24/2019</td></tr>
<tr><td>Received Date</td><td>07/24/2019</td></tr>
<tr><td>PDUFA Goal Date</td><td>01/24/2020</td></tr>
<tr><td>Division/Office</td><td>Division of Anti-Infectives (DAI)<br>Office of Infectious Diseases (OID)</td></tr>
<tr><td>Review Completion Date</td><td>See DARRTS electronic signature page</td></tr>
<tr><td>Established/Proper Name</td><td>Fidaxomicin</td></tr>
<tr><td>Trade Name</td><td>DIFICID</td></tr>
<tr><td>Pharmacologic Class</td><td>Macrolide</td></tr>
<tr><td>Applicant</td><td>Cubist Pharmaceuticals LLC</td></tr>
<tr><td>Dosage Forms</td><td>Tablets for oral use, 200 mg<br>Granules for oral suspension, 200 mg/5 mL</td></tr>
<tr><td>Dosing Regimen</td><td>• Pediatric patients weighing at least 12.5 kg and able to swallow tablets: one 200 mg tablet orally twice daily for 10 days.<br>• Pediatric patients weighing at least 4 kg: weight-based dosing of the oral suspension twice daily for 10 days using an oral dosing syringe as specified in the table below:
<table>
<tr><th>Body Weight</th><th>Dose Administered Twice Daily</th><th>Volume of 40 mg/mL Suspension to be Administered Orally Twice Daily</th></tr>
<tr><td>4 kg to less than 7 kg</td><td>80 mg</td><td>2 mL</td></tr>
<tr><td>7 kg to less than 9 kg</td><td>120 mg</td><td>3 mL</td></tr>
<tr><td>9 kg to less than 12.5 kg</td><td>160 mg</td><td>4 mL</td></tr>
<tr><td>12.5 kg and above</td><td>200 mg</td><td>5 mL</td></tr>
</table></td></tr>
<tr><td>Applicant Proposed Indication/Population</td><td>Treatment of (b) (4) in adult and pediatric patients 6 months of age and older</td></tr>
<tr><td>Regulatory Action</td><td>Approval</td></tr>
<tr><td>Approved Indication/Population</td><td>Treatment of Clostridioides difficile-associated diarrhea (CDAD) in adult and pediatric patients 6 months of age and older</td></tr>
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## Reviewers of Multi-Disciplinary Review and Evaluation

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPV=Division of Pharmacovigilance

## Signatures

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## Glossary

| | |
|---|---|
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| AR | adverse reaction |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| CRF | case report form |
| CSR | clinical study report |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| FDA | Food and Drug Administration |
| GCP | good clinical practice |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NDA | new drug application |
| NME | new molecular entity |
| OPQ | Office of Pharmaceutical Quality |
| OSI | Office of Scientific Investigation |
| PD | pharmacodynamics |
| PI | prescribing information |
| PJP | *Pneumocystis jirovecii* pneumonia |
| PK | pharmacokinetics |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |
| UBM | unformed bowel movements |

# 1 Executive Summary

## 1.1. Product Introduction

Fidaxomicin is a macrolide antibacterial drug that was approved in adults for the treatment of *Clostridioides (formerly Clostridium) difficile*-associated diarrhea (CDAD) in May 2011. The currently approved formulation of fidaxomicin is 200 mg tablet and the recommended dosing in adults is one tablet orally twice daily for 10 days. Fidaxomicin acts locally in the gastrointestinal tract and has minimal systemic absorption following oral administration, with plasma concentration in the ng/mL range at the therapeutic dose.

These applications support the use of fidaxomicin in pediatric patients 6 months and older for the treatment of CDAD, and provide a new fidaxomicin dosage form, granules for oral suspension, 200 mg per 5 mL, which has been developed as a pediatric formulation of the drug. The efficacy supplement (sNDA 201699) supports the extension of the use of tablets in pediatric patients and NDA 213138 supports the use of granules for oral suspension.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The information submitted by the Applicant provides substantial evidence of effectiveness and sufficient safety information to support approval of fidaxomicin for the treatment of CDAD in pediatric patients from 6 months to less than 18 years of age. The efficacy of fidaxomicin in the pediatric population is extrapolated from adults and supported by a Phase 3 randomized, investigator-blinded, controlled trial, comparing the safety and efficacy of fidaxomicin oral suspension or tablets to vancomycin liquid or tablets in pediatric patients from 6 months to less than 18 years. In the efficacy analysis of 142 patients (98 received fidaxomicin, and 44 received vancomycin), confirmed clinical response (CCR) assessed at 2 days following 10 days of treatment, was similar between the fidaxomicin and vancomycin arms 77.6% vs. 70.5% with a 95% CI for the treatment difference of 7.5% (-7.4%, 23.9%). Sustained clinical response, defined as the proportion of treated patients with clinical response and no recurrence at Day 30, was 68.4% in fidaxomicin and 50.0% in vancomycin-treated patients with a 95% CI for the treatment difference of 18.8% (1.5%, 35.3%).

A lower CCR rate was observed in patients < 2 years of age in the fidaxomicin arm as compared to the vancomycin arm, 13/20 (65%) and 9/10 (90%), respectively. The interpretation of this finding is confounded, however, by a small number of patients in the subgroup and difficulties with diagnosing CDAD in children < 2 years due to high rates of colonization with *C. difficile* and frequent coinfection with other diarrheal pathogens.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

The benefit-risk assessment of the information provided in this submission supports the approval of fidaxomicin tablets and oral suspension for the treatment of pediatric patients 6 months of age and older with *Clostridioides difficile* – associated diarrhea (CDAD). Per agreement with the FDA, neonates and infants less than 6 months of age were excluded from the pediatric studies due to high rates of *C. difficile* colonization and co-infection with other diarrheal pathogens, which makes the diagnosis of CDAD and evaluation of treatment outcomes in this population difficult. The approval also provides a pediatric formulation of fidaxomicin which enables the use of the drug in younger children and in children who cannot swallow tablets. Of note, the Applicant had initially sought the indication (b) (4). However, the approved indication is for the treatment of CDAD. The latter indication more accurately describes the disease studied in the DIFICID clinical program where patients with the most severe forms of *C. difficile* infection, such as fulminant infection or toxic megacolon were excluded. Also, the term CDAD has been used in the prescribing information of other products, including fidaxomicin, approved for the treatment of infection with *Clostridioides difficile*, and in the warning on the risk of CDAD included in the prescribing information of antimicrobial products.

Efficacy

The efficacy of fidaxomicin in the treatment of CDAD in pediatric patients is extrapolated from adults as the pathogenicity and course of CDAD and effects of the drug are sufficiently similar in adults and pediatric patients, and is supported by a Phase 3, randomized, investigator-blinded trial, comparing the safety and efficacy of fidaxomicin oral suspension or tablets to vancomycin liquid or tablets in pediatric patients from 6 months to less than 18 years (the SUNSHINE study). Approximately two thirds of patients in the trial received the suspension. There was no prespecified hypothesis testing for this pediatric trial and all analyses were descriptive. In the efficacy analysis of 142 patients (98 received fidaxomicin and 44 received vancomycin), fidaxomicin provided comparable rates of confirmed clinical response (CCR) which was defined as resolution of diarrhea in addition to no need for CDAD treatment for 2 days after the end of 10 days of treatment.

The overall CCR rates were 76/98 (77.6 %) and 31/44 (70.5%) in the fidaxomicin and vancomycin arms, respectively, with a treatment difference of 7.5% and a 95% CI (-7.4%, 23.9%). A lower CCR rate was observed in patients < 2 years in the fidaxomicin arm as compared to the vancomycin arm, 13/20 (65%) and 9/10 (90%), respectively. However, the interpretation of this finding is confounded by a small number of patients treated and difficulties with diagnosing CDAD in children < 2 years. Sustained clinical response rates, defined as the proportion of treated patients with confirmed clinical response and no CDAD recurrence through 30 days after the end of treatment were 68.4% and 50.0% for the fidaxomicin and the vancomycin arms, respectively, with a treatment difference of 18.4% and a 95%CI (1.5%, 35.3%).

Safety

A total of 136 patients aged 1 month to 18 years were exposed to fidaxomicin, 38 patients in a Phase 2 single arm trial (study OPT-80-206), and 98 patients in the SUNSHINE study. Approximately two-thirds of patients received oral suspension (a powder formulation in study OPT-80-206, and a granule

formulation in the SUNSHINE study). The remainder of patients received tablets. The average duration of treatment in both studies were 9.5 days. The most frequent adverse reactions in fidaxomicin-treated patients were pyrexia, vomiting, diarrhea, abdominal pain, constipation, and increased aminotransferases. Adverse reactions did not vary by the age groups.

There were 4 deaths in fidaxomicin-treated patients (1 death in study OPT-80-206 and 3 deaths in the SUNSHINE study). No deaths were reported in the vancomycin arm in the SUNSHINE study during the study period. All patients who died were younger than 2 years of age. The assessments of deaths indicated that they were related to underlying comorbid illnesses including hematologic malignancies, concomitant chemotherapy, complications of hematopoietic stem cell transplantation, and other comorbid conditions known to be associated with poor outcomes. The review did not identify fidaxomicin-related toxicities that could have resulted in the fatal outcomes. In addition, results from pharmacokinetic (PK) studies in pediatric patients demonstrated, similarly to adults, minimal systemic absorption of fidaxomicin across all age groups. No significant differences in non-fatal adverse events, serious adverse events (SAEs) or adverse events leading to treatment discontinuations were seen in the SUNSHINE study between the treatment arms or across the age groups.

The Adverse Reactions section of the fidaxomicin prescribing information has been updated to describe safety findings in the fidaxomicin pediatric studies including the information on the deaths that occurred in fidaxomicin-treated patients less than 2 years of age. The Clinical Studies section has been updated with the information on the lower clinical response in fidaxomicin as compared to vancomycin treated patients less than 2 years of age.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • *C. difficile* is an important cause of health care–associated diarrhea. In the pediatric population the incidence of CDAD has been increasing. However, in younger children the diagnosis of CDAD is difficult as patients may be coinfected with other diarrheal pathogens (i.e., norovirus, rotavirus, astrovirus, sapovirus) and asymptomatic carriage of *C. difficile* is common, especially during the first year of life. The asymptomatic carriage decreases with age and mirrors that of adults (3-6%) by the age of 2 years.<br>• Predisposing factors for infection with *C. difficile* in children include diseases requiring immunosuppressive therapy, inflammatory and structural intestinal disorders.<br>• Complications of severe *C. difficile* infection include dehydration, electrolyte disturbances, bowel perforation, hypotension, renal failure, and sepsis. | The incidence of CDAD in pediatric patients has been increasing but the diagnosis of CDAD is difficult in children less than 2 years of age due to high rates of *C. difficile* colonization and co-infection with other diarrheal pathogens. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | Severe or fatal disease is rare in children; however, complications are more likely to occur among neutropenic children with hematological malignancies. | |
| Current Treatment Options | • Vancomycin oral tablets and liquid are approved for the treatment of CDAD in children and adolescents. Metronidazole has been used off-label; metronidazole oral formulation has been used for mild or moderate CDAD and intravenous formulations for patients with severe disease and inability to tolerate oral therapy. | The only approved therapy for CDAD in the pediatric population is oral vancomycin. There is a need for new antibacterial drugs to treat CDAD in the pediatric population, particularly in age appropriate pediatric formulations. |
| Benefit | • Efficacy of fidaxomicin for the treatment of CDAD in children is extrapolated from adults and supported by a Phase 3, randomized, investigator-blinded trial, comparing safety and efficacy of fidaxomicin oral suspension or tablets to vancomycin liquid or tablets in pediatric patients from 6 months to less than 18 years. The trial enrolled 142 patients, 98 received fidaxomicin, and 44 received vancomycin. There was no prespecified hypothesis testing in this trial.<br>• The rates of CCR, which was defined as the absence of watery diarrhea in children < 2 years or decrease in the number of unformed bowel movements to less than 3 in children ≥ 2 years, in addition to no need for CDAD treatment for 2 days after the end of 10 days of treatment, were similar between the fidaxomicin and vancomycin arms, 77.6% vs. 70.5%, respectively, with a 95% CI for the treatment difference of (-7.4%, 23.9%). Sustained clinical response, defined as the proportion of patients with CCR and no recurrence through 30 days after end of treatment, was 68.4% in the fidaxomicin arm and 50.0% in the vancomycin arm.<br>• In the fidaxomicin arm a lower response rate was observed in the < 2 years age group (65% for fidaxomicin and 90% for vancomycin treatment arm). See table below. | Efficacy of fidaxomicin in the treatment of CDAD in pediatric patients is extrapolated from adults and supported by a Phase 3 pediatric trial where fidaxomicin showed a clinical response comparable to vancomycin and numerically higher rates of sustained clinical response.<br><br>A lower rate of clinical response was noted in patients < 2 years. The significance of this finding is uncertain, however, given a small number of patients studied and difficulties with diagnosing CDAD in children < 2 years of age.<br><br>The availability of an oral suspension formulation of fidaxomicin provides an important option for the treatment of CDAD in children. |

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><th colspan="3">Confirmed Clinical Response Rate by Age Group in SUNSHINE Trial</th></tr>
<tr><th>Age group</th><th>Fidaxomicin<br>n/N (%)</th><th>Vancomycin<br>n/N (%)</th></tr>
<tr><td>Overall</td><td>76/98 (77.6)</td><td>31/44 (70.5)</td></tr>
<tr><td>< 2 years</td><td>13/20 (65.0)</td><td>9/10 (90.0)</td></tr>
<tr><td>≥ 2 to < 6 years</td><td>25/32 (78.1)</td><td>12/16 (75.0)</td></tr>
<tr><td>≥ 6 to < 12 years</td><td>23/26 (88.5)</td><td>5/10 (50.0)</td></tr>
<tr><td>≥ 12 to < 18 years</td><td>15/20 (75.0)</td><td>5/8 (62.5)</td></tr>
</table>
However, clinical significance of this finding is uncertain because of a small number of patients in the subgroup and difficulties to diagnose CDAD with certainty in children less than 2 years, as there are high rates of colonization with C. difficile as well as coinfection with other diarrheal pathogens in this age group. Thus, more than half of patients < 2 years (12 of 20 in the fidaxomicin and 6 of 10 in vancomycin arm) were coinfected with pathogens known to cause diarrheal illness in this age group.<br>
• Palatability of the fidaxomicin suspension was comparable to that of vancomycin liquid.</td><td></td></tr>
<tr><td>Risk and Risk Management</td><td>
• Safety of fidaxomicin was evaluated in 136 patients aged 1 month to 18 years, 38 patients in the single arm Phase 2 trial and 98 patients in the Phase 3 trial. Approximately two-thirds of the patients received suspension (powder formulation for suspension in Phase 2 trial, and granules for suspension, which is the to-be-marketed formulation, in the Phase 3 trial). The remainder of the patients received tablets.<br>
• The most common adverse reactions occurring in fidaxomicin patients were pyrexia, vomiting, diarrhea, abdominal pain, constipation, and increased aminotransferases.<br>
• There were 4 deaths in fidaxomicin-treated patients (1 death in the Phase 2 and 3 deaths in the Phase 3 trial) during the study period. All deaths occurred in patients < 2 years of age. No deaths occurred in the vancomycin</td><td>The safety profile of fidaxomicin for the treatment of CDAD in pediatric patients aged 6 months and older is acceptable. Adverse reactions associated with the use of fidaxomicin in the pediatric population are adequately addressed in the product labeling. Routine postmarketing pharmacovigilance is recommended.</td></tr>
</table>

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | arm in the Phase 3 trial during the study period. The review of the deaths suggested that they were likely related to progression and complications of underlying comorbidities including hematologic malignancies, concomitant chemotherapy, and other comorbid conditions known to be associated with fatal outcomes. The review did not identify fidaxomicin-related toxicities that could have resulted in the fatal outcomes.<br>• No significant differences in non-fatal adverse events, SAEs, or adverse events leading to treatment discontinuations were seen in the SUNSHINE study between the treatment arms and across the age groups. | |

## 1.4. Patient Experience Data

**Patient Experience Data Relevant to this Application** (check all that apply)

| | | | | |
|---|---|---|---|---|
| X | **The patient experience data that were submitted as part of the application include:** | | | Section of review where discussed, if applicable |
| | X | Clinical outcome assessment (COA) data, such as | | |
| | | □ | Patient reported outcome (PRO) | |
| | | □ | Observer reported outcome (ObsRO) | |
| | | X | Clinician reported outcome (ClinRO) | Section 8.1.2, Tables 8-6 through 8-10 |
| | | □ | Performance outcome (PerfO) | |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | □ | Natural history studies | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| □ | **Patient experience data that were not submitted in the application, but were considered in this review:** | | | |
| | □ | Input informed from participation in meetings with patient stakeholders | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | □ | Other: (Please specify): | | |
| □ | **Patient experience data was not submitted as part of this application.** | | | |

# 2 Therapeutic Context

## 2.1. Analysis of Condition

*C. difficile* is an important cause of health care–associated diarrhea among adults in the United States and is associated with significant morbidity and mortality[1]. *C difficile* has been increasingly recognized as an important pathogen among children[2,3,4]. However, in younger children it is difficult to distinguish diarrhea due to *C. difficile* infection (CDI) from other causes of diarrhea (e.g., norovirus, rotavirus, astrovirus, sapovirus) as asymptomatic carriage of *C. difficile* is common in immunocompetent infants through their first year of life. Up to 70% of infants may be asymptomatically colonized with *C. difficile*, including toxigenic strains[5,6]. Rates of colonization decrease with age, falling in the second year and mirror those of adults (3-6%) by age 2 years[7,8,9,10].

The high rates of asymptomatic colonization make the diagnosis of CDI in neonates and infants challenging as infectious diarrhea from other causes is common in this patient population and detection of *C. difficile* in stool may be an incidental finding rather than a true infection. The reasons for high rates of asymptomatic carriage of *C. difficile* in younger children are not clearly established. It has been hypothesized that the gut of neonates and infants lack the receptors needed to bind and process the toxins of *Clostridioides* species[11]. It was also suggested that the

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[1] Lessa FC et al, Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015;372(9):825.
[2] Kim J, Smathers SA, et al, Epidemiological features of *Clostridium difficile*-associated disease among inpatients at children's hospitals in the United States, 2001-2006. Pediatrics. 2008;122(6):1266.
[3] Zilberberg MD, et al; *Clostridium difficile* infections among hospitalized children, United States, 1997-2006. Emerg Infect Dis. 2010;16(4):604.
[4] Deshpande A, et al; *Clostridium difficile* infection in the hospitalized pediatric population: increasing trend in disease incidence. Pediatr Infect Dis J. 2013 Oct;32(10):1138-40.
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[6] Sherertz RJ, Sarubbi FA. The prevalence of *Clostridium difficile* and toxin in a nursery population: a comparison between patients with necrotizing enterocolitis and an asymptomatic group. J Pediatr 1982; 100:435–9.
[7] Centers for Disease Control and Prevention (CDC). Severe *Clostridium difficile*-associated disease populations previously at low risk--four states, 2005. MMWR Morb Mortal Wkly Rep 2005; 54:1201.
[8] Centers for Disease Control and Prevention (CDC). Surveillance for community-associated *Clostridium difficile*--Connecticut, 2006. MMWR Morb Mortal Wkly Rep 2008; 57:340.
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[11] Pothoulakis C, Lamont JT. Microbes and microbial toxins: paradigms for microbial-mucosal interactions II. The integrated response of the intestine to *Clostridium difficile* toxins. Am J Physiol Gastrointest Liver Physiol. 2001;280: G178–G183.

infant's microbiota could provide an environment unfavorable to spore germination[12] associated with a competitive intestinal colonization by nontoxigenic strains and toxin neutralization by maternal antibodies[13,14,15].

Symptomatic CDI is mediated through the production of toxins that are cytotoxic to epithelial cells of the colon, causing extensive inflammation and epithelial tissue damage[16]. Predisposing factors for clinical infection with *C. difficile* in neonates and young children include malignancies, immunosuppressive therapies, receipt of hematopoietic stem cell transplant, inflammatory bowel disease, hypogammaglobulinemia, cystic fibrosis, Down's syndrome, and structural or postoperative intestinal disorders[17,18,19]. Several observational studies suggest that *C. difficile* infection are common in pediatric oncology patients and children who have undergone solid organ transplants[20,21,22,23,24].

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[12] Rousseau C, Levenez F, Fouqueray C, et al. *Clostridium difficile* colonization in early infancy is accompanied by changes in intestinal microbiota composition. J Clin Microbiol. 2011; 49:858–865.
[13] Schutze GE, Willoughby RE; Committee on Infectious Diseases; American Academy of Pediatrics. *Clostridium difficile* infection in infants and children. Pediatrics. 2013; 131:196–200.
[14] Barbut F, Petit JC. Epidemiology of *Clostridium difficile*-associated infections. Clin Microbiol Infect 2001; 7:405.
[15] Larson HE, Barclay FE, Honour P, Hill ID. Epidemiology of *Clostridium difficile* in infants. J Infect Dis 1982; 146:727.
[16] Voth DE, Ballard JD. *Clostridium difficile* toxins: mechanism of action and role in disease. Clin Microbiol Rev. 2005;18:247–63
[17] Castagnola E, Battaglia T, Bandettini R, et al. *Clostridium difficile*–associated disease in children with solid tumors. Support Care Cancer. 2009;17(3):321-324.
[18] van de Wetering MD, Kuijpers TW, Taminiau JA, ten Kate FJ, Caron HN. Pseudomembranous and neutropenic enterocolitis in pediatric oncology patients. Support Care Cancer. 2003;11(9):581-586.
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[24] Tai E, Richardson LC, Townsend J, et al. *Clostridium difficile* infection among children with cancer. Pediatr Infect Dis J 2011; 30:610.

The presence of toxin-producing *C. difficile* in stool is associated with a wide spectrum of gastrointestinal manifestations, ranging from asymptomatic carriage to pseudomembranous colitis. A case definition of CDAD includes the presence of symptoms (usually diarrhea) and either a stool test result that is positive for *C difficile* toxins or colonoscopic findings demonstrating pseudomembranous colitis[25]. Watery diarrhea is the most frequent manifestation of CDAD in children. Diagnosis of *C. difficile*-associated colitis should be considered in any patient who has received antibiotics within the previous 12 weeks, and who has diarrhea with or without systemic symptoms such as fever and abdominal pain.

Severe or fatal disease is rare in children; however, complications are more likely to occur among neutropenic children with hematological malignancies or those treated with hematopoietic stem cell transplantation [26], infants with Hirschsprung's disease and patients with inflammatory bowel disease. Complications that are related to *C. difficile* infection, including toxic megacolon, and colectomy, although relatively rare in children, have been reported[27,28]. Additional complications of severe colitis include dehydration, electrolyte disturbances, bowel perforation, hypotension, renal failure, sepsis, and death. In a multicenter study evaluating *C. difficile* infection among hospitalized children, 1.25% underwent colectomy; the all-cause mortality rate among those children was 4% [29]. Extraintestinal manifestations of *C. difficile* infection are rare but include reports of bacteremia, peritonitis, perianal abscess, surgical site infections, and musculoskeletal infections, including septic arthritis, osteomyelitis, reactive arthritis, and acute flexor tenosynovitis[30,31,32].

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[25] Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010;31(5):431-55

[26] 48.American Academy of Pediatrics. *Clostridium difficile*. In: Pickering LK, Backer CJ, Kimberlin DW, Long SS, eds. Red Book: 2012 Report of the Committee on Infections Diseases, 29th edn. Elk Grove Village: American Academy of Pediatrics, 2012:285-7.

[27] Pokorn M, Radsel A, Cizman M, et al. Severe *Clostridium difficile*–associated disease in children. Pediatr Infect Dis J. 2008;27(10):944-946.

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[31] Durand CL, Miller PF. Severe *Clostridium difficile* colitis and reactive arthritis in a ten-year-old child. Pediatr Infect Dis J. 2009;28(8):750-751.

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Testing for *C. difficile* should only be performed in symptomatic children with clinically significant diarrhea (watery diarrhea in children less than 2 years old or ≥ 3 unformed or loose bowel movements per day in older children) who have clinical features and predisposing conditions suggestive of *C. difficile* disease. Laboratory testing for *C. difficile* infection involves detection of *C. difficile* toxin(s) or toxigenic *C. difficile* organisms in a stool specimen[33,34].

### 2.2. Analysis of Current Treatment Options

Vancomycin is the only FDA approved antimicrobial therapy for the treatment of CDAD in children and adolescents. The dose of vancomycin in pediatric patients is 40 mg/kg per day by mouth in four divided doses. The total daily dosage should not exceed 2 g. The recommended duration of treatment for CDAD is 10 days.

Metronidazole is used off-label for the treatment of CDAD. Metronidazole oral formulation is used for mild or moderate CDAD and intravenous formulations for patients with severe disease and inability to tolerate oral therapy.

Surgery including subtotal colectomy may be required in children with toxic megacolon or colonic perforation. Supportive care includes correction of fluid losses and electrolyte imbalances.

## 3 Regulatory Background

### 3.1. U.S. Regulatory Actions and Marketing History

DIFICID (fidaxomicin) tablets, 200 mg, was approved for the treatment of *C. difficile*-associated diarrhea in adults (≥ 18 years of age) on May 27, 2011.

### 3.2. Summary of Pre-submission/Submission Regulatory Activity

At the time of the approval of fidaxomicin tablets in adults, two postmarketing requirements (PMRs) for pediatric studies were required under the Pediatric Research Equity Act as follows:

[33] McDonald LC et al; Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):e1.
[34] American Academy of Pediatrics. *Clostridium difficile*. In: Red Book: 2018 Report of the Committee on Infectious Diseases, 31st ed, Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds), American Academy of Pediatrics, Itasca, IL 2018. p.288.

- **PMR 1757-001**: Conduct a prospective clinical trial of 10 days of DIFICID (fidaxomicin) in at least 32 pediatric patients (6 months to less than 18 years of age) with *C. difficile*-associated diarrhea to evaluate the safety and pharmacokinetics (including serum and fecal concentrations) of DIFICID (fidaxomicin);
  and,
- **PMR 1757-002**: Conduct a prospective, randomized clinical trial to demonstrate safety and effectiveness of DIFICID (fidaxomicin) compared to vancomycin in pediatric patients (6 months to less than 18 years of age) with *C. difficile*-associated diarrhea.

Studies OPT-80-206 and SUNSHINE were designed and conducted to fulfill PMRs 1757-001 and 1757-002, respectively. The final study report for OPT-80-206 was submitted to FDA on November 13, 2014. On February 24, 2015, FDA concluded that PMR 1757-01 was fulfilled.

On May 16, 2018, FDA issued a Pediatric Written Request to the Applicant in response to their January 23, 2018, Proposed Pediatric Study Request (PPSR). On July 24, 2019, sNDA-201699/S-012 for fidaxomicin tablets and NDA 213138 for fidaxomicin oral suspension with the final study report for the SUNSHINE study were received by FDA. During the review of these applications, the results of the SUNSHINE study were presented to the Pediatric Exclusivity Board. The Board concluded that the trial met the terms of the Written Request and fidaxomicin was granted pediatric exclusivity, effective December 13, 2019. The following table summarizes key regulatory activities of the fidaxomicin pediatric development program.

**Table 3-1. Key Regulatory Activities of Fidaxomicin Pediatric Development Program**

| Description | Date |
|---|---|
| Pediatric PMRs were issued with approval of adult indication for fidaxomicin. | 27 May 2011 |
| Protocol for OPT-80-206 study (PMR 1757-001) was submitted to FDA. | 25 Aug 2011 |
| Protocol for SUNSHINE study (PMR 1757-002) was submitted to FDA. | 30 Sep 2013 |
| Final report for OPT-80-206 study (PMR 1757-001) was submitted to FDA. | 13 Nov 2014 |
| FDA concluded that PMR 1757-001 was fulfilled. | 24 Feb 2015 |
| Per agreement with FDA, neonates and infants less than 6 months of age were excluded from the pediatric studies. (b) (4) | 12 Jan 2015 |
| A 2-year extension for study completion and final report submission was granted for PMR 1757-002. | 04 May 2017 |
| PPSR was submitted by the Sponsor (Merck). | 23 Jan 2018 |
| Pediatric Written Request was issued by FDA. | 16 May 2018 |
| The Sponsor (Merck) notified FDA of its agreement to the Written Request. | 17 Oct 2018 |
| Supplemental NDA 201699 for fidaxomicin tablets and NDA 213138 for fidaxomicin oral suspension with the final report for SUNSHINE study were received by FDA. | 24 July 2019 |
| Pediatric exclusivity for fidaxomicin was granted. | 13 Dec 2019 |

# 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

Two clinical sites that were among the highest enrollers of patients for the SUNSHINE study were inspected by OSI. On-site inspections demonstrated no significant findings at either of the audited sites related to data integrity or human patient protection. There was no evidence of underreporting of adverse events. The inspection concluded that the trial appears to have been conducted adequately, and the data generated by the inspected clinical sites appear acceptable in support of the proposed indication.

## 4.2. Product Quality

NDA 213138 for the oral suspension, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for Approval by the Office of Pharmaceutical Quality (OPQ) at this time. The Overall Manufacturing Inspection recommendation was entered as Approve on 12/18/2019. This product has been granted a 9-month shelf life under controlled room temperature, and the Applicant committed to submitting a CBE-30 supplement to extend the shelf life when additional long-term stability data is available.

There were no CMC issues related to NDA 201699 Supplement 12.

## 4.3. Clinical Microbiology

**Executive summary**

Fidaxomicin is a macrolide antibacterial drug that inhibits RNA synthesis by binding to RNA polymerases, thereby preventing it from binding to DNA. Fidaxomicin demonstrates *in vitro* activity against *C. difficile*. The fidaxomicin minimal inhibitory concentration (MIC) for 90% of *C. difficile* isolates ($MIC_{90}$) is 0.5 mcg/mL. Data from postmarketing surveillance studies (2011-2015) conducted after DIFICID approval did not show any change in the fidaxomicin MIC. The fidaxomicin $MIC_{90}$ against *C. difficile* isolates from the Phase 3 trial (2819-CL-0202; SUNSHINE study) in the pediatric population was 0.25 mcg/mL.

**Phase 3 Trial (SUNSHINE Study)**

The clinical microbiology assessments covered the testing methodology used in the Phase 3 trial.

Microbiological methods used in the SUNSHINE study

Stool samples were collected from all randomized patients at screening, end of treatment (EOT), and any unscheduled visit after the follow-up period due to the recurrence/reinfection of

*C. difficile*. The stool samples were split into 2 aliquots: one aliquot used by the local site for the detection of toxigenic *C. difficile* (either by *C. difficile* toxin A/B ELISA, *C. difficile* genes PCR or by anaerobic culture) and another aliquot used for the central laboratory analysis. The central laboratory conducted *C. difficile* identification, polymerase chain reaction (PCR) ribotyping and susceptibility testing on all culture confirmed positive samples. The central laboratory used FDA cleared test for diagnosis (C. DIFF QUIK CHEK COMPLETE™; FilmArray Gastrointestinal (GI) Panel (b) (4)

Results of Microbiological Assessment in the SUNSHINE study

A total of 60/87 (69%) and 31/39 (79.5%) *C. difficile* isolates were identified from the patients in fidaxomicin and vancomycin treatment arms respectively. A summary of confirmed *C. difficile* cultures and susceptibility to fidaxomicin and vancomycin clinical isolates is provided in Table 4-1. Against 58 *C. difficile* baseline isolates in the fidaxomicin arm, the MIC ranged from ≤0.015-1.0 mcg/mL, and the $MIC_{90}$ was 0.25 mcg/mL. Against 30 *C. difficile* baseline isolates in the vancomycin arm, the MIC ranged from 0.5-1.0 mcg/mL, and the $MIC_{90}$ was 1.0 mcg/mL.

**Table 4-1. Summary of Confirmed *C. difficile* Culture and Susceptibility of Isolates in Fecal Samples (FAS)**

| | Fidaxomicin (n = 98) | | | Vancomycin (n = 44) | | |
|---|---|---|---|---|---|---|
| Result Statistic | SCRN (n = 87) | EOT (n = 83) | REC (n = 24) | SCRN (n = 39) | EOT (n = 33) | REC (n = 10) |
| Confirmed C. difficile culture n (%) | 60 (69.0) | 1 (1.2) | 8 (33.3) | 31 (79.5) | 2 (6.1) | 5 (50.0) |
| Susceptibility of isolates (mg/L)† | | | | | | |
| *Fidaxomicin* | | | | | | |
| n | 58 | 1 | 8 | 29 | 2 | 5 |
| Mean | 0.2 | 0.1 | 0.2 | 0.2 | 0.2 | 0.1 |
| Min, Max | 0.0, 1.0 | 0.1, 0.1 | 0.1, 0.3 | 0.1, 0.5 | 0.1, 0.3 | 0.1, 0.3 |
| Geometric mean | 0.1 | 0.1 | 0.1 | 0.2 | 0.2 | 0.1 |
| MIC50 | 0.12 | 0.12 | 0.12 | 0.12 | 0.19 | 0.12 |
| MIC90 | 0.25 | 0.12 | 0.25 | 0.25 | 0.25 | 0.25 |
| *Vancomycin* | | | | | | |
| n | 60 | 1 | 8 | 30 | 2 | 4 |
| Mean | 1.1 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Min, Max | 0.5, 4.0 | 1.0, 1.0 | 0.5, 2.0 | 0.5, 1.0 | 1.0, 1.0 | 1.0, 1.0 |
| Geometric mean | 1.0 | 1.0 | 0.9 | 1.0 | 1.0 | 1.0 |
| MIC50 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| MIC90 | 1.00 | 1.00 | 2.00 | 1.00 | 1.00 | 1.00 |

CCR: confirmed clinical response; EOT: end of treatment; FAS: full analysis set; Max: maximum; MIC50: minimum inhibitory concentration of 50% of isolates tested; MIC90: minimum inhibitory concentration of 90% of isolates tested; Min: minimum; REC: recurrence (first recurrence after CCR assessment used); SCRN: screening.

† Susceptibility values below limit of quantification were set to 0.015 mg/L and values above limit of quantification were set to 64 mg/L.

Source: Table 30, the SUNSHINE study Clinical Study Report

FilmArray PCR Test for *C. difficile* and Other Pathogens

Toxigenic *C. difficile* isolates were detected with a mix of other bacterial and/or viral GI pathogens from stool specimens by the (b) (4) GI FilmArray PCR test in the central laboratory. PCR testing was positive for *C. difficile* in 64/85 (75.3%) and 32/38 (84.2%) patients in fidaxomicin and vancomycin arms, respectively.

A substantial number of patients were positive for other GI pathogens besides *C. difficile* at different time points. At least one pathogen other than *C. difficile* was detected in 43/98 (43.9%) patients in the fidaxomicin arm and 22/44 (50.0%) patients in the vancomycin arm. Overall, the most frequent and significant GI pathogens detected in both arms were enteropathogenic *Escherichia coli* (19 [13.4%] patients), norovirus (14 [9.9%] patients), and rotavirus A (7 [4.9%] patients), (Table 4-2).

**Table 4-2. Toxin Test Results, (b) (4) PCR Test – FAS**

| Pathogen | Fidaxomicin (n = 98) | Vancomycin (n = 44) |
|---|---|---|
| Enteropathogenic Escherichia coli (EPEC) | 14 (14.3) | 5 (11.4) |
| Norovirus GI/GII | 8 (8.2) | 6 (13.6) |
| Astrovirus | 9 (9.2) | 0 |
| Sapovirus | 6 (6.1) | 3 (6.8) |
| Adenovirus F40/41 | 6 (6.1) | 1 (2.3) |
| Rotavirus A | 3 (3.1) | 4 (9.1) |
| Giardia lamblia | 3 (3.1) | 1 (2.3) |
| Enteroaggregative Escherichia coli (EAEC) | 2 (2.0) | 1 (2.3) |
| Salmonella | 3 (3.1) | 0 |
| Campylobacter | 0 | 4 (9.1) |
| Enterotoxigenic Escherichia coli (ETEC) | 2 (2.0) | 0 |
| ETEC toxins LT/ST | 2 (2.0) | 0 |
| Cryptosporidium | 1 (1.0) | 1 (2.3) |
| Yersinia enterocolitica | 1 (1.0) | 1 (2.3) |
| Shiga toxin-producing Escherichia coli (STEC) | 1 (1.0) | 0 |
| Shiga toxins STX1/STX2 | 1 (1.0) | 0 |

FAS: full analysis set; PCR: polymerase chain reaction.

The table gives the number (percentage) of patients.

Source: Table 32, the SUNSHINE study Clinical Study Report

<u>*C. difficile* Ribotyping using Capillary Electrophoresis (CE) of stool specimens</u>

A total of 106 stool samples from 88 patients from both treatment arms at different time points (screening, EOT, and recurrence visits) were analyzed by ribotyping. Overall, various *C. difficile* ribotypes were present among both treatment arms with ribotype 027 (n=11) being most frequent followed by ribotypes 014 (n=8), 020 (n=7), 001 (n=6), 002 (n=6), and 039 (n=6). Historically, ribotype 027 is the most virulent type. No PFGE or REA typing was conducted on *C. difficile* isolates.

<u>Correlation of *C. difficile* ribotypes at baseline and recurrence</u>

Recurrence of CDAD was determined at EOS among 9 patients in the fidaxomicin arm and 9 patients in the vancomycin arm. However, ribotyping results were not available for all positive

*C. difficile* stool samples at screening and recurrence. In the fidaxomicin arm, recurrence was due to the same ribotypes in 5 patients and with different ribotypes in 3 patients. In the vancomycin arm, recurrence was due to the same ribotype in 1 patient and with different ribotypes in 4 patients.

Fecal fidaxomicin concentrations

Fecal concentrations of fidaxomicin were determined within 24 hours of a dose taken on any day from day 5 through day 10. The geometric mean (%CV) of fidaxomicin fecal concentration was 1903.25 (92.2) mcg/g and the metabolite OP-1118 fecal concentration was 625.63 (92.0) mcg/g. The fecal concentration of fidaxomicin and its main metabolite OP-1118 was much higher than the highest MICs of clinical *C. difficile* isolates.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

Merck submitted a letter to cross-reference the new NDA to the sNDA submission to support the pediatric formulation, as well as to the relevant INDs 64435 (b) (4). The composition of DIFICID for oral suspension and the mixed berry flavor included in the proposed formulation for oral suspension are provided in the tables below (the Mixed Berry formulation appears in the referenced Drug Master File (DMF) No. (b) (4)). The excipients included in the formulation for the granules for suspension are at levels similar to or less than other FDA approved products for oral administration.

**Table 5-1. Composition of Fidaxomicin Granules for Oral Suspension**

| Component | Functionality | Specification | Quantity (mg/5 mL) | Quantity (g/bottle) |
|---|---|---|---|---|
| Fidaxomicin | Active | In house | 200.0 | 5.446 |
| Cellulose, microcrystalline | (b) (4) | USP/NF | | (b) (4) |
| Sodium starch glycolate | | USP/NF | | |
| Xanthan gum | | USP/NF | | |
| Citric acid | | USP/NF | | |
| Sodium citrate | | USP/NF | | |
| Sodium benzoate | | USP/NF | | |
| Sucralose | | USP/NF | | |
| Mixed berry flavor | | In house | | |
| Total | | | | |

*(Table 1, 3.2.P.1, Description and Composition of the Drug Product)*

This review includes 3 studies submitted to NDA 201699 including 1) a GLP 7-day comparative toxicokinetic (TK) study of OPT-80 in beagle dogs upon oral (gavage and capsule) administration; 2) a non GLP 14-day range finding OPT-80 study in juvenile beagle dogs; and 3) a definitive GLP 28-day OPT-80 study in juvenile beagle dogs with a 56-day recovery period.

The 7-day comparative TK study in adult dogs showed that both the fidaxomicin suspension and tablets were well tolerated, with generally higher levels of OPT-80 and its metabolite, OP-1118, in plasma and feces of animals receiving tablets than those receiving suspension. However, high inter-animal variability in plasma concentrations within each group limited the reliability of TK comparisons between formulations and genders. Overall, significantly higher concentrations of fidaxomicin and OP-1118 were detected in feces (mcg/g levels) compared to plasma (ng/mL levels) regardless of the formulation.

In juvenile animals, OPT-80 was well tolerated in both studies without notable systemic findings. A comparison of pharmacokinetic parameters (e.g., AUCs) of OPT-80 or the metabolite between juvenile beagles and pediatric patients were not possible because these PK values were not calculated in the Phase 2a or Phase 3 clinical studies due to the low plasma levels (3-33 ng/mL). Similar to humans, fidaxomicin appears to be poorly absorbed via the gastrointestinal tract of juvenile beagles with both parent and primary metabolite being largely excreted in the feces.

## 5.2. Referenced NDAs, BLAs, DMFs, INDs

INDs 64435 (b) (4)

## 5.3. Toxicology

- Study No. (b) (4)-609011. Title: A 7-day comparative toxicokinetic study of fidaxomicin (OPT-80, PAR-101) in beagle dogs upon oral (gavage and capsule) administration.
- Study No. 902517. Title: A 14-day Dose Range Finding Study by Oral Gavage Administration of Fidaxomicin (OPT-80) in the Juvenile Beagle Dog.
- Study No.902518. Title: A 28-day Study by Oral Gavage Administration of Fidaxomicin (OPT-80) in the Juvenile Beagle Dog with a 56-day Recovery Period.

These studies have been reviewed in full for this review; See Appendix 15.3 Pharmacology/Toxicology.

# 6 Clinical Pharmacology

## 6.1. Executive Summary

The Office of Clinical Pharmacology (Division of Infectious Diseases Pharmacology; OCP/DIDP) reviewed the clinical pharmacology information contained in sNDA 201699 and NDA 213138. OCP's recommendations and comments on key review issues are summarized in the table below.

**Table 6-1. Summary of OCP's Recommendations & Comments on Key Review Issues**

<table>
<tr><th>Review Issue</th><th>Recommendations and Comments</th></tr>
<tr><td>Pivotal and Supportive Evidence of Effectiveness</td><td>Fidaxomicin is a locally-acting drug that is mainly confined to the gastrointestinal (GI) tract (site of action/infection). Systemic absorption is minimal following oral administration, with plasma concentrations of fidaxomicin and OP-1118 in the ng/mL range at the therapeutic dose. The efficacy assessment for the treatment of CDAD in pediatric patients (from 6 months to less than 18 years of age) is extrapolated from adults and supported by a Phase 3 randomized, investigator-blinded, controlled trial, comparing safety and efficacy of fidaxomicin oral suspension or tablets to vancomycin liquid or tablets in pediatric patients from 6 months to less than 18 years (Study 2819-CL-0202; SUNSHINE).<br><br>Supportive information is provided by pharmacokinetic assessments demonstrating that, similar to adults, fidaxomicin has minimal systemic absorption following oral administration across all age groups in pediatric patients.</td></tr>
<tr><td>General Dosing Instructions for pediatric patients (6 months to less than 18 years of age)</td><td>Oral Suspension<br>Pediatric patients weighing at least 4 kg: Weight-based dosing of the oral suspension twice daily for 10 days is specified in the table below.<br><br>
<table>
<tr><th>Body Weight</th><th>Dose Administered Twice Daily</th><th>Volume of 40 mg/mL Suspension to be Administered Orally Twice Daily</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>4 kg to less than 7 kg</td><td>80 mg</td><td>2 mL</td></tr>
<tr><td>7 kg to less than 9 kg</td><td>120 mg</td><td>3 mL</td></tr>
<tr><td>9 kg to less than 12.5 kg</td><td>160 mg</td><td>4 mL</td></tr>
<tr><td>12.5 kg and above</td><td>200 mg</td><td>5 mL</td></tr>
</table>
<br>Tablets<br>Pediatric patients weighing at least 12.5 kg and able to swallow tablets: One 200 mg tablet orally twice daily for 10 days.
</td></tr>
<tr><td>Dosing in Patient Sub-Groups</td><td>No dose individualization is recommended based on intrinsic and extrinsic factors.</td></tr>
<tr><td>Labeling</td><td>The Applicant’s proposed labeling required minor edits. The review team has specific content and formatting change recommendations that were communicated to the Applicant.</td></tr>
<tr><td>Bridge between the to-be-marketed and clinical trial formulations</td><td>The to-be-marketed granule for oral suspension formulation was used in the Phase 3 study.</td></tr>
</table>

## 6.2. Summary of Clinical Pharmacology Assessment

The PK of fidaxomicin in pediatric patients with CDAD were evaluated in one Phase 2a study (OPT-80-206) and one Phase 3 study (SUNSHINE). A powder for reconstitution formulation was investigated in the OPT-80-206 study and the to-be-marketed granules for oral suspension formulation was used in the SUNSHINE study. For both formulations, fidaxomicin concentrations were low in plasma (ng/mL range) and high in fecal samples (mcg/g range).

The approved 200-mg fidaxomicin film-coated tablet was used for patients with a weight of ≥12.5 kg who were able to swallow tablets. A comparison of plasma and fecal concentrations between the tablet and granules for oral suspension formulations administered to pediatric patients in the SUNSHINE study is highlighted in Appendix 15.4. For both formulations, fecal concentrations were high and plasma concentrations were generally low. Mean (± standard deviation) plasma concentrations of the to-be-marketed products at the therapeutic dose in pediatric patients were 39.41 (±62.15) ng/mL of fidaxomicin and 116.64 (±259.10) ng/mL of OP-1118 at 1 to 5 hours postdose in the SUNSHINE study.

Overall, plasma concentrations in pediatric patients were similar (ng/mL range) to adults (See Appendix 15.4). Results from these studies indicate that fidaxomicin has minimal systemic absorption following oral administration across all age groups in pediatric patients.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology profile of fidaxomicin in adults has been characterized and detailed in the original marketing application (NDA 201699).

**Table 6-2. General Pharmacology and Pharmacokinetic Characteristics**

| | |
|---|---|
| Mechanism of Action | Fidaxomicin inhibits ribonucleic acid (RNA) synthesis by bacterial RNA polymerase. |
| QT Prolongation | The impact of drug concentrations on QT prolongation was not assessed due to the drug's limited systemic absorption. |
| Active Moieties | Fidaxomicin and OP-1118 (major active metabolite of fidaxomicin) |
| Bioanalysis | Plasma and fecal samples in pediatric patients were assayed for fidaxomicin and OP-1118 concentrations using multiple validated LC-MS/MS assays. |
| Bioavailability | Bioavailability was not evaluated due to limited systemic absorption. |
| Half-life | Could not be determined in pediatric patients due to limited systemic absorption. |
| Pharmacokinetic Drug Interactions with Fidaxomicin | Fidaxomicin and its main metabolite, OP-1118, are substrates of the efflux transporter, P-glycoprotein (P-gp), which is expressed in the gastrointestinal tract. However, this interaction is not considered clinically relevant. |

### 6.3.2. Clinical Pharmacology Questions

**Does the clinical pharmacology program provide supportive evidence of effectiveness?**

Fidaxomicin is a locally acting drug with poor systemic absorption. The primary evidence of effectiveness is based on extrapolation from adults and results from a Phase 3, randomized, investigator-blinded trial, comparing safety and efficacy of fidaxomicin oral suspension or tablets to vancomycin liquid or tablets in pediatric from 6 months to less than 18 years of age (See Section 8 for details on the efficacy assessment).

**Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

In the Phase 2 and Phase 3 trials, pediatric patients with a weight of >12.5 kg received the full adult fidaxomicin dose of 400 mg/day (administered as 200 mg twice daily) using the tablet formulation (if > 6 years of age and able to swallow tablets) or as oral suspension (if < 6 years of age or unable to swallow tablets). Patients with a weight of ≤12.5 kg received the reconstituted oral suspension at a dose of 32 mg/kg per day divided in two daily doses (Table 6-3). Refer to Section 8 for details on the efficacy and safety assessment of the proposed dosing regimen.

**Table 6-3. Recommended Dosage of DIFICID Oral Suspension in Pediatric Patients, Based on Weight**

| Body Weight | Dose Administered Twice Daily | Volume of 40 mg/mL Suspension to be Administered Orally Twice Daily |
|---|---|---|
| 4 kg to less than 7 kg | 80 mg | 2 mL |
| 7 kg to less than 9 kg | 120 mg | 3 mL |
| 9 kg to less than 12.5 kg | 160 mg | 4 mL |
| 12.5 kg and above | 200 mg | 5 mL |

The weight-based dosing schedule was selected by scaling against oral vancomycin. The standard dose of vancomycin in adults is 500 mg/day, while that for fidaxomicin in adults is 20% lower at 400 mg/day. Applying similar scaling (i.e., a reduction in dose of 20%) to the weight-based dosing of the oral suspension in pediatric patients, the recommended dose of fidaxomicin was selected to be 32 mg/kg/day as compared to 40 mg/kg/day for vancomycin. This approach was considered appropriate because both drugs act locally in the GI tract with limited systemic absorption.

Both the weight-based and fixed dose regimens resulted in comparable fidaxomicin pharmacokinetic profiles in pediatric patients ≥ 6 months with those in adults, with low plasma concentrations and high fecal concentrations reflective of the poor systemic absorption of the drug.

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

No. Fidaxomicin acts locally in the GI tract on *C. difficile*. Minimal systemic absorption suggests that various intrinsic factors such as age, body weight or race would not significantly affect systemic or GI exposure.

# 7 Sources of Clinical Data and Review Strategy

The overview of the clinical studies reviewed for these applications is provided in Table 7-1.

## 7.1. Table of Clinical Studies

**Table 7-1. Clinical Studies Reviewed**

| Study | Study Population | Study Design | Study Treatment by Age group/Duration | Primary study endpoints | No. of patients enrolled | Treatment Duration/Follow up |
|---|---|---|---|---|---|---|
| OPT-80-206 | Pediatric patients ≥ 6 months to < 18 years of age with CDAD | Phase 2a, open-label, uncontrolled, safety, tolerability, and PK study in pediatric patients with CDAD (defined by a positive stool *C. difficile* toxin A and/or toxin B assay result within 48 hours of enrollment). | Oral fidaxomicin<br>- **Age ≥ 6 months to <6 years**: weight-based doses of fidaxomicin oral suspension 32 mg/kg/day (maximum 400 mg/day), divided into 2 doses (every 12 hours) for 10 days<br>- **Age ≥ 6 years to <18 years**: One 200 mg tablet every 12 hours for 10 days | The main efficacy endpoint was percentage of patients with a clinical response | 38 | 10-day treatment and 28-day follow-up period |
| 2819-CL-0202 (SUNSHINE) | Pediatric patients ≥ 6 months to < 18 years of age with CDAD<br><br>(Note: 1 patient who was 1 month old was enrolled in this study and included in all analyses) | Phase 3, multicenter, investigator-blind, randomized, parallel group study to investigate safety and efficacy of fidaxomicin granules for oral suspension or tablets taken every 12 hours, and vancomycin oral liquid or capsules taken every 6 hours for 10 days in pediatric patients with CDAD.<br><br>Patients were randomized in a 2:1 ratio to either fidaxomicin or vancomycin. | Oral fidaxomicin<br>200 mg tablets or<br>32 mg/kg per day<br>oral suspension<br>twice daily (every 12 hours) beginning day 1, for 10 days | The primary endpoint was the proportion of patients with a confirmed clinical response assessed by the investigator 2 days after EOT | 148 fidaxomicin n=100; vancomycin n=48 | 10-day treatment and 30-day follow-up period |

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Studies Used to Support Efficacy

### 8.1.1. SUNSHINE Study

**Trial Design**

The SUNSHINE study was a Phase 3 multicenter, investigator-blind, randomized parallel group study to investigate the safety and efficacy of fidaxomicin oral suspension or tablets and vancomycin oral liquid or capsules in pediatric patients with *Clostridioides difficile*-associated diarrhea (CDAD). The study was a multinational study conducted at sites in North America and Europe including the following countries (# of enrolling sites): United States (13 sites), Poland (6 sites), France (5 sites), Germany (3 sites), Romania (1 site), Hungary (2 sites), Spain (4 sites), Italy (2 sites), Belgium (3 sites), and Canada (1 site).

Eligible patients included males and females from birth (6 months in the United States) to < 18 years of age with a diagnosis of CDAD. At a minimum the diagnosis of CDAD required positive detection (within 72 hours prior to randomization) of either toxin A and/or B in stool or positive detection of toxigenic *C. difficile* in stool and:

a. For patients < 2 years, watery diarrhea in the 24 hours prior to screening
b. For patients ≥ 2 years to < 18 years, 3 or more unformed bowel movements in the 24 hours prior to screening.

Patients < 5 years were to have a negative rotavirus test. Patients were not eligible if they had concurrent use of metronidazole, oral vancomycin or any other antibacterial treatments for CDAD. However, if the investigator felt treatment was needed prior to knowing the laboratory result for toxigenic *C. difficile*, up to 4 doses but no more than 24 hours of treatment with an effective treatment for CDAD was allowed. Additionally, patients were not eligible if they had pseudomembranous colitis, fulminant colitis, toxic megacolon or ileus, a history of inflammatory bowel disease, or diarrhea caused by something other than *C. difficile* (e.g., infections, infestations, drugs).

Patients were randomized in a 2:1 ratio to either fidaxomicin or vancomycin for 10 days. Randomization was stratified by age at screening (< 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years). Dosing was to be with the oral suspension/oral liquid formulation for patients < 6 years of age and with the tablet/capsule formulation for patients 6 years to < 18 years. However, if it was determined prior to randomization that a patient aged 6 years to < 18 years could not swallow tablets or capsules then the oral suspension/oral liquid could be given to that patient. Dosing was the following:

| | Fidaxomicin | Vancomycin |
|---|---|---|
| < 6 years of age | Fidaxomicin oral suspension: 32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses/day | Vancomycin oral liquid: 40 mg/kg/day with a maximum dose of 500 mg/day, divided in 4 doses/day |
| 6 years to < 18 years of age | Fidaxomicin 200 mg tablets 2 times daily | Vancomycin 125 mg capsules 4 times daily |

The dose of vancomycin chosen is considered the standard dose for children. For adults, the standard total daily dose of fidaxomicin is 20% lower than the standard total daily dose of vancomycin. Therefore, the total daily dose of fidaxomicin for children was chosen to be 20% lower than the standard dose of vancomycin in children. The duration of treatment for 10 days was the same as used in the adult Phase 3 studies for which acceptable cure rates were observed.

Given the differences in the study medications (suspension/liquid or tablets/capsules), frequency of dosing (twice a day vs 4 times a day), and the pediatric population, blinding of the patient was not considered feasible. Therefore, patients, the parents/legal guardian and staff involved in dispensing, administering or collecting the study products and drug concentration blood sampling were unblinded to randomized treatment. The investigator evaluating the safety and efficacy outcomes was blinded to randomized treatment. Patients, parents/legal guardians and unblinded staff were instructed not to discuss the treatment (appearance, frequency of dosing, times of individual doses, palatability, etc.) and drug concentration blood sampling with the blinded staff. Every effort was taken to maintain the investigator-blind.

**Study Endpoints**

The primary efficacy endpoint is confirmed clinical response at end of treatment (EOT) + 2 days based on the assessment by the investigator. For patients < 2 years, confirmed clinical response was defined as the absence of watery diarrhea for 2 consecutive days during treatment and the patient remained well until the time of study drug discontinuation. For patients aged 2 to < 18 years, confirmed clinical response was defined as < 3 unformed bowel movements for 2 consecutive days during treatment and patients remained well until the time of study drug discontinuation. In addition, for all ages, patients were not to require further CDAD therapy within 2 days after completing study drug.

Secondary efficacy endpoints include sustained clinical response at the end of study (EOT + 30 days), sustained clinical response 14 days after the confirmed clinical response assessment (EOT + 16 days), time to resolution of diarrhea, recurrence of CDAD through the follow-up period, and time to recurrence of CDAD through the follow-up period. Sustained clinical response is defined as confirmed clinical response without CDAD recurrence. Recurrence is defined as follows:

- For patients < 2 years, the reestablishment of watery diarrhea to an extent that was greater than that noted on the last day of study drug with the demonstration of a positive direct or indirect testing for the presence of toxigenic *C. difficile* in stool and that, in the investigator's opinion, would have required retreatment with CDAD anti-infective therapy.
- For patients aged 2 to < 18 years, the reestablishment of diarrhea to an extent (as measured by the frequency of passed unformed stools) that was greater than that noted on the last day of study drug with the demonstration of a positive direct or indirect testing for the presence of toxigenic *C. difficile* in stool and that, in the investigator's opinion, would have required retreatment with CDAD anti-infective therapy.

Palatability (acceptance of the formulation) was assessed for all patients receiving fidaxomicin oral suspension and vancomycin oral liquid on day 1 and day 7. This was assessed by means of a 5-point rating scale (awful, poor, fair, good excellent) by staff if hospitalized and by the patient/parent/legal guardian when at home.

The endpoints assessed are those typically used in trials for the treatment of CDAD and were those stated in the Pediatric Written Request. One variation is in the definition of confirmed clinical response at EOT + 2 days. For this study, response was ultimately based on the Investigator's assessment. In recently conducted studies, response was based on the number of daily unformed stools to determine if there was resolution of diarrhea that was maintained through EOT+ 2 days. Any impact of this will be discussed in Section 8.1.2 under the Additional Analyses Conducted subheading.

**Statistical Analysis Plan**

The statistical analysis plan was finalized prior to database hard lock and full unblinding to ensure lack of bias.

Analysis Populations

The full analysis set (FAS) includes all randomized patients who received at least 1 dose of study drug. Patients in the FAS are analyzed based on the treatment arm to which they were randomized regardless of the actual treatment received. The FAS was used as the primary efficacy analysis population. Typically, since the study was not fully blinded, exclusion of patients for not receiving at least one dose of study drug would not be acceptable for a primary efficacy analysis population as the knowledge of study drug to be received may have an impact on why the study drug was not received. This issue will be further considered when discussing the results in Section 8.1.2.

The intent-to-treat (ITT) analysis set includes all randomized patients. Patients in the ITT are

analyzed based on the treatment arm to which they were randomized regardless of the actual treatment received. The ITT was used as a secondary efficacy analysis population.

The safety analysis set includes all randomized patients who received at least 1 dose of study drug. Patients in the safety set are analyzed based on the study drug that was first administered even if it differed from the treatment arm the patient was randomized to.

Analysis Methods

Analyses are primarily based on descriptive statistics. Efficacy in the pediatric population is supported by extrapolation of efficacy observed from adults.

The proportion of patients with confirmed clinical response were summarized within each treatment arm overall as well as by age group for the FAS. Corresponding 2 sided 95% confidence intervals were calculated based on an exact binomial distribution. The difference in proportions (fidaxomicin – vancomycin) was calculated. Additionally, the adjusted treatment difference of rates was calculated using a stratified Cochran-Mantel-Haenszel method and the 95% confidence interval was calculated using the Newcombe method. The strata were the age grouping levels.

In the study report, the Applicant calculated the sustained clinical response rate out of those patients with a confirmed clinical response at EOT + 2 days rather than the entire FAS/ITT. Therefore, the Applicant defined an additional endpoint of global cure where the proportion was calculated as the number of patients with sustained clinical response divided by the total number of patients in the FAS/ITT regardless of confirmed clinical response status. In the past, the Division has used the terms “global cure” and “sustained response” interchangeably and calculated the rate for this endpoint as described for global cure in the study report. The Division does not typically calculate the rate of “sustained response (global cure)”, especially when treatment comparisons are made, based on those with a confirmed clinical response as this is a subset that is based on post-randomization/treatment factors and those that failed treatment initially are not taken into consideration. Therefore, for this review the assessment of “sustained clinical response” will be based on the analyses of “global cure” as described in the study report.

For the endpoints of confirmed clinical response at EOT + 2 days and sustained clinical response (global cure), missing data were treated as failures in the primary analysis. In an additional analysis, for confirmed clinical response, missing data was also handled using logical derivation. For example, if a patient was not assessed on EOT + 2 days but it was noted that they had resolution of diarrhea at EOT and then were assessed at EOT + 9 days for recurrence, confirmed clinical response at EOT + 2 days was assumed to be a success. The statistical analysis plan also stated that missing data would also be handled using a multiple imputation approach. Given the extremely limited amount of missing data for these endpoints observed in this study and similar results by treating missing data as failures, the analyses conducted using the multiple imputation approach will not be discussed in this review.

Time to resolution of diarrhea was estimated using the Kaplan-Meier method. The log-rank test was used to compare the survival cures of the 2 treatment arms. Patients who did not show resolution of diarrhea were censored at day 10 if they completed treatment or the day of discontinuation or day of last dose taken if they did not complete 10 days of treatment.

Time to recurrence of CDAD was analyzed in a similar manner as time to resolution of diarrhea. Patients with confirmed clinical response at EOT + 2 days who completed the follow-up period but did not experience a recurrence of CDAD were censored at EOT + 30 days. Patients with confirmed clinical response at EOT + 2 days who did not completed the follow-up period and did not experience a recurrence of CDAD were censored at the day of discontinuation.

Results from the assessments of palatability were summarized by a frequency table using the reported categories.

Sample Size Calculation

A total of 144 patients were to be randomized (96 to fidaxomicin and 48 to vancomycin). At least 24 patients were to be in each age groups with a minimum of 16 randomized to fidaxomicin and 8 to vancomycin. The sample size was based on clinical and practical considerations and not statistical considerations, as the prevalence of CDAD in the pediatric population is low.

**Protocol Amendments**

The original protocol was dated September 17, 2013. There were 4 amendments to the protocol: 1 non-substantial and 3 substantial. No patients were enrolled under the original protocol. Eighteen patients enrolled under protocol amendment 1, 23 patients enrolled under protocol amendment 2, 100 patients enrolled under protocol amendment 3, and 7 patients enrolled under protocol amendment 4.

Significant changes to the protocol include the following:

Amendment 1 dated June 5, 2014: More specific instructions about blinding were added. Updated the efficacy assessment by adding the recording of the last episode of watery diarrhea or unformed bowel movement. Added the recording of CDAD signs and symptoms. Clarified details of the palatability testing.

Amendment 2 dated November 21, 2014: (b) (4) Palatability of the oral suspension was added as a secondary objective and as such moved from an exploratory endpoint to a secondary endpoint. Updated the timeframe for positive detection of CDAD from within 48 hours to within 72 hours prior to randomization. Added weight-based dosing instructions of the fidaxomicin oral suspension and the vancomycin liquid.

Amendment 3 dated July 21, 2015: Clarified that in the United States, patients could only enroll if aged ≥ 6 months.

(b) (4)

Modifications to the protocol were implemented following applicable approvals and did not have an impact on the integrity of the study or the interpretation of the results.

### 8.1.2. SUNSHINE Study Results

**Compliance with Good Clinical Practices**

The Applicant states that "the study was conducted in accordance with the protocol, Good Clinical Practice (GCP), International Council on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki."

**Patient Disposition**

A total of 148 patients were randomized in the study and make up the ITT population: 100 randomized to fidaxomicin and 48 randomized to vancomycin. Six patients did not receive treatment: 2 randomized to fidaxomicin and 4 randomized to vancomycin. Therefore, the FAS consists of 98 fidaxomicin-treated patients and 44 vancomycin-treated patients. All patients received at least 1 dose of the study drug to which they were randomized. Therefore, the FAS and the Safety populations are the same (Table 8-1.).

**Table 8-1. Analysis Populations**

| Analysis Population | Fidaxomicin | Vancomycin |
|---|---|---|
| Randomized/ITT | 100 (100%) | 48 (100%) |
| FAS/Safety | 98 (98%) | 44 (92%) |

As seen above, there was a slight imbalance in the number of patients who did not receive study treatment (4 in the vancomycin arm compared to 2 in the fidaxomicin arm). One vancomycin patient's parent withdrew consent prior to dosing. The remaining patients were discontinued from the study by the principal investigator before dosing. Since the investigator was to be blinded to randomized treatment, knowledge of randomized treatment should not have been the reason for no treatment for all but possibly the one vancomycin patient whose parent withdrew consent. Therefore, use of the FAS as the primary analysis population is of less concern.

Overall, 96.5% of FAS patients completed treatment with study drug. Three (3.1%) fidaxomicin-treated patients and 2 (4.5%) vancomycin-treated patients discontinued treatment early. The reasons for discontinuing treatment early were due to adverse event (1 patient in each treatment group) and other (2 fidaxomicin-treated patients and 1 vancomycin-treated patient). Other reasons were investigator decision due to patient unable to take oral fluids and medications, parents needed to leave the country, and patient taking forbidden concomitant medication not for CDAD.

The majority (95.1%) of FAS patients completed the study. Six (6.1%) fidaxomicin-treated patients and 1 (2.3%) vancomycin-treated patient discontinued the study early. Three fidaxomicin-treated patients and no vancomycin-treated patients discontinued the study early due to death. One fidaxomicin-treated patient was lost-to-follow-up. The remaining patients discontinued the study early due to other reasons which were drug withdrawn because patient unable to take medication by mouth (1 fidaxomicin-treated patient), recurrence of diarrhea (1 fidaxomicin-treated patient) and worsening of general state due to other infections (1 vancomycin-treated patient).

**Table 8-2. Patient Disposition (FAS)**

| | **Fidaxomicin (n=98)** | **Vancomycin (n=44)** |
|---|---|---|
| **Completed Treatment** | 95 (96.9%) | 42 (95.5%) |
| **Discontinued Treatment** | 3 (3.1%) | 2 (4.5%) |
| Adverse event | 1 (1.0%) | 1 (2.3%) |
| Other | 2 (2.0%) | 1 (2.3%) |
| **Completed Study** | 92 (93.8%) | 43 (97.7%) |
| **Discontinued Study** | 6 (6.1%) | 1 (2.3%) |
| Death | 3 (3.1%) | 0 |
| Lost-to-follow-up | 1 (1.0%) | 0 |
| Other | 2 (2.0%) | 1 (2.3%) |

Source: Reviewer's Analysis using ADSL dataset

**Protocol Violations/Deviations**

Overall, 20 patients in the FAS had at least one protocol deviation. The most common deviation was patient received an excluded concomitant medication (8 fidaxomicin-treated patients and 2-vancomycin treated patients). This was followed by patient receiving the wrong treatment or incorrect dose (2 fidaxomicin-treated patients and 5-vancomycin treated patients). All of these patients received the oral suspension/liquid formulation. One vancomycin-treated patient used a bottle of study drug past the expiration date. The 2 fidaxomicin-treated patients and remaining 4 vancomycin-treated patients were dispensed an incorrect dose (<80% or > 120% of dose planned). The remaining patients had a protocol deviation of not satisfying all entry criteria. Additionally, 1 fidaxomicin treated patient who was included in the ITT population but

not the FAS had a protocol violation of entering the study without satisfying the entry criteria.

**Table 8-3. Protocol Deviations (FAS)**

| | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| **Any Deviation** | 11 (11.2%) | 9 (20.5%) |
| Entered study without satisfying all entry criteria | 1 (1.0%) | 2 (4.5%) |
| Received wrong treatment or incorrect dose | 2 (2.0%) | 5 (11.4%) |
| Received excluded concomitant medication | 8 (8.2%) | 2 (4.5%) |

Source: Reviewer's Analysis using ADDV dataset

**Demographic and Other Baseline Characteristics**

The following table summarizes demographic and baseline characteristics of patients in the FAS. The two treatment groups were balanced regarding sex and race where 58% of the patients were male and the majority (82%) were white. The mean age of fidaxomicin-treated patients was slightly older (80 months or 6.7 years) than vancomycin-treated patients (73.9 months or 6.2 years). The number of patients enrolled in each age group ranged from 20-32 for fidaxomicin and 8-16 for vancomycin which met the minimum required in the pediatric written request (PWR). A single patient less than 6 months was enrolled in the fidaxomicin arm. Enrollment was divided between the United States and Europe. However, more fidaxomicin-treated patients (44.9%) than vancomycin-treated patients (25.0%) were from the United States. Approximately 68% of patients received the oral suspension/liquid formulation. This includes all patients less than 6 years and 19 patients older than 6 years (15 fidaxomicin -treated patients and 4 vancomycin treated patients).

**Table 8-4. Demographic and Baseline Characteristics (FAS)**

| Parameter | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| **Sex** | | |
| Male | 57 (58.2%) | 25 (56.8%) |
| Female | 41 (41.8%) | 19 (43.2%) |
| **Race** | | |
| White | 81 (82.7%) | 35 (79.5%) |
| Black | 6 (6.1%) | 2 (4.5%) |
| Asian | 2 (2.0%) | 0 |
| Other | 4 (4.1%) | 1 (2.3%) |
| Missing* | 5 (5.1%) | 6 (13.6%) |
| **Age (months)** | | |
| Mean (sd) | 80.0 (62.2) | 73.9 (60.0) |

| Parameter | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| Median | 60 | 48 |
| Min, Max | 1, 204 | 8, 204 |
| **Age Group** | | |
| < 2 years | 20 (20.4%)** | 10 (22.7%) |
| 2 years to < 6 years | 32 (32.7%) | 16 (36.4%) |
| 6 years to < 12 years | 26 (26.5%) | 10 (22.7%) |
| 12 years to < 18 years | 20 (20.4%) | 8 (18.2%) |
| **Country** | | |
| United States | 44 (44.9%) | 11 (25.0%) |
| Belgium | 4 (4.1%) | 2 (4.6%) |
| Canada | 1 (1.0%) | 0 |
| France | 5 (5.1%) | 6 (13.6%) |
| Germany | 4 (4.1%) | 1 (2.3%) |
| Hungary | 12 (12.2%) | 5 (11.4%) |
| Italy | 5 (5.1%) | 2 (4.6%) |
| Poland | 8 (8.2%) | 6 (13.6%) |
| Romania | 6 (6.1%) | 3 (6.8%) |
| Spain | 9 (9.2%) | 8 (18.2%) |
| **Formulation Received** | | |
| Suspension/Liquid | 67 (68.4%) | 30 (68.2%) |
| Tablet/Capsule | 31 (31.6%) | 14 (31.8%) |

* Race not allowed to be collected in France

** Includes 1 patient less than 6 months (1 month)

Source: Reviewer's Analysis using ADSL dataset

Diarrhea and bowel movement history and CDAD risk factors are summarized in the following table. More fidaxomicin-treated patients (42.9%) reported at least 1 prior episode of diarrhea in the 3 months prior to screening than vancomycin-treated patients (34.1%). A confirmed CDAD prior episode was noted for 28.6% fidaxomicin-treated patients and 22.7% vancomycin-treated patients. All patients less than 2 years of age had the presence of watery diarrhea in the previous 24 hours and all but 1 patient 2 years or older (treated with vancomycin) reported 3 or more unformed bowel movements in the previous 24 hours. The median number of unformed bowel movements in the previous 24 hours was 5 for fidaxomicin-treated patients and 4 for vancomycin-treated patients.

The majority of patients had at least 1 risk factor that contributed to the current episode of CDAD, although slightly more in the vancomycin arm (84.1%) compared to the fidaxomicin arm (77.6%). The most commonly reported risk factor was the use of antibiotics in 51.0% of fidaxomicin-treated patients and 65.9% vancomycin-treated patients. Cancer was reported in 42.3% of the patients overall with a similar proportion in the two treatment arms. Other risk factors reported, which included hospitalization, immunosuppression, surgery, and contact

with a CDAD-infected relative, also occurred with a similar proportion in the treatment arms.

**Table 8-5. Diarrhea and Bowel Movement History and CDAD Risk Factors (FAS)**

| Parameter | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| **Diarrhea History in Prior 3 Months** | | |
| **Prior Episode of Diarrhea** | | |
| No | 56 (57.1%) | 29 (65.9%) |
| Yes | 42 (42.9%) | 15 (34.1%) |
| Confirmed CDAD | 28 (28.6%) | 10 (22.7%) |
| Not confirmed | 11 (11.2%) | 2 (4.5%) |
| Unknown | 3 (3.1%) | 3 (6.8%) |
| **Prior Diarrhea Episode Treated with Antibacterial Medication** | | |
| Yes | 28 (28.6%) | 8 (18.8%) |
| No | 14 (14.3%) | 7 (15.9%) |
| **Bowel Movement History in 24 Hours Prior to Screening** | | |
| **Watery diarrhea or ≥ 3 UBMs** | | |
| Yes | 98 (100.0%) | 43 (97.7%) |
| No | 0 | 0 |
| Unknown | 0 | 1 (2.3%) |
| **Number of UBMs** | | |
| n | 78 | 33 |
| Mean (sd) | 6.4 (6.3) | 6.3 (5.8) |
| Median | 5 | 4 |
| Min, Max | 3, 48 | 3, 24 |
| **CDAD Risk Factors** | | |
| **Currently Treated with Antibacterial Medication** | | |
| Yes | 32 (32.7%) | 17 (38.6%) |
| No | 66 (67.3%) | 27 (61.4%) |
| **Presence of Any Risk Factor that Contributed to Current Episode** | | |
| Yes | 76 (77.6%) | 37 (84.1%) |
| No | 22 (22.5%) | 7 (15.9%) |
| **Risk Factor that Contributed to Current Episode*** | | |
| Antibiotics | 50 (51.0%) | 29 (65.9%) |
| Cancer | 42 (42.9%) | 18 (40.9%) |
| Other | 17 (17.3%) | 7 (15.9%) |

UBM: Unformed Bowel Movement
*More than 1 risk factor could be reported
Source: Reviewer's Analysis using ADSL dataset

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Treatment compliance was high with most patients in both treatment arms receiving the recommended duration of treatment. Slightly more vancomycin-treated patients (5, 11.4%) than fidaxomicin treatment patients (4, 4.1%) had treatment compliance < 80%. Except for 1 vancomycin-treated patient, all patients with treatment compliance < 80% received the oral suspension/liquid formulation.

Overall, concomitant medication use was high with 96.9% of fidaxomicin-treated patients and 93.2% of vancomycin-treated patients receiving at least 1 concomitant medication during the study. The most frequent concomitant medications used that could possibly have had an impact on the assessment of response were antidiarrheal, intestinal anti-inflammatory/anti-infective agents and antibacterials for systemic use. A similar proportion of patients received antibacterials for systemic use: 71.4% of fidaxomicin-treated patients and 70.5% of vancomycin-treated patients. A greater proportion of fidaxomicin-treated patients (67.3%) compared to vancomycin-treated patients (50%) received concomitant antidiarrheal, intestinal anti-inflammatory/anti-infective agents.

The review of the drugs listed as antidiarrheal and intestinal anti-inflammatory/anti-infective agents revealed that their high use can be explained by imprecise categorization of these medications by the Applicant. Thus, intravenous vancomycin was misclassified as 'intestinal anti-infective' for some patients. Consequently, 49 (50%) of fidaxomicin patients and 19 (43.2%) of vancomycin patients were counted as receiving vancomycin as an intestinal anti-infective agent. Other antimicrobial drugs that were erroneously categorized as intestinal anti-infectives and used by a substantial proportion of study patients in the fidaxomicin and vancomycin arm, respectively, included amphotericin B, 7 (7.1%) and 3 (6.8%), and nystatin, 7 (7.1%) and 8 (18.2%).

Intestinal anti-inflammatory agents mainly included systemic corticosteroids and were administered to 34 (34.6%) and 10 (22.7%) of fidaxomicin and vancomycin patients, respectively. While case reports on the use of corticosteroids in severe *C. difficile* infection have been published[35,36], their use in non-severe disease in not recommended and corticosteroids were associated with poorer outcomes in some patients with *C. difficile* infection[37]. A greater use of corticosteroids in the fidaxomicin arm may also be related to a greater proportion of patients with underlying comorbidities requiring the use of these medications.

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[35] Cavagnaro. C et al. Corticosteroid treatment of severe, non-responsive *Clostridium difficile* induced colitis. Arch Dis Child. 2003 Apr; 88(4):342-4.
[36] Sykes E et al. Corticosteroids in the Treatment of Pseudomembranous Colitis: A Report of 3 Cases. Gastroenterology Res. 2012 Oct;5(5):211-214.
[37] Lim HW et al. The impact of corticosteroid use on inpatients with inflammatory bowel disease and positive polymerase chain reaction for *Clostridium difficile*. Intest Res. 2019 Apr;17(2):244-252.

Anti-diarrheal drugs used in the fidaxomicin and vancomycin arm, respectively, included acetorphan, 7 (7.1%) and 6 (13.6%), and loperamide, 0 and 1 (2.3%). Probiotics were also categorized as anti-diarrheal drugs; they were used in 24 (24.5%) and 12 (27.2%) patients in the fidaxomicin and vancomycin arm, respectively. Overall, an imbalance in the use of concomitant medications categorized as antidiarrheal and intestinal anti-inflammatory/anti-infective agents should not confound the assessment of fidaxomicin efficacy in the study.

**Efficacy Results – Primary Endpoint**

In the FAS, confirmed clinical response at EOT + 2 days was observed in 77.6% of patients in the fidaxomicin arm and 70.5% of patients in the vancomycin arm. The adjusted (by age strata) difference in proportions of patients with confirmed clinical response was 7.5% with a 95% confidence interval of (-7.4%, 23.9%). In the ITT, confirmed clinical response at EOT + 2 days was observed in 76.0 % of patients in the fidaxomicin arm and 64.6% of patients in the vancomycin arm. The adjusted difference in proportions of patients with confirmed clinical response was 11.3% with a 95% confidence interval of (-4.0%, 27.3%).

The only difference between the FAS and ITT populations is that the ITT population includes the 6 patients who were randomized but did not receive any study drug. These patients were treated as not having a confirmed clinical response in the ITT analysis. Since there were more patients on the vancomycin arm who did not receive any treatment, an additional analysis was conducted treating these patients as a having a confirmed response while still considering the fidaxomicin patients as not having a confirmed clinical response. In this analysis, the rates are 76.0% (76/100) for fidaxomicin and 72.9% (35/48) for vancomycin. As the results for the various analyses (including the multiple imputation approach conducted by the Applicant not presented here) conducted for the ITT are fairly consistent with the FAS, the remainder of this review will focus on the FAS only.

**Table 8-6. Confirmed Clinical Response at EOT + 2 days**

| Population | Fidaxomicin | Vancomycin | Adjusted Difference (95% CI) |
|---|---|---|---|
| **FAS** | n=98 | n=44 | |
| Yes | 76 (77.6%) | 31 (70.5%) | 7.5% |
| 95% CI | (68.0%, 85.4%) | (54.8%, 83.2%) | (-7.4%, 23.9%) |
| No | 19 (19.4%) | 12 (27.3%) | |
| Missing | 3 (3.1%) | 1 (2.2%) | |
| **ITT** | n=100 | n=48 | |
| Yes | 76 (76.0%) | 31 (64.6%) | 11.3% |
| 95% CI | (66.4%, 84.0%) | (49.5%, 77.8%) | (-4.0%, 27.3%) |
| No | 19 (19.0%) | 12 (25.0%) | |
| Missing | 5 (5.0%) | 5 (10.4%) | |

Source: Reviewer's Analysis using ADEFFD dataset

There were minimal missing data for confirmed clinical response at EOT + 2 days in the FAS: 3 in the fidaxomicin arm and 1 in the vancomycin arm. However, 2 of these fidaxomicin treated patients and the 1 vancomycin-treated patient were assessed at EOT as having an initial clinical response. Although these patients did not have an assessment at EOT + 2 days, they had an assessment for recurrence at EOT + 9 days. At the EOT + 9 days visit, the 2 fidaxomicin-treated patients were assessed as not having a recurrence since the last visit (i.e., EOT) and the vancomycin treated patient had a recurrence noted to have occurred 7 days after EOT. Therefore, it can be assumed that these patients had clinical response at EOT + 2 days. When imputing these patients as having confirmed clinical response at EOT + 2 days, the rates are 79.6% (78/98) for fidaxomicin and 72.7% (32/44) for vancomycin.

The results for confirmed clinical response at EOT + 2 days are summarized in the following table by age group in the FAS. In the age group < 2 years, the confirmed clinical response rate was numerically lower for fidaxomicin (65.0%) than vancomycin (90.0%). In the remaining age groups, the confirmed clinical response rate was numerically higher for fidaxomicin than vancomycin with the greatest difference observed between treatment groups seen in the > 6 years to < 12 years age group. Due to the small sample sizes, caution should be taken when interpreting the differences observed for the various age groups.

**Table 8-7. Confirmed Clinical Response at EOT + 2 days by Age Group (FAS)**

| | Fidaxomicin | Vancomycin | Difference (95% CI) |
|---|---|---|---|
| **Age < 2 years** | n=20 | n=10 | |
| Yes | 13 (65.0%) | 9 (90.0%) | -25.0% |
| 95% CI | (40.8%, 84.6%) | (55.5%, 99.7%) | (-53.0, 3.0%) |
| **Age ≥ 2 to < 6 years** | n=32 | n=16 | |
| Yes | 25 (78.1%) | 12 (75.0%) | 3.1% |
| 95% CI | (60.0%, 90.7%) | (47.6%, 92.7%) | (-22.5%, 28.7%) |
| **Age ≥ 6 to < 12 years** | n=26 | n=10 | |
| Yes | 23 (88.5%) | 5 (50.0%) | 38.5% |
| 95% CI | (69.8%, 97.6%) | (18.7%, 81.3%) | (5.1%, 71.8%) |
| **Age ≥ 12 to < 18 years** | n=20 | n=8 | |
| Yes | 15 (75.0%) | 5 (62.5%) | 12.5% |
| 95% CI | (50.9%, 91.3%) | (24.5%, 91.5%) | (-26.0%, 51.0%) |

Source: Reviewer's Analysis using ADEFFD dataset

Given the caveat above regarding the small sample sizes in the various age groups, further investigation of the data was done to explain the lower efficacy observed for fidaxomicin compared to vancomycin in the < 2 years age group. For this age group, it is known that diagnosis of CDAD is difficult as other reasons for watery diarrhea and colonization with *C. difficile* are common. It was noted that the low confirmed clinical response at EOT + 2 days in the fidaxomicin arm may have been impacted for these reasons.

Confirmed clinical response at EOT + 2 days by various subgroups is summarized in the following table for the FAS. Interpretation of these results must be made with caution given the small sample sizes in some of the subgroups.

**Table 8-8. Confirmed Clinical Response at EOT + 2 days by Various Subgroups (FAS)**

| | Fidaxomicin | Vancomycin |
|---|---|---|
| **Sex** | | |
| Male | 42/57 (73.7%) | 19/25 (76.0%) |
| Female | 34/41 (82.9%) | 12/19 (63.2%) |
| **Race** | | |
| White | 66/81 (81.5%) | 25/35 (71.4%) |
| Non-White | 10/17 (58.8%) | 6/9 (66.7%) |
| **Country** | | |
| United States | 34/44 (77.3%) | 8/11 (72.7%) |
| Belgium | 3/4 (75.0%) | 1/2 (50.0%) |
| Canada | 1/1 (100.0%) | - |
| France | 4/5 (80.0%) | 4/6 (66.7%) |
| Germany | 4/4 (100.0%) | 1/1 (100.0%) |
| Hungary | 11/12 (91.7%) | 3/5 (60.0%) |
| Italy | 4/5 (80.0%) | 2/2 (100.0%) |
| Poland | 6/8 (75.0%) | 5/6 (83.3%) |
| Romania | 6/6 (100.0%) | 3/3 (100.0%) |
| Spain | 3/9 (33.3%) | 4/8 (50.0%) |
| **Formulation Received** | | |
| Suspension/Liquid | 52/67 (77.6%) | 23/30 (76.7%) |
| Tablet/Capsule | 24/31 (77.4%) | 8/14 (57.1%) |

Source: Reviewer's Analysis using ADEFFD dataset

During the conduct of the study, noncompliance with the hospital's IRB policies was noted by the IRB of Site 10014. This site enrolled 2 patients both randomized to the fidaxomicin arm. Although no signs of misconduct were observed for these patients by the Applicant, a sensitivity analysis was conducted excluding these patients. In this analysis, confirmed clinical response at EOT + 2 days was 77.6 % (74/96) for the fidaxomicin arm and 70.5% (31/44) for the vancomycin arm. The adjusted difference in proportions of patients with confirmed clinical response was 7.2% with a 95% confidence interval of (-7.8%, 23.7%). The results of the sensitivity analysis indicate minimal impact of these patients on the results as observed for the FAS overall.

**Efficacy Results – Secondary and other relevant endpoints**

Sustained clinical response (analyzed as global response in the Clinical Study Report) was assessed at EOT + 16 days and EOT + 30 days. In the overall FAS, sustained clinical response was higher for fidaxomicin than for vancomycin and the 95% confidence interval about the difference between treatment groups excluded 0 (Table 8-9). The higher sustained clinical response rate for fidaxomicin than vancomycin was observed for each of the age groups except those < 2 years (Table 8-10). This is primarily due to the lower confirmed clinical response at EOT + 2 days that was observed for fidaxomicin compared to vancomycin.

**Table 8-9. Sustained Clinical Response (FAS)**

| | **Fidaxomicin (n=98)** | **Vancomycin (n=44)** | **Adjusted Difference (95% CI)** |
|---|---|---|---|
| **EOT + 16 days** | | | |
| Sustained Response | 70 (71.4%) * | 23 (52.3%) | 19.4% |
| 95% CI | (61.4%, 80.1%) | (36.7%, 67.5%) | (2.3%, 35.9%) |
| Failure | 28 (28.6%) | 21 (47.7%) | |
| Initial Failure | 19 (19.4%) | 12 (27.3%) | |
| Recurrence | 6 (6.1%) | 9 (20.5%) ** | |
| Missing | 3 (3.1%) | 0 | |
| **EOT + 30 days** | | | |
| Sustained Response | 67 (68.4%) * | 22 (50.0%) | 18.8% |
| 95% CI | (58.2%, 77.4%) | (34.6%, 65.4%) | (1.5%, 35.3%) |
| Failure | 31 (31.6%) | 22 (50.0%) | |
| Initial Failure | 19 (19.4%) | 12 (27.3%) | |
| Recurrence | 9 (9.2%) | 10 (22.7%) ** | |
| Missing | 3 (3.1%) | 0 | |

*Includes 2 patient with missing EOT+2 days assessment but had response at EOT and follow-up visits indicating no recurrence

**Includes 1 patient with missing EOT + 2 days assessment but had response at EOT and visit at EOT + 9 days indicating recurrence.

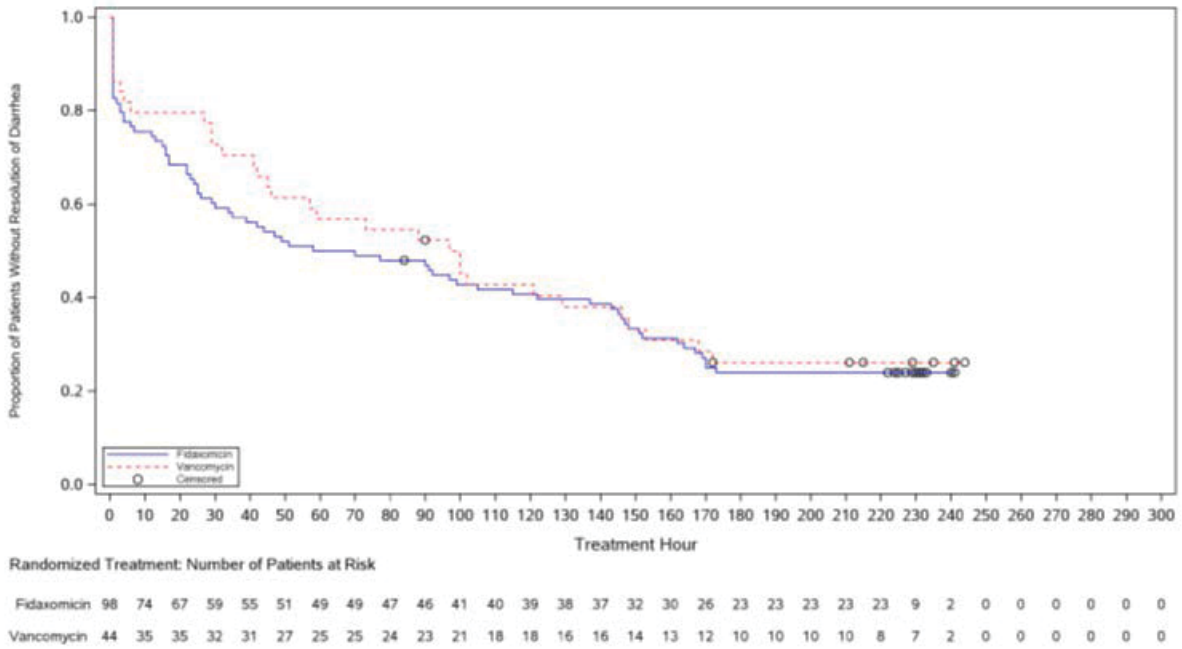
Source: Reviewer's Analysis using ADEFFD dataset

**Table 8-10. Sustained Clinical Response at EOT + 30 days by Age Group (FAS)**

| | Fidaxomicin | Vancomycin | Difference (95% CI) |
|---|---|---|---|
| **Age < 2 year** | n=20 | n=10 | |
| Sustained Response | 11 (55.0%) | 7 (70.0%) | -15.0% |
| 95% CI | (31.5%, 76.9%) | (34.8%, 93.3%) | (-50.8%, 20.8%) |
| Failure | 9 (45.0%) | 3 (30.0%) | |
| Initial Failure | 7 (35.0%) | 1 (10.0%) | |
| Recurrence | 2 (10.0%) | 2 (20.0%) | |
| Missing | 0 | 0 | |
| **Age ≥ 2 to < 6 years** | n=32 | n=16 | |
| Sustained Response | 21 (65.6%) | 8 (50.0%) | 15.6% |
| 95% CI | (46.8%, 81.4%) | (24.7%, 75.3%) | (-13.9%, 45.1%) |
| Failure | 11 (34.4%) | 8 (50.0%) | |
| Initial Failure | 7 (21.9%) | 3 (18.8%) | |
| Recurrence | 3 (9.4%) | 5 (31.3%) * | |
| Missing | 1 (3.1%) | 1 (6.3%) | |
| **Age ≥ 6 to < 12 years** | n=26 | n=10 | |
| Sustained Response | 22 (84.6%) ** | 4 (40.0%) | 44.6% |
| 95% CI | (65.1%, 95.6%) | (12.2%, 73.8%) | (11.2%, 78.0%) |
| Failure | 4 (15.4%) | 6 (60.0%) | |
| Initial Failure | 1 (3.8%) | 5 (50.0%) | |
| Recurrence | 2 (7.6%) | 1 (10.0%) | |
| Missing | 1 (3.8%) | 0 | |
| **Age ≥ 12 to < 18 years** | n=20 | n=8 | |
| Sustained Response | 13 (65.0%) ** | 3 (37.5%) | 27.5% |
| 95% CI | (40.8%, 84.6%) | (8.5%, 75.5%) | (-12.0%, 67.0%) |
| Failure | 7 (35.0%) | 5 (62.5%) | |
| Initial Failure | 4 (20.0%) | 3 (37.5%) | |
| Recurrence | 2 (10.0%) | 2 (25.0%) | |
| Missing | 1 (5.0%) | 0 | |

*Includes 1 patient with missing EOT + 2 days assessment but had response at EOT and visit at EOT + 9 days indicating recurrence.
*Includes 1 patient with missing EOT+2 days assessment but had response at EOT and follow-up visits indicating no recurrence
Source: Reviewer's Analysis using ADEFFD dataset

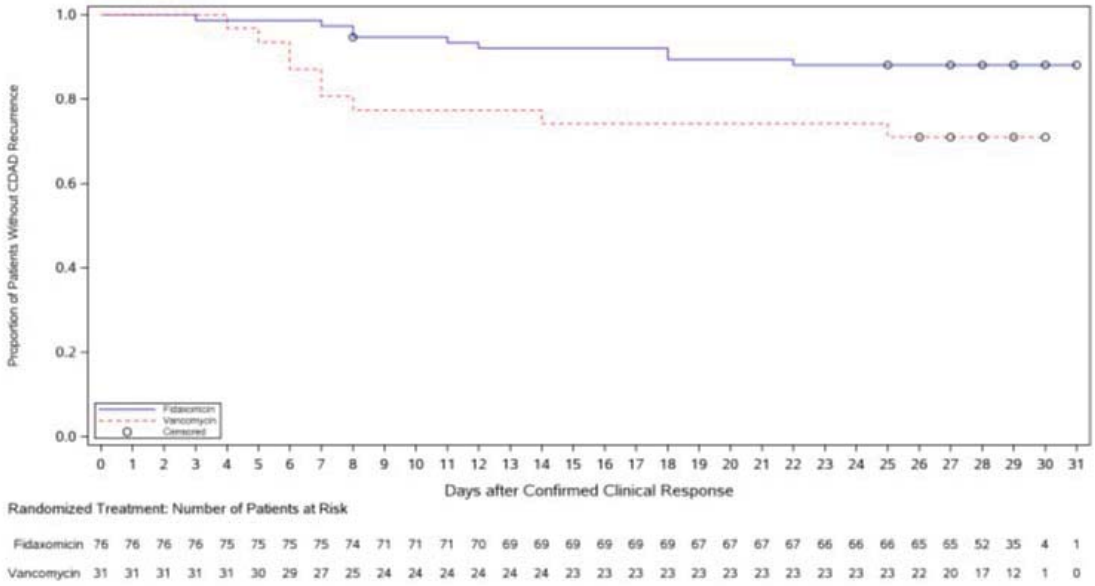
The median time to resolution of diarrhea was 58 hours (2.4 days) for fidaxomicin and 97 hours (4.0 days) for vancomycin. However, there was not a significant difference in the time to resolution of diarrhea curves between the treatment groups (log rank test, p=0.579).




Source: Figure 3 of clinical study report.

**Figure 1: Kaplan Meier Plot for Time to Resolution of Diarrhea (FAS)**

Recurrence through the end of the study was observed in 9 (9.2%) fidaxomicin-treated patients and 10 (22.7%) vancomycin-treated patients (Table 8-9.). The recurrences were spread across the age groups (Table 8-10). Most of the recurrences (8 of 10) in the vancomycin arm occurred by the EOT + 9 days visit, whereas the recurrences in the fidaxomicin arm were more spread out (4 by EOT + 9 days, 2 between EOT + 9 days and EOT + 16 days, and 3 between EOT + 16 days and EOT + 23 days). All recurrences occurred by EOT + 23 days. In patients with a confirmed clinical response at EOT + 2 days (i.e., those who could experience a recurrence), there was a significant difference in the time to recurrence curves between the two treatment groups (log-rank test, p=0.023).




Source: Figure 4 of Clinical Study Report

**Figure 2: Kaplan-Meier Plot for Time to Recurrence in Patients with Confirmed Clinical Response at EOT + 2 days (FAS)**

Palatability was assessed in patients who received the oral suspension or oral liquid formulation. For fidaxomicin oral suspension, the palatability was assessed as "good" or "excellent" in 47.8% of patients on Day 1 and by Day 7 this had increased to 55.2% of patients (Table 8-11.). For vancomycin oral liquid, the palatability was assessed as "good" or "excellent" in 36.7% of patients on Day 1 and 40.0% of patients on Day 7. While the acceptance rates (i.e., assessed as "good" or "excellent") increased with repeated use in both treatment groups, the palatability of fidaxomicin oral suspension was accepted by slightly more patients than those who accepted the vancomycin oral liquid.

Palatability assessments were missing for 18% of fidaxomicin-treated patients on Day 1, 22% of fidaxomicin-treated patients on Day 7, and 17% of vancomycin-treated patients on both Days 1 and 7. In response to an information request dated 12/11/19, the Applicant responded that reasons for these missing data were not specifically captured. However, the Applicant noted that the majority of the patients missing palatability assessments at both Days 1 and 7 (7 of 12 fidaxomicin patients and 4 of 5 vancomycin patients) were 3 years old or younger and may have been preverbal which would have limited the ability to make the assessment. The remaining 5 fidaxomicin patients and 1 vancomycin patient with missing assessments on both days were noted to be receiving concomitant medications through the nasogastric (NG) route. This suggests that the study drug may have also been delivered through the NG route which would have precluded the palatability assessment in these patients.

**Table 8-11. Palatability of Fidaxomicin Oral Suspension or Vancomycin Oral Liquid (FAS)**

| | Fidaxomicin (n=67) | | Vancomycin (n=30) | |
|---|---|---|---|---|
| **Assessment** | Day 1 | Day 7 | Day 1 | Day 7 |
| Awful | 4 (6.0%) | 2 (3.0%) | 5 (16.7%) | 3 (10.0%) |
| Poor | 6 (9.0%) | 5 (7.5%) | 3 (10.0%) | 5 (16.7%) |
| Fair | 13 (19.4%) | 8 (11.9%) | 6 (20.0%) | 5 (16.7%) |
| Good | 19 (28.4%) | 21 (31.3%) | 7 (23.3%) | 9 (30.0%) |
| Excellent | 13 (19.4%) | 16 (23.9%) | 4 (13.3%) | 3 (10.0%) |
| Missing | 12 (17.9%) | 15 (22.4%) | 5 (16.7%) | 5 (16.7%) |

Source: Reviewer's Analysis using ADEFF dataset

**Additional Analyses Conducted**

Although there was a protocol-specified definition for confirmed clinical response, the response was ultimately based on the assessment of the Investigator. Further review of the reported number of episodes of watery diarrhea/unformed bowel movements collected on Days 1 to 10, suggest that there were occurrences where the Investigator's assessment of response may not have exactly followed the definition. Specifically, there were cases where the Investigator assessed the patient as a success but one of the following was noted:

- The patient did not have at least 2 consecutive days while on treatment without unformed bowel movements (i.e., less than 3) (3 fidaxomicin/4 vancomycin)
- The patient had 2 consecutive days without unformed bowel movements but there was a return of unformed bowel movements (3 or more) while on treatment (4 fidaxomicin)
- The patient had at least 2 consecutive days without unformed bowel movements through EOT but there was a return of unformed bowel movements at EOT+ 2 days (4 fidaxomicin /1 vancomycin).

By the definition of confirmed clinical response these patients should have been considered a failure. Additionally, there were cases where the Investigator's assessment was a failure, but bowel movements were considered normal for at least 2 consecutive days while on treatment and remained so thorough the EOT, no return of unformed bowel movements at EOT + 2 days was noted, and no alternative CDAD therapy was received (2 vancomycin). By the definition of confirmed clinical response these patients should have been considered a success.

Therefore, additional sensitivity analyses were conducted to assess the impact of these discrepancies. Since at EOT + 2 days, the case report forms only asked if there was a return of unformed bowel movements but did not collect the number episodes of unformed bowel movements, it is possible that less than 3 unformed bowel movements could have been observed which would not meet the definition for diarrhea. Thus, Sensitivity Analysis A treats "did not have at least 2 consecutive days while on treatment without unformed bowel movements" and "had 2 consecutive days without unformed bowel movements but return of

unformed bowel movements while on treatment" as "failures". Sensitivity Analysis B also treats "had at least 2 consecutive days without unformed bowel movements through EOT but return of unformed bowel movements at EOT + 2 days" as "failures". Both sensitivity analyses include the cases that were called failure by the Investigator but met the definition of successful response as "successes".

The results of these sensitivity analyses are presented in the following table. Since most patients are changed to "failures" in these analyses, the response rates are lower than previously observed. For the population overall, while the observed difference between treatment groups goes down, fidaxomicin still trended to being numerically higher than vancomycin. The < 2 years age group is consistent with the previous results. The difference for the 2 to < 6 years age group is slightly better for fidaxomicin than before, whereas for the 6 to < 12 years age group, the difference isn't as large but is still numerically better for fidaxomicin. For the 12 to < 18 years age group, sensitivity analysis A is consistent with what was observed before with the difference being slightly smaller. However, in sensitivity analysis B fidaxomicin is lower than vancomycin. This difference is mainly because of 3 patients on fidaxomicin whose diarrhea was resolved through EOT, but unformed bowel movements were noted at EOT + 2 days. Since it is not known if the number of episodes of unformed bowl movements was 3 or more which is what defines diarrhea, this result should be interpreted with caution.

**Table 8-12. Additional Sensitivity Analyses on Confirmed Clinical Response at EOT + 2 days (FAS)**

| | Fidaxomicin | Vancomycin | Difference (95% CI) |
|---|---|---|---|
| **Sensitivity Analysis A** | | | |
| Overall | 69/98 (70.4%) | 29/44 (65.9%) | 4.5% (-12.2%, 21.2%) |
| From birth to <2 years | 11/20 (55.0%) | 8/10 (80.0%) | -25.0% (-58.0%, 8.0%) |
| ≥2 to < 6 years | 23/32 (71.9%) | 9/16 (56.3%) | 15.6% (-13.3%, 44.5%) |
| ≥6 to < 12 years | 21/26 (80.8%) | 7/10 (70.0%) | 10.8% (-21.4%, 43.0%) |
| ≥12 to < 18 years | 14/20 (70.0%) | 5/8 (62.5%) | 7.5% (-31.6%, 46.6%) |
| **Sensitivity Analysis B** | | | |
| Overall | 65/98 (66.3%) | 28/44 (63.6%) | 2.7% (-14.3%, 19.7%) |
| From birth to <2 years | 11/20 (55.0%) | 8/10 (80.0%) | -25.0% (-58.0%, 8.0%) |
| ≥2 to < 6 years | 23/32 (71.9%) | 8/16 (50.0%) | 21.9% (-7.1%, 50.9%) |
| ≥6 to < 12 years | 20/26 (76.9%) | 7/10 (70.0%) | 6.9% (-25.8%, 39.6%) |
| ≥12 to < 18 years | 11/20 (55.0%) | 5/8 (62.5%) | -7.5% (-47.5%, 32.5%) |

Source: Reviewer's analysis using ADEFF and ADEFFD datasets

### 8.1.3. Assessment of Efficacy Across Studies

In addition to the Phase 3 SUNSHINE study, a Phase 2 study, OPT-80-206, was conducted. OPT-80-206 was primarily designed to obtain PK and safety data of fidaxomicin in pediatric patients with CDAD. The formulation of the oral suspension used in OPT-80-206 was based on

a powder rather than granules, which was used in the SUNSHINE study and is the to-be-marketed product. Given the difference in the formulation of the oral suspension, small sample size, and lack of a comparator, OPT-80-206 provides limited additional information for assessing the efficacy of fidaxomicin.

However, for completeness, the results for clinical response in OPT-80-206 which was defined similarly to the SUNSHINE definition of confirmed clinical response are presented alongside the results for fidaxomicin from the SUNSHINE study.

**Table 8-13. Clinical Response for Fidaxomicin in OPT-80-206 and the SUNSHINE Study**

| Age Group | OPT-80-206 | SUNSHINE* |
|---|---|---|
| < 2 years | 8/9 (88.9%) | 13/20 (65.0%) |
| ≥ 2 to < 6 years | 6/8 (75.0%) | 25/32 (78.1%) |
| ≥ 6 to < 12 years | 9/9 (100.0%) | 23/26 (88.5%) |
| ≥ 12 to < 18 years | 12/12 (100.0%) | 15/20 (75.0%) |
| All patients | 35/38 (92.1%) | 76/98 (77.6%) |

*Confirmed Clinical Response
Source: Adapted from Table 5.7.3 of NDA Summary of Clinical Efficacy for OPT-80-206 and from Table 8-6. and Table 8-7. of this review for SUNSHINE study.

### 8.1.4. Statistical Issues

Only a single randomized comparative trial in the pediatric population with CDAD was conducted. As evidence of efficacy of fidaxomicin in pediatric patients is based on extrapolation of the efficacy seen in adults, the study was conducted to primarily provide descriptive results with a sample size for the study based on a minimum number of patients requested and not powered for inferential testing. Therefore, comparative conclusions should be made with caution especially when looking at the results by age group as the sample sizes in the individual age groups are small.

### 8.1.5. Integrated Assessment of Effectiveness

In the SUNSHINE study, fidaxomicin and vancomycin provided acceptable and comparable rates of confirmed clinical response at EOT + 2 days in the overall population studied. Additionally, sustained clinical response at the end of the study trended to be higher in the fidaxomicin group compared the vancomycin group.

Although, a lower confirmed clinical response was observed in patients < 2 years old, about 60% of these patients in both treatment arms were coinfected with one or more diarrheal pathogens, which makes the diagnosis of CDAD in this age group and, subsequently, efficacy assessments less certain. Additionally, interpretation of this finding is limited by a small sample size in this age group with even a smaller number of comparator patients due to 2:1

randomization.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

The evaluation of the safety of fidaxomicin in pediatric patients is primarily based on the results of the Phase 3 (the SUNSHINE) study. Results of the Phase 2 (OPT-80-206) single arm study is used as a supportive evidence. The studies used different fidaxomicin pediatric formulations. The granules for oral suspension tested in the SUNSHINE study is the final formulation proposed for marketing. The fidaxomicin powder for oral suspension developed for use in OPT-80-206 will not be marketed.

Both studies (SUNSHINE and OPT-80-206) enrolled children 6 months to less than 18 years of age, stratified into the following age groups:

- ≥ 6 months to < 2 Years
- ≥ 2 years to < 6 years
- ≥ 6 years to < 12 years
- ≥ 12 years to < 18 years

In both studies, patients < 2 years of age, or patients who were > 2 years or > 12.5 kg and were unable to swallow tablets were given weight-based dosing of fidaxomicin for oral suspension (powder formulation in study OPT-80-206 and granules for suspension in the SUNSHINE study).

Using the Applicant's STDM and ADAM datasets, the clinical reviewer conducted all safety analyses presented in this section using MAED, and JMP 14.0 software unless otherwise specified. Safety data for patients treated with fidaxomicin include 98 patients in the SUNSHINE study and 38 patients in the OPT-80-206 study; 44 patients were treated with vancomycin in the SUNSHINE study.

Safety assessments included analyses of the incidence of all adverse events (AEs), including treatment emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, adverse events leading to premature discontinuation of study treatment, changes in vital signs, body weight, hematology, and blood chemistry parameters. Descriptive statistics are used to describe the observed findings.

The safety analysis set (SAF) consists of all randomized patients who received at least 1 dose of study drug (fidaxomicin or vancomycin). The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability-related analyses.

*Clinical Reviewer's Comment: The SUNSHINE study eligibility criteria required enrollment of children 6 months or older, however, there was one patient enrolled in the fidaxomicin arm who was one month old. This patient is included in all analyses of this review.*

**Categorization of Adverse Events**

Investigator-reported verbatim terms were translated into preferred terms (PTs) using the MedDRA dictionary version 20.1 by the Applicant. Coding of adverse events appeared to be an accurate reflection of those noted in the case report forms. Adverse events in any age category in the SUNSHINE and OPT-80-206 studies are summarized in Table 8-14..

**Table 8-14. Overview of Treatment-Emergent Adverse Events in OPT-80-206 and SUNSHINE Studies**

| | OPT-80-206 | SUNSHINE | |
|---|---|---|---|
| | Fidaxomicin (n=38) | Fidaxomicin (n=98) | Vancomycin (n=44) |
| Any TEAE | 28 (73.7%) | 72 (73.5%) | 33 (75.0%) |
| Drug-related TEAEs | 6 (15.8%) | 7 (7.1%) | 5 (11.4%) |
| SAEs | 9 (23.7%) | 24 (24.5%) | 12 (27.3%) |
| Drug-related SAEs | 0 | 0 | 0 |
| TEAE leading to death | 1 (2.6%) | 3 (3.1%) | 0* |
| TEAE leading to withdrawal of treatment | 3 (7.9%) | 1 (1.0%) | 1 (2.3%) |

* Two patients in the vancomycin arm died after the end of the study follow-up period: a 7-year-old due to fungal sepsis and a *Scedosporium* infection on Day 43, and a 13-year-olddue to a desmoplastic tumor on Day 47.
Source: Reviewer's analysis using ADAE data set

*Clinical Reviewer's Comment: The primary focus of the safety analysis is characterization of adverse events in the SUNSHINE study. Also, the safety data from both pediatric trials (OPT-80-206 and SUNSHINE) were compared with the safety data for fidaxomicin in adults included in the Fidaxomicin USPI.*

*Pertinent findings noted in the review were 4 deaths in the fidaxomicin treatment arm (1 death in OPT-80-206, and 3 deaths in SUNSHINE). All deaths occurred during the study follow-up period after the completion of fidaxomicin treatment. Notably, all 4 deaths occurred in children < 2 years age group and all of them received fidaxomicin oral suspension formulation.*

*Although no deaths occurred in the vancomycin arm during the SUNSHINE study, 2 deaths were reported in vancomycin treated patients after the study follow-up period (Day 43 and Day 47). Both deaths occurred in children > 6 years old. Detailed analysis of the deaths in fidaxomicin treated patients is discussed in the section 8.2.4 of this review.*

### 8.2.2. Review of the Safety Database

**Overall Exposure**

In total, 136 pediatric patients aged 1 month to less than 18 years were treated with fidaxomicin including 38 patients in the OPT-80-206, and 98 patients in the SUNSHINE study. The mean duration of exposure to fidaxomicin was 9.6 days in OPT-80-206, and 10.6 days in the SUNSHINE study. The mean duration of exposure to vancomycin was 10.5 days.

In the SUNSHINE study approximately two thirds (68%) of patients received fidaxomicin oral suspension, and one third (32%) received fidaxomicin tablets. Similarly, in the OPT-80-206 study approximately two thirds (63%) of patients received the oral suspension, and one third (37%) received tablets. Exposure to fidaxomicin by age group is summarized in Table 8-15.

**Table 8-15. Exposure to Fidaxomicin by Age Group in Both Fidaxomicin Pediatric Studies**

| | OPT-80-206 (n=38) | SUNSHINE (n=98) | Total (n=136) * |
|---|---|---|---|
| < 2 years** | 9 | 20 | 29 |
| >= 2 years to < 6 years | 8 | 32 | 40 |
| >= 6 years to < 12 years | 9 | 26 | 35 |
| >= 12 years to < 18 years | 12 | 20 | 32 |

*Both tablets and suspension
**1 patient <6 months old was exposed to fidaxomicin in SUNSHINE trial
Source: Reviewer's analysis

Exposure to fidaxomicin by age and formulation is presented in Table 8-16..

**Table 8-16. Exposure to Study Drug by Age Group and Formulation in Both Fidaxomicin Pediatric Studies**

| | OPT-80-206 | | SUNSHINE | | | |
|---|---|---|---|---|---|---|
| | Fidaxomicin (n=38) | | Fidaxomicin (n=98) | | Vancomycin (n=44) | |
| | Oral Suspension (Powder) | Tablet | Oral Suspension (Granules) | Tablet | Oral Liquid | Capsule |
| <2 Years | 9 | 0 | 20 | 0 | 10 | 0 |
| ≥2 to <6 years | 6 | 2 | 32 | 0 | 16 | 0 |
| ≥6 to <12 years | 5 | 4 | 12 | 14 | 3 | 7 |
| ≥12 to <18 years | 4 | 8 | 3 | 17 | 1 | 7 |
| **Total** | 24 (63.2%) | 14 (36.8%) | 67 (68.4%) | 31 (31.6%) | 30 (68.2%) | 14 (31.8%) |

Source: Reviewer's analysis

**Relevant characteristics of the safety population**

**OPT-80-206 Study**

Patients were eligible for enrollment if they were ≥ 6 months to < 18 years old with confirmed CDAD. The diagnosis of CDAD required the detection, within 72 hours prior to randomization, of either toxin A and/or toxin B in stool or detection of toxigenic *C. difficile* in stool and:
a. Patients ≥ 6 months to < 2 years: watery diarrhea in the 24 hours prior to enrollment.
b. Patients ≥ 2 years to < 18 years: > 3 unformed bowel movements in the 24 hours prior to enrollment.

The majority of patients in this trial were male (57.9%) and white (86.8%). The youngest patient was 11 months old and the oldest was 17 years of age. Baseline disease severity was similar between the age categories and the majority of patients had mild CDAD (60.5%), defined as 4 to 5 unformed bowel movement (UBMs) per day or a white blood cell count ≤12000/$mm^3$. The mean number of UBMs at 24 hours before the first administration of study drug ranged from 4 to 20 and were similar between the age groups. All patients were required to have positive test result for *C. difficile* toxins A and/or B to be eligible for enrollment.

**SUNSHINE Study**

The design of the SUNSHINE study and its patients' demographics are described in Sections 8.1.1 and 8.1.2 of this review. History of diarrhea and characteristics of baseline diarrhea in the SUNSHINE study are presented in Table 8-17. Of note, for patients < 5 years rotavirus test was required at enrollment. None of the patients tested positive.

**Table 8-17. History of Diarrhea and Characteristics of Baseline Diarrhea in the SUNSHINE Study (SAF)**

| | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| History of Diarrhea in the 3 Months Prior to Screening | | |
| None | 56 (57.1%) | 29 (65.9%) |
| Yes | 42 (42.9%) | 15 (34.1%) |
| 1 episode | 29 (29.6%) | 12 (27.3%) |
| 2 episodes | 9 (9.2%) | 2 (4.5%) |
| ≥ 3 episodes | 4 (4.1%) | 1 (2.3%) |
| History of Diarrhea with positive CDAD testing | | |
| Treated with antibacterial drugs for CDAD | 4 (4.1%) | 3 (6.8%) |
| Not treated for CDAD | 24 (24.5%) | 7 (15.9%) |
| Number of UBMs 24 Hours Prior to Screening (patients ≥ 2years) | n=78 | n=33 |
| < 3 | 0 | 0 |
| 3 to 5 | 49 (50.0%) | 23 (52.3%) |
| 6 to 10 | 22 (22.4%) | 6 (13.6%) |
| ≥ 11 | 7 (7.1) | 4 (9.1) |
| Unknown | 0 | 1 (2.3%) |

UBM = unformed bowel movement
All patients < 2 years had watery diarrhea within 24 hours prior to screening
Source: Sunshine Study Clinical Study Report, Table-8

Diagnosis of CDAD and CDAD risk factors in the SUNSHINE study are summarized in Table 8-18. and Table 8-19. Risk Factors for , respectively.

**Table 8-18. Diagnosis of CDAD in the SUNSHINE Study (SAF)**

| | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| **Test for Toxigenic *Clostridium Difficile*** | | |
| Positive | 98 (100%) | 43 (97.7%) |
| Not done | 0 | 1 (2.3%) |
| **Method of Test** | | |
| PCR | 44 (44.9%) | 15 (34.1%) |
| *C. difficile* toxin A/B ELISA | 44 (44.9%) | 22 (50.0%) |
| Culture | 9 (9.2%) | 4 (9.1%) |
| Other | 1 (1.0%) | 2 (4.5%) |

Source: Reviewer's analysis

**Table 8-19. Risk Factors for the Development of CDAD in the SUNSHINE Study (SAF)**

| | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| **Patients with known risk factors for CDAD**** | | |
| Yes | 76 (77.6%) | 37 (84.1%) |
| No | 22 (22.4%) | 7 (15.9%) |
| **Specific risk factors associated with the development of CDAD*** | | |
| Exposure to antibacterial drugs | 50 (51.0%) | 29 (65.9%) |
| Malignancies | 42 (42.9%) | 18 (40.9%) |
| Other** | 17 (17.3%) | 7 (15.9%) |
| **Receipt of concomitant antibacterial drugs for infections other than CDAD during study treatment***** | | |
| Yes | 32 (32.7%) | 17 (38.6%) |
| No | 66 (67.3%) | 27 (61.4%) |

PCR: polymerase chain reaction
* A patient may have more than one risk factor
** Including (but not limited to) hospitalization, immunosuppression, surgery (e.g., liver transplant, intestinal resection) and contact with a CDAD-infected relative.
*** Systemic antibacterial drugs could be administered at the investigator's discretion for other suspected or confirmed bacterial infections during the trial.
Source: SUNSHINE Clinical Study Report, Table 9, and Reviewer's analysis using ADMB data set

Baseline signs and symptoms of CDAD are provided in **Error! Reference source not found.**.

**Table 8-20. CDAD Signs and Symptoms at Screening in the SUNSHINE Study (SAF)**

| Characteristic | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| **Body Temperature (°C)** | | |
| mean (SD) | 37.6 (1.1) | 38.0 (1.2) |
| Min - Max | 35.9 – 40.7 | 36.0-40.6 |
| **WBC Count ($10^9$/L)** | | |
| mean (SD) | 7.3 (5.1) | 8.8 (7.7) |
| Min - Max | 0- 26.2 | 0.1 – 31.7 |
| **Abdominal Tenderness** | | |
| Absent | 50 (51.0%) | 26 (59.1%) |
| Mild | 24 (24.5%) | 8 (18.2%) |
| Moderate | 20 (20.4%) | 8 (18.2%) |
| Severe | 4 (4.1%) | 2 (4.5%) |

Source: SUNSHINE Clinical Study Report, Table 10, and Reviewer's analysis of ADSL data set

Table 8-21. describes underlying comorbidities in the SUNSHINE study patients.

**Table 8-21. Baseline Comorbidities in Patients in the SUNSHINE Study (SAF)**

| System Organ Class | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| Infections and Infestations (other than CDAD) | 51 (52.0%) | 30 (68.2%) |
| Gastrointestinal Disorders (other than CDAD) | 53 (54.1%) | 25 (56.8%) |
| Neoplasms Benign, Malignant and Unspecified * | 44 (44.9%) | 19 (43.2%) |
| Metabolism and Nutrition Disorders* | 43 (43.9%) | 11 (25.0%) |
| Blood and Lymphatic System Disorders* | 40 (40.8%) | 13 (29.5%) |
| Nervous System Disorders* | 24 (24.5%) | 10 (22.75) |
| Congenital, Familial and Genetic Disorders | 24 (24.5%) | 8 (18.2%) |
| Immune System Disorders* | 24 (24.5%) | 2 (4.5%) |
| Musculoskeletal and Connective Tissue Disorders | 18 (18.4%) | 5 (11.4%) |
| Respiratory, Thoracic and Mediastinal Disorders | 19 (19.4%) | 2 (4.5%) |
| Psychiatric Disorders | 13 (13.3%) | 3 (6.8%) |
| Cardiac Disorders | 11 (11.2%) | 4 (9.15) |
| Vascular Disorders | 12 (12.2%) | 3 (6.8%) |

| System Organ Class | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|

* Neoplasms Benign, Malignant and Unspecified mainly included hematological malignancies, with few cases of other childhood neoplasms e.g. Ewing's sarcoma (4 in the fidaxomicin, 1 in the vancomycin arm), embryonic rhabdomyosarcoma, testicular germ cell tumor, and malignant glioma (1 patient with each diagnosis in the fidaxomicin arm), neuroblastoma (1 patient in the fidaxomicin and 1 in the vancomycin arm)
*Blood and lymphatic disorders included neutropenia, anemia, thrombocytopenia, and pancytopenia.
*Immune system disorders mainly included seasonal and drug related allergies at baseline except 1 case each of graft versus host disease, and hypogammaglobulinemia in the fidaxomicin treatment arm
*Metabolism and Nutrition disorders included decreased appetite, malnutrition, and dehydration.
*Nervous system disorders included simple and complex seizure disorders, metabolic encephalopathy, brain injury, neuropathy, dystonia and headache
Source: Reviewer's analysis

*Clinical Reviewer's Comment: Overall, the two treatment arms were balanced in terms of patients' demographics and CDAD severity. However, there were numerical disparities in underlying comorbidities with higher proportions of patients in the fidaxomicin arm as compared to vancomycin arm having blood and lymphatic system disorders (40.8% vs 29.5%) which mainly included neutropenia, anemia, thrombocytopenia, or pancytopenia secondary to chemotherapy given for hematological and other malignancies; immune system disorders (24.5% vs 4.5%) which mainly included seasonal and drug allergies; respiratory, thoracic and mediastinal disorders (19.4% vs 4.5%), which mainly included, asthma, pleural effusions, allergic rhinitis, sleep apnea syndrome, pulmonary hypertension, epistaxis, laryngeal stenosis, bronchopulmonary dysplasia, bronchospasm, and pulmonary edema; and metabolism and nutrition disorders (43.9% vs 25.0%), respectively. Conversely, other than CDAD infections and infestations were observed in a higher of vancomycin as compared to fidaxomicin patients, 68.2% vs. 52.0%, respectively, which mainly included infections, e.g., appendicitis, anal abscess, adenovirus infection, enterovirus infection, BK virus infection, device related infections, cellulitis, fungal infections, herpes virus infections, meningitis, urinary tract infections, other viral infections.*

**Patient disposition**

**OPT-80-206 Study**

In study OPT-80-206, of the 38 patients enrolled and received fidaxomicin, 35 patients completed the EOT visit and 24 patients completed the EOS visit. During the treatment period, 2 patients withdrew due to adverse events and 1 patient withdrew consent. One patient in the < 2 years age group was withdrawn at EOT due to treatment failure. The most frequently reported reason for withdrawal during the follow-up period was a recurrence of CDAD (9/38 [23.7%] patients). Disposition of patients in OPT-80-206 study is summarized in Table 8-22.

**Table 8-22. Disposition of Patients in OPT-80-206 Study**

| | 6 months to <2 years (n=9) | 2 to <6 years (n=8) | 6 to <12 years (n=9) | 12 to <18 years (n=12) | All Patients (N=38) |
|---|---|---|---|---|---|
| **Completed the EOT visit** | 9 (100%) | 5 (62.5%) | 9 (100%) | 12 (100%) | 35 (92%) |
| **Withdrawn during treatment period** | | 3 (37.5%) | | | 3 (8%) |
| ***Reason for withdrawal*** | | | | | |
| Adverse event | | 2 (25.0%) | | | 2 (5.3%) |
| Withdrawal by patient | | 1 (12.5%) | | | 1 (2.6%) |
| **Withdrawn during follow-up period** | 4 (44%) | 2 (25%) | 2 (22%) | 3 (25%) | 11 (29%) |
| **Reason for withdrawal** | | | | | |
| Adverse event | 1 (11.1%) | | | | 1 (2.65) |
| Recurrence | 2 (22.2%) | 2 (25.0%) | 2 (22.2%) | 3 (25.0%) | 9 (23.7%) |
| Treatment failure | 1 (11.1%) | 0 | 0 | 0 | 1 (2.6%) |
| Lost to follow-up | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 0 |
| **Completed the EOS visit** | 5 (55.6%) | 3 (37.5%) | 7 (77.8%) | 9 (75.0%) | 24 (63.2%) |

Source: SUNSHINE Clinical Study Report, Table 5

**SUNSHINE Study**

In the SUNSHINE study, a total of 148 patients were randomized (100 patients to fidaxomicin and 48 patients to vancomycin), and 142 received study drug treatment (98 patients received fidaxomicin, and 46 patients received vancomycin). Study drug was discontinued by 3 patients in the fidaxomicin arm (1 patient due to AE and 2 patients as a result of other events), and 2 patients in the vancomycin arm (1 patient due to AE and 1 patient for other reason). Disposition of patients in the SUNSHINE study is summarized in Table 8-23.

**Table 8-23. Disposition of Patients in the SUNSHINE Study**

| | Fidaxomicin n (%) | Vancomycin n (%) |
|---|---|---|
| Patients randomized | 100 | 48 |
| Patients who received study drug | 98 (98%) | 44 (91.7) ** |
| Completed EOT | 95 (95%) | 44 (91.7) |
| Patients who completed study | 95 (95%) | 43 (89.5) |
| Treatment Discontinuation | 3 (3%) | 2 (4.2) |
| Primary Reason for Treatment Discontinuation | | |
| *AdverseEvent* | *1* | *1* |
| *Death* | *0* | *0* |
| *Other* | *2* | *1* |
| Study Discontinuation | 5 (5%) | 1 (2%) |
| Primary Reason for Study Discontinuation | | |
| *Adverse Event* | *0* | *0* |

| | Fidaxomicin n (%) | Vancomycin n (%) |
|---|---|---|
| *Death* | *3* | *0* |
| *Other* | *2* | *1* |
| * Among the 48 patients randomized to vancomycin 4 patients did not receive treatment - 2 patients did not satisfy entry criteria as they had a history of inflammatory bowel disease, 1 patient's parent withdraw consent and 1 patient never received study drug. | | |

Source: Reviewer's analysis using ADSL dataset

**Adequacy of the Safety Database**

The safety database was adequate in terms of its size and population characteristics. Most of the baseline demographics, clinical characteristics, underlying comorbidities, and baseline CDAD status appeared comparable among the two treatment arms. The Applicant's safety analysis plan was acceptable with an appropriate focus on the anticipated safety issues. The definitions of AEs and the use of descriptive statistics were acceptable.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

**Issues Regarding Data Integrity and Submission Quality**

The data were submitted in standardized formats. The submission was adequately organized and based on the electronic common technical document (eCTD) format described in the ICH M2 EWG Electronic Common Technical Document Specification of 2008.

Minor issues with regards to data quality were encountered during the review. While the key data transcriptions and outcome assessments were accurate for most patients, a number of discrepancies between the clinical reviewer's assessment and the Applicant's assessments of clinical outcomes were identified. Case Report Forms were requested for further review. One of the notable findings in SUNSHINE study was observed in the comparator arm for age group 6 to < 12 years. Five of 10 patients were recorded as CCR failure with unusually low success rate in this age group for comparator (success rate of 88.5% in the fidaxomicin arm, as compared to 50% in the comparator arm). Detailed review of clinical signs and symptoms and case definitions suggested that 3 of 5 patients were incorrectly recorded as CCR failure. These patients had resolution of diarrhea or achieved < 3 UBM by EOT and had resolution of abdominal discomfort and pain and other clinical signs with no recurrence at EOT + 2 days based on parent/legal guardian interview. Re-adjudication for CCR outcomes would have increased the success rate in comparator arm from 50% to 80% for the age group 6 to < 12 years. However, efficacy assessment for fidaxomicin for overall pediatric population in the study would have remained comparable. Similarly, there were some other discrepancies which were analyzed, and the reviewer concluded that those discrepancies would not alter the overall efficacy and safety assessments of fidaxomicin.

**Routine Clinical Tests**

The schedule of routine clinical testing was acceptable. The Applicant's safety assessment included monitoring of TEAEs and SAEs, vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature), physical examination findings, 12-lead ECG parameters, and changes in clinical chemistry, hematology, coagulation, and urinalysis laboratory values. Additional testing occurred as indicated or deemed clinically necessary by the Investigator during the trials.

### 8.2.4. Safety Results

## Deaths

There were 4 deaths that occurred in fidaxomicin-treated patients during the study period in the two pediatric trials. One patient died in the OPT-80-206 study and 3 patients died in the SUNSHINE study. Notably, all deaths in the fidaxomicin arm occurred in patients < 2 years of age. No deaths were observed in vancomycin-treated patients in the SUNSHINE study during the study period; however, information on two patient deaths was reported following the end of the study. None of the TEAEs leading to death were considered drug-related by the Investigator.

Due to the observed mortality imbalance in the trials, data were examined to assess the contribution of fidaxomicin to the fatal outcomes. Study reports, case report forms, and applicant's narratives describing patients' deaths were reviewed. Independent data review committee meeting minutes were also reviewed. The assessment of the deaths, reflecting both the Applicant's and the reviewer's analyses are presented in Table 8-24.

**Table 8-24. Deaths in Both Fidaxomicin Pediatric Studies (SAF)**

| Patient ID/Country | Age/Sex/Race | Day of Death /Days from last dose of study drug | *Adverse Events leading to death* (Underlying ongoing medical conditions) |
|---|---|---|---|
| **OPT-80-206: *Fidaxomicin Arm (N=38)*** | | | |
| (b) (6) | 17 months/M/W | 13/3 | ***Septic Shock; Bacteremia with E. cloacae; Respiratory failure*** (ALL with CNS relapse, seizures, hemophagocytic lymphohistiocytosis, mucositis, QT prolongation, *C. glabrata* candidiasis, hepatosplenomegaly) |
| **SUNSHINE: *Fidaxomicin Arm (N=98)*** | | | |
| (b) (6) | 14 months/F/W | 17/7 | ***Refractory leukemia*** (AML, anemia, bone pain, device related infection, thrombocytopenia, tachycardia) |

| Patient ID/Country | Age/Sex/Race | Day of Death /Days from last dose of study drug | *Adverse Events leading to death* (Underlying ongoing medical conditions) |
|---|---|---|---|
| (b) (6) | 7 months/M/A | 31/21 | ***Leigh's syndrome- Sepsis and multiorgan failure*** (Mitochondrial encephalomyopathy) |
| (b) (6) | 16 months/F/W | 40/30 | ***Sepsis; Bacteremia due to Klebsiella Species, refractory leukemia.*** (AML, neutropenia, hepatosplenic candidiasis, fungal esophagitis, cardiomyopathy, anal abscess, gastritis, HHV-6 reactivation, hypokalemia, nausea, vomiting) |
| **SUNSHINE:** ***Vancomycin Arm (N=44)*** | | | |
| (b) (6) | 7 years/M/NA | 43*/33 | *Scedosporium infection* (Acute leukemia, febrile bone marrow aplasia) |
| (b) (6) | 13 years/F/W | 47*/37 | ***Abdominal desmoplastic tumor with malignant ascites*** (Anorexia, neutropenia, vomiting) |

Note: All patients received 10 days of study treatment.
* After study follow-up period
F=female, M=male, W= white, A= Asian, NA=not available, GVHD= graft-versus-host disease, BMT= bone marrow transplant, ALL= acute lymphocytic leukemia, AML= acute myelocytic, leukemia
Source: Reviewer's Analysis using ADSL and ADEFF datasets

**Deaths' Narratives**

**Fidaxomicin Patients:**

OPT-80-206 Study

**Patient #** (b) (6)
**Day of Death: 13**
The patient was a 17-month-old male with following medical issues:

- Acute lymphoblastic leukemia and hemophagocytic lymphohistiocytosis (HLH)
- Seizures due ALL with central nervous system relapse
- Concomitant chemotherapy including cytarabine, mercaptopurine, vincristine, and etoposide
- Neutropenia, anemia, thrombocytopenia
- Receipt of gentamicin, vancomycin, piperacillin/tazobactam and amphotericin B for empiric antimicrobial coverage
- Hypogammaglobulinemia
- Rectal hemorrhage
- Malnutrition

- Severe electrolyte abnormalities

The patient had a history of a prior episode of CDAD treated with metronidazole 11 days prior to study entry. On screening no other coinfections with diarrheagenic pathogens were identified. The patient was started on fidaxomicin suspension 160 mg every 12 hours via nasogastric tube. On Day 6, patient experienced septic shock due to bacteremia with gram negative rods, which were later identified as *Enterobacter cloacae;* the source was not specified. On Day 7, the patient further decompensated with respiratory distress requiring mechanical ventilation. Fidaxomicin was completed as planned on Day 11 although the patient continued to have watery diarrhea at the EOT. No further treatment for CDAD was administered.

On Day 13 the patient died from respiratory failure secondary to septic shock.
According to the Investigator, none of the TEAEs leading to death were attributable to the study drug. Death was attributed to progression of underlying lymphoblastic leukemia and lymphohistiocytosis.

*Clinical Reviewer's Comment: This patient with a serious underlying illness resulting in sepsis leading to death 3 days after EOT. However, lack of effectiveness of CDAD treatment as a contributory factor cannot be completely ruled out, assuming the patient's diarrheal illness was due to CDAD, although no additional treatment for CDAD after completion of study treatment was deemed needed by the Investigator. Yet, there is no documentation of other diarrheal pathogens.*

*It should be noted that prior history of CDAD, ongoing malignancy, prolonged neutropenia, continued immunosuppression, hypogammaglobulinemia and concomitant administration of antibacterial drugs may have predisposed this patient to CDAD. At the same time the seriousness of underlying condition, immunosuppression, malnutrition and gram-negative bacteremia may have contributed to the poor response to CDAD treatment.*

<u>SUNSHINE Study</u>

**Patient #** (b) (6)
**Day of death: 17**
The patient was a 4-month-old female with following medical issues:

- Acute myelocytic leukemia
- Secondary diffuse large B cell lymphoma
- Neutropenia, anemia, and thrombocytopenia requiring multiple platelet and RBC transfusions
- Chemotherapy 14 days prior to study entry (idarubicin/cytarabine/ etoposide)
- Concomitant antibacterial treatments including, sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis, daptomycin, followed by linezolid and ciprofloxacin for S. epidermidis infection, and itraconazole for empiric anti-fungal therapy

The patient had no prior history of CDAD and no coinfections with other diarrheal pathogens were identified on enrollment. The patient was started on fidaxomicin suspension 240 mg per day (33.8 mg/kg/day) and completed the treatment on Day 11. The following table displays the course of diarrhea during the treatment period.

The patient continued to have watery diarrhea at the EOT. No additional CDAD therapy after completion of study treatment was administered. Post-treatment stool test for *C. difficile* was negative. On Day 17, the patient experienced an SAE of 'worsening of leukemia' and died later the same day. No further information was provided by the sponsor. Autopsy was not performed. The Investigator assessed the SAE of worsening of leukemia as the cause of death.

*Clinical Reviewer's Comment: This patient's death could be the result of progression of underlying malignancy, however, worsening of underlying conditions due lack of CDAD treatment efficacy cannot be completely ruled out given that patient continued to have watery diarrhea at the EOT. Considering no further information provided for this patient, the causality of death cannot be determined.*

**Patient #** (b) (6)
**Day of Death: 31**
The patient was a 7-month-old male with following ongoing major medical issues:

- Congenital metabolic mitochondrial encephalopathy
- Metabolic acidosis associated with mitochondrial encephalopathy
- Severe sepsis 35 days prior to study entry treated with amikacin, imipenem, piperacillin/tazobactam, and intravenous vancomycin.

The patient had no prior history of CDAD. He also had positive stool PCR for astrovirus and rotavirus A at screening and at the EOT. The patient was started on fidaxomicin suspension 180 mg per day (32.1 mg/kg/day) for CDAD. On Day 5, he experienced an SAE of 'worsening acidosis' which was life threatening and considered not to be related to study drug by the Investigator. Fidaxomicin was completed on Day 11. The patient continued to have watery diarrhea at the EOT.

No further CDAD treatment was administered. Post-treatment stool test for *C. difficile* was negative. From day 8 to day 30, the patient remained hospitalized and received treatment for unspecified infections (piperacillin/tazobactam, imipenem, and vancomycin) and cardiac failure (furosemide, captopril, and sildenafil). On study day 30, worsening SAE of 'Leigh syndrome' was reported which was characterized by severe sepsis, and multi organ failure. Patient died on day 31. An autopsy was not performed. According to Investigator the SAE leading to death was not related to study drug.

*Clinical Reviewer's Comment: The cause of diarrhea is uncertain in this 7-month-old infant. The detection of C. difficile may be explained by colonization with C. difficile, which is common in this*

*age group, whereas the presence of rotavirus and astrovirus in stool suggests that diarrhea may not be related to C. difficile. Also, this patient's clinical course leading to death is characteristic of the consequence of 'Leigh syndrome' (infantile necrotizing encephalopathy), which is a rapidly progressive neurological disorder, marked by a variety of symptoms, usually begin between the ages of 3 months and 2 years. It leads to episodes of severe lactic acidosis and multiorgan failure resembling sepsis.*

*Thus, given the uncertainty of CDAD diagnosis in this patient, and based on the clinical course, it can be assumed that the patient's death was unlikely related to study treatment or worsening of C. difficile disease.*

**Patient #** (b) (6)
**Day of Death: 40**

The patient was a 16-month-old female with following medical issues:

- Acute myelocytic leukemia, status post hematopoietic stem cell transplantation (HSCT)
- Ongoing neutropenia
- Cardiomyopathy
- Presumed hepatosplenic candidiasis
- Receipt of multiple antibacterial medications (amikacin, cefepime, ceftriaxone, ciprofloxacin, clindamycin, levofloxacin, meropenem, vancomycin and metronidazole) and chemotherapeutic agents prior to study enrollment, and during the study
- Perianal abscess.

The patient had no history of prior episodes of CDAD. No other diarrheal pathogens were identified in stool on screening. Patient was started on fidaxomicin suspension 320 mg per day (35.6 mg/kg/day). From Day 4 to Day 7 the patient received IV cyclophosphamide for unspecified reason. On Day 7 the patient was diagnosed with graft versus host disease (GVHD) and was treated with IV cyclosporine, which was continued through Day 28. Fidaxomicin treatment was completed treatment on Day 10.

The patient continued to have watery diarrhea at the EOT. On Day 15, the patient was diagnosed with *Klebsiella pneumoniae* bacteremia (the source was not specified) and started meropenem. On Day 17 and 18, hepatomegaly with moderate ascites and hyperbilirubinemia attributed to hepatic veno-occlusive disease were reported and the patient was treated with IV defibrotide, ursodiol, and hydrochlorothiazide for presumed hepatic veno-occlusive disease.

On Day 22 the patient developed sepsis and was transferred to intensive care unit. On Day 24 the patient was diagnosed with recurrence of *C. difficile* infection. CDAD treatment, however, was not started. Patient's condition remained critical and on Day 28, the patient experienced an SAE of "progressive refractory leukemia" and was started on mycophenolate mofetil for transplant rejection. She was also started on oral vancomycin for recurrent CDAD on that day. On the same day, the patient's family decided to place the patient on palliative care with

'comfort measures only'. On study day 29, all antibacterial drugs and other drugs were discontinued except the drugs for supportive measures.

On day 40, patient experienced an SAE of recurrent *Klebsiella pneumoniae* bacteremia while on palliative care, and subsequently died of cardiopulmonary arrest later that day.

An autopsy was performed, and death was attributed to progressive refractory primary cancer complicated by *K. pneumoniae* bacteremia. All events were considered not related to study drug.

*Clinical Reviewer's Comment: This reviewer agrees with the Investigator's assessment that the patient's demise was unlikely related to study drug but was caused by the progression of the underlying comorbidities. Major contributors to this patient's death included refractory leukemia, transplant rejection, GVHD, bacteremia and sepsis. It does not seem that recurrence of CDAD diagnosed shortly before the patient was switched to comfort care could have significantly contributed to the fatal outcome. Abnormalities in liver tests observed in this patient were likely related to hepatic veno-occlusive disease and sepsis.*

**Clinical Reviewer's Overall Assessment of Deaths**

As all deaths occurred in patients less than 2 years of age, the overall assessment of mortality will focus on this age group (20 patients in the fidaxomicin and 10 patients in vancomycin arm in the SUNSHINE study).

1. **Was imbalance in mortality related to an imbalance in patients' baseline characteristics between study arms?**

*The two treatment arms were well balanced with regard to baseline demographic and disease characteristics. Underlying conditions with high association with mortality such as malignancy treated with chemotherapy, or progressive difficult to control diseases were also balanced between treatment arms. In the fidaxomicin arm 6/20 (30%) patients had such conditions, 5 patients had malignancies, and one patient had progressive metabolic mitochondrial encephalopathy. In the vancomycin arm 2/10 (20%) had malignancies associated with receipt of chemotherapy and neutropenia. It is difficult to conclude whether this slight imbalance could be a factor.*

2. **Was the imbalance in mortality related to fidaxomicin toxicity and/or the use of the suspension formulation?**

*Conducted safety analyses have nor revealed fidaxomicin related toxicities that could have contributed to the deaths. The suspension was used in approximately two thirds of the patients, was well tolerated and was found to have palatability similar to the vancomycin liquid. Also, pharmacokinetic assessments have not demonstrated substantial differences in plasma and stool concentrations between tablets and suspension and between the age groups, which could*

*raise concerns for the association with mortality. Plasma concentrations of fidaxomicin and its metabolite were minimal after the use of both formulations, i.e., in nanogram/mL ranges, and overall similar to those in adults. No decreases in stool concentrations concerning for potential decrease in efficacy were found.*

*There was no reason to suspect toxicities related to suspension excipients. The fidaxomicin suspension contains microcrystalline cellulose, sodium starch glycolate, xanthan gum,* (b) (4) *citric acid, sodium citrate, sodium benzoate, sucralose, and mixed berry flavor. All excipients were evaluated as safe by the review team.*

3. **Could the imbalance in mortality be related to lower efficacy of fidaxomicin in patients less than 2 years?**

*As discussed in other sections of this review, overall uncertain diagnosis of CDAD related to high rates of colonization with C. difficile and coinfection with other diarrheal pathogens makes efficacy assessments in this age group less certain. Interpretation of the efficacy results in the SUNSHINE study is also limited by a small number of patients less than 2 years of age and uneven to 2:1 randomization. It should also be noted that in study OPT-80-206 where clinical response was defined similarly to the SUNSHINE study, the response rate in the < 2 age group was 8/9 (88.9%) which was comparable to the other age groups in the study.*

*In conclusion, the deaths occurred in fidaxomicin-treated patients appear to be related to underlying comorbidities. No toxicities or clear indications for a decrease in efficacy in the age group < 2 years have been identified. It should also be noted that considering the severity of underlying comorbidities in patients treated with fidaxomicin in this clinical trial, the observed mortality rate may, unfortunately, be anticipated.*

## Serious Adverse Events

OPT-80-206 Study

In this study 9 (23.7%) patients had at least 1 SAE. Four of 9 patients had SAEs that were related to *C. difficile* and represented recurrence of disease. All events were mild to moderate in severity except for 2 severe SAEs: septic shock in 1 patient who died (< 2 years age group), and adenovirus infection in 1 patient (2 to < 6 years age group). None of the SAEs were considered related to study medication (Table 8-25.).

**Table 8-25. Serious Adverse Events by Age Group in OPT-80-206 Study (SAF)**

| | < 2 years | 2 to < 6 years | 6 to < 12 years | 12 to < 18 years | All Patients |
|---|---|---|---|---|---|
| **Preferred Term** | **(n=9)** | **(n=8)** | **(n=9)** | **(n=12)** | **(N=38)** |
| **Any SAE** | **4 (44.4%)** | **3 (37.5)** | **1 (11.1%)** | **1 (8.3%)** | **9 (23.7%)** |
| *Clostridium difficile* | 2 (22.2%) | | 1 (11.1%) | | 3 (7.9%) |
| Vomiting | | 1 (12.5%) | | 1 (8.3%) | 2 (5.3%) |
| Adenovirus infection | | 1 (12.5%) | | | 1 (2.6%) |
| Clostridial infection | | 1 (12.5%) | | | 1 (2.6%) |

| | | | | | |
|---|---|---|---|---|---|
| Febrile neutropenia | | 1 (12.5%) | | | 1 (2.6%) |
| Gastrostomy failure | 1 (11.1%) | | | | 1 (2.6%) |
| Hematemesis | | 1 (12.5%) | | | 1 (2.6%) |
| Respiratory failure | 1 (11.1%) | | | | 1 (2.6%) |
| Septic shock | 1 (11.1%) | | | | 1 (2.6%) |

Source: Reviewer's Analysis

**SUNSHINE Study**

In this study, 24.5% (24/98) patients in the fidaxomicin and 27.3% (12/44) patients in the vancomycin arm had at least one SAEs. Most commonly reported SAEs in the SUNSHINE study were from the SOCs of infections and infestations (9.2% patients), gastrointestinal disorders (5.6% patients), and blood and lymphatic system disorders (4.2% patients). Infections and infestations and blood and lymphatic system disorders were slightly more frequently reported in the fidaxomicin as compared to vancomycin arm, (10/98 (10.2%) vs 3/44 (6.8%), and (5/98 (5.1%) vs 1/44 (2.3%), respectively.

The most frequently reported SAEs by preferred term were febrile neutropenia, 3/98 (3.1%) in the fidaxomicin and 1/44 (2.3%) in the vancomycin arm, and pyrexia, 2/98 (2%) in the fidaxomicin and 2/44 (4.5%) in the vancomycin arm. None of the SAEs were considered related to study drug. Table 8-26. provides a summary of SAEs in OPT-80-206 and the SUNSHINE study.

**Table 8-26. Serious Adverse Events by System Organ Class and Preferred Term in OPT-80-206 and SUNSHINE Study (SAF)**

| | OPT-80-206 | SUNSHINE | |
|---|---|---|---|
| | Fidaxomicin (n=38) | Fidaxomicin (n=98) | Vancomycin (n=44) |
| **Any serious adverse event** | **9 (23.7%)** | **24 (24.5%)** | **12 (27.3%)** |
| **Infections and Infestations** | **6 (15.8%)** | **10 (10.2%)** | **3 (6.8%)** |
| Sepsis/Septic shock | 1 (2.6%) | 2 (2.0%) | 0 |
| Bacterial sepsis | 0 | 1 (1.0%) | 0 |
| Staphylococcal sepsis | 0 | 1 (1.0%) | 0 |
| Fungal sepsis | 0 | 0 | 1 (2.3%) |
| Bacterial diarrhea | 0 | 1 (1.0%) | 0 |
| *Clostridium difficile* infection | 1 (2.6%) | 1 (1.0%) | 0 |
| *Clostridium difficile* colitis | 3 (7.9%) | 0 | 1 (2.3%) |
| Herpes simplex meningoencephalitis | 0 | 1 (1.0%) | 0 |
| Klebsiella bacteremia | 0 | 1 (1.0%) | 0 |
| Pneumonia | 0 | 1 (1.0%) | 0 |
| Respiratory syncytial virus infection | 0 | 1 (1.0%) | 0 |
| Respiratory tract infection | 0 | 1 (1.0%) | 0 |
| Influenza | 0 | 0 | 1 (2.3%) |
| Adenovirus infection | 1 (2.6%) | 0 | 0 |
| **Blood and Lymphatic System Disorders** | **1 (2.6%)** | **5 (5.1%)** | **1 (2.3%)** |
| Febrile neutropenia | 1 (2.6%) | 3 (3.1%) | 1 (2.3%) |

| | OPT-80-206 | SUNSHINE | |
|---|---|---|---|
| | Fidaxomicin (n=38) | Fidaxomicin (n=98) | Vancomycin (n=44) |
| Febrile bone marrow aplasia | 0 | 1 (1.0%) | 0 |
| Thrombocytosis | 0 | 1 (1.0%) | 0 |
| **Gastrointestinal Disorders** | **2 (5.3%)** | **4 (4.1%)** | **4 (9.1%)** |
| Vomiting | 2 (5.3%) | 0 | 0 |
| Hematemesis | 1 (2.6%) | 0 | 0 |
| Abdominal pain lower | 0 | 1 (1.0%) | 0 |
| Pancreatitis | 0 | 1 (1.0%) | 0 |
| Rectal hemorrhage | 0 | 1 (1.0%) | 0 |
| Small intestinal obstruction | 0 | 1 (1.0%) | 0 |
| Colitis | 0 | 0 | 1 (2.3%) |
| Diarrhea | 0 | 0 | 1 (2.3%) |
| Gastrointestinal necrosis | 0 | 0 | 1 (2.3%) |
| Ileus paralytic | 0 | 0 | 1 (2.3%) |
| Intestinal obstruction | 0 | 0 | 1 (2.3%) |
| **General Disorders and Administration Site** | **0** | **3 (3.1%)** | **2 (4.5%)** |
| Pyrexia | | 2 (2.0%) | 2 (4.5%) |
| Mucosal inflammation | | 1 (1.0%) | 0 |
| Pain | | 1 (1.0%) | 0 |
| **Metabolism and Nutrition Disorders** | **0** | **3 (3.1%)** | **0** |
| Dehydration | | 2 (2.0%) | 0 |
| Acidosis | | 1 (1.0%) | 0 |
| **Renal and Urinary Disorders** | **0** | **2 (2.0%)** | **1 (2.3%)** |
| Renal failure acute | | 2 (2.0%) | 0 |
| Renal failure | | 0 | 1 (2.3%) |
| **Neoplasms Benign, Malignant and** | **0** | **2 (2.0%)** | **1 (2.3%)** |
| Acute myeloid leukemia | | 1 (1.0%) | 0 |
| Leukemia | | 1 (1.0%) | 0 |
| Malignant ascites | | 0 | 1 (2.3%) |
| **Nervous System Disorders** | **0** | **2 (2.0%)** | **0** |
| Amnesia | | 1 (1.0%) | 0 |
| Convulsion | | 1 (1.0%) | 0 |
| Headache | | 1 (1.0%) | 0 |
| **Immune System Disorders** | **0** | **2 (2.0%)** | **0** |
| Anaphylactic reaction | | 1 (1.0%) | 0 |
| Food allergy | | 1 (1.0%) | 0 |
| **Respiratory, Thoracic and Mediastinal** | **1 (2.6%)** | **1 (1.0%)** | **1 (2.3%)** |
| Respiratory distress | 0 | 1 (1.0%) | 0 |
| Respiratory failure | 1 (2.6%) | 0 | 1 (2.3%) |
| **Congenital, Familial and Genetic** | **0** | **1 (1.0%)** | **0** |
| Mitochondrial encephalomyopathy | | 1 (1.0%) | 0 |
| **Psychiatric Disorders** | **0** | **1 (1.0%)** | **0** |
| Abnormal behavior | | 1 (1.0%) | 0 |
| **Surgical and Medical Procedures** | **1 (2.6%)** | **1 (1.0%)** | **0** |
| Radiotherapy | | 1 (1.0%) | 0 |
| Gastrostomy failure | 1 (2.6%) | 0 | 0 |

| | OPT-80-206 | SUNSHINE | |
|---|---|---|---|
| | Fidaxomicin (n=38) | Fidaxomicin (n=98) | Vancomycin (n=44) |
| **Investigations** | **0** | **0** | **1 (2.3%)** |
| Heart rate irregular | | 0 | 1 (2.3%) |

Source: Reviewer's analysis

## Discontinuations Due to Adverse Effects

### OPT-80-206 Study

In OPT-80-206 study, 3 patients had 4 TEAEs that led to discontinuation of the study drug and withdrawal from the study. These included 1 patient (Patient (b) (6), see the narrative below) with moderate urticaria considered definitely related to study medication; 1 patient with mild flatulence considered not related to study medication; and 1 patient with mild tachycardia and increased body temperature both considered possibly related to study medication by the Investigator.

**Patient** (b) (6) was a 3-year-old male with CDAD with no medical or surgical history or concomitant medications who received 200 mg fidaxomicin orally every 12 hours. On Day 3, the patient experienced urticaria and received 2 doses of oral 12.5 mg diphenhydramine hydrochloride, with urticaria resolution on the same day. Study drug was discontinued on Day 3 due to urticaria. The AE was moderate and was considered definitely related to study drug by the Investigator.

### SUNSHINE Study

In this study, 2 patients, one in each treatment arm, had TEAEs that led to discontinuation of the study drug. Fidaxomicin was discontinued on Day 5 due to lack of efficacy when the patient was diagnosed with pancolitis. However, the patient was not started on an alternative CDAD therapy but was treated with broad spectrum antibacterial drugs including levofloxacin, cefepime, and intravenous vancomycin. Pancolitis resolved on Day 12. In the vancomycin patient the study drug was stopped due to severe vomiting. Both patients with study drug discontinuations were considered treatment failure. The reviewer did not consider these TEAEs related to study drug.

## Adverse events of Special Interest

Adverse events of special interest were not defined in OPT-80-206. The adverse events of special interest in the SUNSHINE study were hypersensitivity to fidaxomicin, gastrointestinal hemorrhage, hematological adverse events e.g. decrease in white blood cell, neutrophil and lymphocyte counts, hepatic and renal laboratory value abnormalities, and QT interval prolongation. The AEs of special interest were selected based on some known toxicities

associated with the macrolide class of antibacterial drugs, and on experience from adult trials. The incidence of TEAEs of special interest is summarized in Table 8-27.

**Table 8-27. TEAEs of Special Interest in the SUNSHINE Study (SAF)**

| | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| Hematological adverse events | 12 (12.2%) | 4 (9.1%) |
| Hypersensitivity | 9 (9.2%) | 4 (9.1%) |
| Hepatic laboratory abnormalities | 5 (5.1%) | 1 (2.3%) |
| Renal adverse events | 5 (5.1%) | 1 (2.3%) |
| Gastrointestinal hemorrhage | 1 (1.0%) | 0 |
| QTprolongation | 0 | 0 |

Source: Reviewer's analysis and Table 41 in the SUNSHINE study report

TEAEs of special interest by age are summarized in Table 8-28.

**Table 8-28. TEAEs of Special Interest by Age in the SUNSHINE Study (SAF)**

| | Fidaxomicin (n=20) | | Vancomycin (n=10) | |
|---|---|---|---|---|
| | < 2 years | 2 to < 18 years | < 2 years | 2 to < 18 years |
| Hematological adverse events | 4(20.0%) | 8 (10.3%) | 0 | 4 (11.8%) |
| Hepatic laboratory abnormalities | 3(15.0%) | 2 (10%) | 0 | 1 (2.9%) |
| Hypersensitivity | 2 (10.0%) | 7 (9.0%) | 1(10.0%) | 3 (8.8%) |
| Renal adverse events | 1 (5.0%) | 4 (5.1%) | 1(10.0%) | 0 |
| Gastrointestinal hemorrhage | 0 | 1 (1.3%) | 0 | 0 |
| QT prolongation | 0 | 0 | 0 | 0 |

Source: Reviewer's analysis

**Hypersensitivity**

Hypersensitivity was reported for 9 (9.2%) patients in the fidaxomicin and 4 (9.1%) patients in vancomycin arm. None of the hypersensitivity reactions in either arm was considered related to study drug, or was life threatening, or required study drug discontinuation.

All hypersensitivity reactions were reported mild or moderate except for 1 patient in the fidaxomicin arm in the age group ≥ 2 years to < 6 years, who experienced an event of severe anaphylactic reaction. The event occurred on Day 28 (17 days after the last dose of study drug). The patient had a history of B cell lymphoma which was treated with IV immunoglobulin (IVIG) on day 28. The anaphylactic reaction was considered related to the IVIG treatment and not to fidaxomicin. It resolved the following day. Hypersensitivity reactions by patients is summarized in Table 8-29.

**Table 8-29. Hypersensitivity Reactions in the SUNSHINE Study (SAF)**

| Study Drug | Age | Preferred Term | Start Day | End Day | Severity |
|---|---|---|---|---|---|
| Fidaxomicin | 20 m | Rash | 1 | 41 | Mild |
| | | Urticaria | 9 | 11 | Mild |
| | 14 m | Exfoliative rash | 2 | 10 | Moderate |
| | 10 y | Urticaria | 36 | 40 | Moderate |
| | 8 y | Face edema | 11 | 11 | Mild |
| | 17 y | Rash | 3 | 8 | Mild |
| | 13 y | Rash | 32 | 38 | Mild |
| | 3 y | Anaphylactic reaction | 28 | 29 | Severe |
| Vancomycin | 5 y | Drug eruption | 24 | 29 | Moderate |
| | 8 y | Rhinitis allergic | 23 | 35 | Mild |
| | 20 m | Urticaria | 34 | 36 | Mild |

All reactions were considered not related to study drug.
m = months; y = year;
Source: Reviewer's analysis

*Clinical Reviewer's Comment: Hypersensitivity reactions occurred in similar frequency between the treatment arms in the SUNSHINE study. None of the hypersensitivity reactions observed during the study appeared to be directly related to fidaxomicin.*

*Hypersensitivity was identified as an important adverse event during post marketing surveillance, and subsequently this information was added to the "Warnings and Precautions" section of USPI. Acute hypersensitivity reactions that have been reported during post marketing surveillance were mostly rash, pruritus, angioedema and dyspnea. There was no temporal association of the reported events to fidaxomicin.*

**Hematological Adverse Events**

Hematological AEs including decreases in WBC, neutrophil, lymphocyte and platelet counts were recorded as an AE or as laboratory value abnormalities. Hematological AEs occurred in 10 (10.2%) of patients in the fidaxomicin arm and 4 (9.1%) of patients in the vancomycin arm. Two (2) of 10 patients with hematological AEs belonged to age group < 2 years. All hematological AEs resolved. Incidence of hematological AEs is listed in Table 8-30 and summarized by preferred terms in Table 8-31.

**Table 8-30. Incidence of Hematological Adverse Events in the SUNSHINE Study (SAF)**

| | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| Anemia | 4 (4.1%) | 1 (2.3%) |
| Febrile neutropenia | 3 (3.1%) | 2 (4.5%) |
| Neutropenia | 1 (1.0%) | 1 (2.3%) |
| Thrombocytopenia | 1 (1.0%) | 1 (2.3%) |
| Febrile bone marrow aplasia | 1 (1.0%) | 0 |

| | | |
|---|---|---|
| Total | 10 (10.2%) | 4 (9.1%) |

Source: Reviewer's analysis

**Table 8-31. Hematological Adverse Events by Preferred Term in the Fidaxomicin Arm of the SUNSHINE Study (SAF)**

| Age | Preferred Term | Start Day | End Day |
|---|---|---|---|
| 10 months | Anemia | 1 | 31 |
| | Neutropenia | 3 | 41 |
| | Thrombocytopenia | 5 | 31 |
| 15 months | Febrile bone marrow aplasia | 9 | 15 |
| 8 years | Febrile neutropenia | 21 | 51 |
| 6 years | Febrile neutropenia | 6 | 39 |
| 2 years | Febrile neutropenia | 1 | 6 |
| | Thrombocytopenia | 1 | 6 |
| 5 years | Anemia | 1 | 40 |
| 3 years | Anemia | 2 | 24 |
| 5 years | Anemia | 4 | 21 |
| | Leukopenia | 1 | 19 |
| 17 years | Anemia | 1 | 12 |
| 11 years | Febrile neutropenia | 30 | 31 |

Source: Reviewer's analysis

*Clinical Reviewer's comment: Overall in SUNSHINE study, hematological adverse events occurred in similar frequency in the fidaxomicin (10.2%) as compared to vancomycin (9.1%) arm. All patients with hematologic AEs received chemotherapy including the patient with febrile bone marrow aplasia. This patient with Langerhans histiocytosis was started on vinblastine of Day 2.*

*It should also be noted that 6 patients experienced hematological AEs on Day 1, which makes their relation to study drug unlikely as adverse events related to bone marrow suppression requires a longer time to manifest in laboratory findings. In addition, the majority of patients had baseline abnormalities at the study entry. As mentioned in prior sections of this review, there were numerical disparities in medical history of underlying 'Blood and lymphatic system disorders' which mainly included cytopenia, between treatment arms (40.8% vs 29.5%).*

*Similar trends for hematological AEs were noted in the adult trials where more patients in the fidaxomicin arm as compared to vancomycin arm experienced hematological AEs. Similar to the pediatric trials, the majority of fidaxomicin-treated adult patients had underlying comorbidities or received medications that may have contributed to the decrease in hematological counts. Post marketing monitoring of adverse events has not raised specific concerns with regards to hematological events. These events are already included in the product label.*

**Renal Adverse Events**

Renal adverse events were reported for 5 (5.1%) patients in the fidaxomicin arm and 1 patient (2.3%) in the vancomycin treatment arm. None of the renal events were assessed as related to study drug. One of 5 patients with renal adverse event in the fidaxomicin arm was reported to have 'decreased urine output', which occurred on Day 20 and resolved on Day 28 without any sequelae. Three of 5 patients in the fidaxomicin arm were reported to have 'acute renal failure'. None of the renal AEs were considered related to the study drug but to underlying comorbidities such as sepsis, and/or concomitant nephrotoxic medications.

**Gastrointestinal hemorrhage**

Serious Adverse Event of rectal hemorrhage was reported for 1 patient in the fidaxomicin arm on day 11. The event was considered moderate in severity and not related to study drug.

The patient was a 17-year-old white female with past medical history of *Helicobacter pylori* gastritis, anemia, coagulation disorder, ascites (the patient was later diagnosed with Wilson disease), prior history of CDAD, and a recent history of 'colitis' for which she completed 8 days of ciprofloxacin 1 day prior to randomization. The patient received fidaxomicin tablets 400 mg per day as outpatient. On Day 11 after completion of study treatment, the patient developed rectal hemorrhage associated with fever, which led to hospitalization. The patient was discharged from the hospital on Day 28 and completed the study follow-up on Day 41.

*Clinical Reviewer's Comment: Causality of rectal hemorrhage in this 17-year-old patient is confounded by other medical conditions, including coagulation disorders. Possibility of worsening of underlying colitis as a complication of CDAD, however, cannot be completely ruled out. The clinical signs/symptoms of fever, and blood with stools after completion of study drug treatment could represent worsening C. difficile colitis although no additional CDAD treatment was given.*

*This reviewer also examined the data for stool occult blood positivity rates during treatment in both arms. The proportions of patients who tested positive for occult blood at baseline and at the EOT were not significantly different in either treatment arms.*

*GI hemorrhages were reported at higher frequencies in the fidaxomicin as compared to vancomycin treatment arm (3.5% versus 1.7%) in the adult clinical trials. The significance of this finding was not ascertained. GI hemorrhages were not identified as a safety signal in post marketing reports.*

**Hepatic abnormalities**

Liver tests abnormalities during the study period, irrespective of baseline levels were reported for 5 (5.1%) patients in the fidaxomicin and 1 (2.3%) patient in the vancomycin arm. Hepatic AEs in patients with normal values of baseline liver tests are summarized by patient in Table 8-32.

**Table 8-32. Hepatic Adverse Events by Patient in the Fidaxomicin Arm in the SUNSHINE Study (SAF)**

| | Age | Adverse Event | Start Day | End Day | Highest Elevation | Study drug discontinuation |
|---|---|---|---|---|---|---|
| **Age group ≤2 years** | | | | | | |
| 1. | 16 months | ALT increased<br>AST increased<br>T. Bili increased | 22 | 25 | 4x ULN<br>4.5x ULN<br>2x ULN | No |
| 2. | 23 months | ALT increased | 39 | Not reported | 3.1x ULN | No |
| 3. | 2 years | AST increased | 19 | 23 | 6x ULN | Yes |
| 4. | 2 years | ALT increased<br>AST increased | 11<br>11 | Not reported<br>Not reported | 3.7x ULN<br>1.6x ULN | No |
| **Age group >2 years to <18 years** | | | | | | |
| 5. | 11 years | ALT increased<br>AST increased | 8 | 42 | 7.3x ULN<br>1.5x ULN | No |

All patients had normal baseline values of liver tests; ALT= alanine aminotransferase; AST = aspartate aminotransferase; T. Bili= Total bilirubin
Source: Reviewer's analysis

**Patient #** (b) (6)

Case history of this patient is also described in 'Section 8.2.4- Deaths'. The patient was a 16-month-old female, white patient, with ongoing medical conditions including acute myeloid leukemia, recipient of HSCT, presumed hepatosplenic candidiasis and intermittent neutropenia, received fidaxomicin suspension 320 mg per day (35.6 mg/kg/day) from day 1 to 11 for the treatment of CDAD. Patient's hospital course was complicated by bacteremia with *Klebsiella sp.*, and GVHD. On Day 15, the patient was diagnosed with *Klebsiella pneumoniae* bacteremia and started on meropenem. On Day 17 the patient was noted to have hepatomegaly with moderate ascites followed by elevation in bilirubin and was diagnosed with hepatic veno-occlusive disease. Eventually she was transitioned to palliative measures and died on day 40 due to progressive refractory leukemia. The liver test results in this patient are summarized below:

| **Liver test trends for Patient #** (b) (6) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Test/ ULN | Day 1 | Day 11/ EOT | Day 18 | Day 21 | Day 22 | Day 23 | Day 24 | Day 25 | Day 29 |
| ALT/ 45 | 10 | 18 | 12 | 117<br>2.6 x ULN | 186<br>4x ULN | 184<br>4x ULN | 122 | 80 | 11 |
| AST/ 60 | 16 | 15 | 25 | 220<br>3.7x ULN | 271<br>4.5x ULN | 200<br>3.7x ULN | 84 | 42 | 15 |
| TBili/ 21 | 3.4 | 6.8 | 24 | 39<br>1.8x ULN | 80<br>3.8x ULN | 91 | 82 | 68 | 51 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ALP/ 320 | 183 | 204 | 142 | 180 | 173 | 145 | 117 | 110 | 217 |

ULN = Upper limit of normal; Tbili = total bilirubin;

*Clinical Reviewer's Comment: The elevations of liver tests in this patient are likely related to hepatic veno-occlusive disease and sepsis. GVHD could have also contributed to liver test abnormalities. Fidaxomicin and OP-1118 plasma concentrations plasma concentration measured on Day 6 were in nanogram ranges and were 33.3 ng/dL and 71.9 ng/mL, respectively.*

**Patient #** (b) (6)

The patient was a 23-month-old female with acute lymphocytic leukemia, febrile neutropenia, *Pneumocystis jirovecii* pneumonia (PJP), typhlitis, anorexia, and vomiting. The patient completed treatment with fidaxomicin suspension 320 mg per day on Day 11.

The patient was also receiving prophylactic treatment for PJP with sulfamethoxazole and pentamidine for 80 days prior to study entry and during the study, with the last dose of pentamidine administered on Day 28. Patient also received micafungin from Day 7 to Day 10, and chemotherapy with doxorubicin, vincristine and mercaptopurine from day 12 and through Day 40, and cytarabine with methotrexate was from day 28 through Day 40.

On Day 39 (28 days after the EOT with study drug), the patient was found to have an ALT elevation of 3.1 x ULN. ALT remained elevated at the last follow-up visit on Day 42. The LFT trends in this patient is summarized below:

| **Liver test trends for Patient #** (b) (6) | | | | |
|---|---|---|---|---|
| Test / ULN | Day 1 | Day 11 / EOT | Day 39 | Day 42 |
| ALT / 45 | 16 | 21 | 140 (3.1x ULN) | 122 |
| AST / 60 | 24 | 29 | 81 | 65 |
| Tbili / 21 | 3.4 | 3.4 | 5 | 6.8 |
| ALP / 320 | 100 | 112 | 216 | 161 |

ULN = Upper limit of normal; Tbili = total bilirubin

*Clinical Reviewer's Comment: ALT elevation of 3X ULN accompanied by a slight elevation in AST 28 days after completion of fidaxomicin treatment was unlikely related to study drug. The more likely reason for liver test abnormalities in this patient are multiple concomitant medications with known hepatotoxicity.*

*Patient's day 5 post-dose fidaxomicin and OP-1118 plasma concentrations were 18.4 ng/dL and 47.8 ng/mL, respectively. Thus, no unusual systemic exposure to fidaxomicin or its metabolite that could explain transaminase elevation was noted.*

**Patient #** (b) (6)

The patient was a 2-year-old female with acute lymphocytic leukemia, intermittent fever, nausea, who received fidaxomicin suspension 400 mg per day. Concomitantly with fidaxomicin the patient received levofloxacin, and micafungin for an unspecified infection. On Day 5 fidaxomicin was discontinued due to lack of efficacy after the patient experienced an AE of 'pancolitis.' No additional CDAD treatment was administered, however. The patient was started on intravenous vancomycin, cefepime, and voriconazole. The AE of 'pancolitis' resolved on day 12.

On Day 19 (14 days after the last dose of study drug), the patient had an AST elevation of >3 x ULN, which further rose to 6 x ULN on Day 20 and resolved on Day 23. The remainder of liver tests remained within normal ranges. The liver enzyme trends in this patient are summarized below:

**Liver test trends for Patient #** (b) (6)

| Test / ULN | Day 1 | Day 5 / EOT | Day 6 | Day 19 | Day 20 | Day 23 |
|---|---|---|---|---|---|---|
| ALT / 45 | 25 | 21 | 21 | 46 | 86 | 50 |
| AST / 60 | 51 | 81 | 78 | 183 (3xULN) | 359 (6x ULN) | 90 |
| Tbili / 21 | 3.4 | 3.4 | 5 | 3.4 | 17 | 6.8 |
| ALP / 320 | 113 | 106 | 95 | 175 | 196 | 185 |

ULN = Upper limit of normal; Tbili = total bilirubin

*Clinical Reviewer's Comment: This patient was discontinued from study treatment on Day 5 due to worsening colitis and lack of efficacy. The transient elevation in AST observed on Day 19 seems unlikely to be related to fidaxomicin although the assessment is confounded by concurrent systemic medications known to cause hepatotoxicity. It should also be noted that AST elevation without concomitant ALT elevation is less specific for liver damage as the enzyme is present in other tissues, for instance in muscles. No information on the levels of creatine kinase, to ascertain this assumption, was provided.*

**Patient #** (b) (6)

The patient was a 2-year-old male with Ewing's sarcoma treated with IV vincristine, actinomycin, ifosfamide, and uromitexan started 8 days prior to study entry and completed prior to Day 1, bone marrow aplasia, febrile neutropenia, and anitis, who was started on fidaxomicin suspension 400 mg per day and completed treatment on Day 11. Concomitant medications included sulfamethoxazole (started months prior to study entry), IV vancomycin, meropenem and morphine (started 3 days prior to study entry and continued during hospitalization). Enzymes were not reported in the submission.

On Day 11, the patient was found to have an increase in ALT level to 3.5 x ULN. No subsequent liver tests were provided although the liver test abnormalities are reported as 'resolved' at a later point. The liver test trends in this patient is summarized below:

**Liver test trends for Patient #** (b) (6)

| Test / ULN | Day 1 | Day 11 / EOT |
|---|---|---|
| ALT / 40 | 46 | 157 (3.7x ULN) |
| AST / 60 | 32 | 97 (1.6x ULN) |
| Tbili / 21 | 9 | - |
| ALP / 320 | 151 | 46 |

ULN = Upper limit of normal; Tbili = total bilirubin

*Clinical Reviewer's Comment: While the assessment of causality of transaminases elevations in this patient was confounded by concomitant medications, given a temporal relationship between fidaxomicin dosing and transaminase elevation, the contribution of study drug to liver test abnormalities cannot be completely ruled out. Patient's day 8 post dose fidaxomicin and OP-1118 plasma concentrations were 22.5 ng/dL and 54.7 ng/mL, respectively, that is in the expected nano-gram range.*

**Patient #** (b) (6)

The patient was an 11-year-old female with metastatic medulloblastoma, febrile neutropenia, anorexia, anemia, thrombocytopenia, Intermittent nausea, vomiting, and abdominal pain, who completed treatment with fidaxomicin suspension 400 mg per day on Day 11. Concomitant medications included gemcitabine and pemetrexed for medulloblastoma, granulocyte colony stimulating factor for neutropenia, sulfamethoxazole for PJP prophylaxis, and dronabinol and granisetron for nausea.

On Day 8, the patient was found to have an ALT elevation of 7 x ULN, and an AST elevation of 1.5 x ULN. Fidaxomicin dosing was continued, and the ALT level decreased to 3 x ULN by Day 11. Transaminase levels remained elevated, however, throughout the study period with an overall decreasing trend. The liver test trends in this patient is summarized below:

| **Liver test trends for Patient #** (b) (6) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Test / ULN | Day 1 | Day 8 | Day 11 / EOT | Day 14 | Day 22 | Day 28 | Day 32 | Day 36 | Day 42 |
| ALT / 30 | 16 | 219 7.3x ULN | 125 | 87 | 351 | 155 | 176 | 152 | 69 |
| AST / 40 | 18 | 60 1.5x ULN | 45 | 39 | 139 | 62 | 82 | 59 | 39 |
| Tbili / 21 | 6.8 | 5 | 6.8 | 6.8 | 10 | 12 | 15 | 5 | 7 |
| ALP / 560 | 66 | 142 | 126 | 117 | 109 | 116 | 116 | 178 | 138 |

ULN= Upper limit of normal reference range

*Clinical Reviewer's Comment: As for patient #* (b) (6) *while the assessment of causality of transaminases elevations in this patient was confounded by concomitant medications known to be associated with drug induced liver injury, it is possible that liver test abnormalities were related to fidaxomicin. However, patient was receiving other concurrent medications with known hepatotoxicity which confounds the causality. Patient's day 8 post dose fidaxomicin and OP-1118 plasma concentrations were 10.2 ng/dL and 25.6 ng/mL, respectively.*

**Shifts in Liver Tests in the SUNSHINE Study**

Shifts in liver tests in the SUNSHINE study are presented in Table 8-33.

**Table 8-33. Shifts in Liver Enzymes in the SUNSHINE Study (SAF)**

| Parameter | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| **Alanine aminotransferase** | | |
| Shift to Low | 2/94 (2.1%) | 1/41 (2.4%) |
| Shift to High | 13/76 (17.1%) | 6/29 (20.7%) |
| No Change | 73/96 (76.0%) | 30/43 (69.8%) |
| **Aspartate aminotransferase** | | |
| Shift to Low | 1/89 (1.1%) | 0/40 |
| Shift to High | 9/84 (10.7%) | 5/32 (15.6%) |
| No Change | 78/96 (81.3%) | 32/42 (76.2%) |
| **Gamma-glutamyl transferase** | | |
| Shift to Low | 4/69 (5.8%) | 1/36 (2.8%) |
| Shift to High | 12/65 (18.5%) | 3/22 (13.6%) |
| No Change | 61/86 (70.9%) | 31/40 (77.5%) |
| **Bilirubin** | | |
| Shift to Low | 8/54 (14.8%) | 9/23 (39.1%) |
| Shift to High | 0/93 | 0/40 |
| No Change | 66/96 (68.8%) | 28/41 (68.3%) |

Shift to low: High to lower, normal to lower, or missing at baseline to below normal 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.

Shift to High: High to higher, normal to higher, or low to higher. The denominator for categorized increase is the number of patients who had any postbaseline value and did not have high at baseline.

*Clinical Reviewer's Comment: There was no significant difference between treatment arms in terms of shifts in liver tests towards higher values from any baseline values.*

***Clinical Reviewer's overall assessment of hepatic abnormalities***

*Fidaxomicin belongs to macrolide class of antibacterial drugs which are known to cause hepatotoxicity. However, fidaxomicin has minimal systemic absorption and not expected to exhibit the similar spectrum of adverse events as systemic macrolides. In non-clinical and in vitro studies, fidaxomicin and its metabolite, OP-1118 were hydroxylated in a nicotinamide adenine dinucleotide phosphate (NADPH)-dependent fashion in human liver microsomes and hepatocytes. Small amounts of a sulfate metabolite of OP-1118 were also detected in human hepatocytes in vitro. CYP enzymes does not appear to play a significant role in the metabolism of fidaxomicin.*

*In adult trials, adverse reaction of "increased hepatic enzymes" was reported in < 2% of patients and is listed in the current product label. Transaminase elevations appear to have occurred at*

*higher frequency in the pediatric trial. However, the population in the pediatric trial may not be fully comparable with that in the adult trials in terms of underlying comorbidities so the comparison between safety outcomes in adult and pediatric patients treated with fidaxomicin should be taken with caution.*

*In 3 of 5 fidaxomicin pediatric patients with hepatic AEs, liver test abnormalities seem unlikely to be related to study drug. In 2 patients hepatic AEs could have possibly been related to study drug although concomitant medications received by these patients' limit causality assessments. Of note, these patients received the suspension formulation of fidaxomicin but no increase in systemic exposures to fidaxomicin was noted. Overall, the assessment of hepatic AEs in the fidaxomicin pediatric development program does not raise a safety signal. Adverse event of "transaminases elevation" will be added to the pediatric section of product labeling.*

## Treatment Emergent Adverse Events

Treatment emergent adverse events (TEAE) were defined as adverse events reported after the first dose of the study drug until the end of the study follow-up period (Day 10 + 28 days in OPT-80-206 and Day 10 + 30 days in SUNSHINE study). TEAEs for both studies are summarized in Table 8-34.

**Table 8-34. Treatment-Emergent Adverse Events by System Organ Class in Fidaxomicin Pediatric Studies (SAF)**

| | OPT-80-206 | SUNSHINE | |
|---|---|---|---|
| | Fidaxomicin (n=38) | Fidaxomicin (n=98) | Vancomycin (n=44) |
| **Any treatment-emergent adverse event** | 28 (73.7%) | 72 (73.5%) | 33 (75.0%) |
| Gastrointestinal disorders | 10 (26.3%) | 31 (31.6%) | 19 (43.2%) |
| Infections and infestations | 11 (28.9%) | 31 (31.6%) | 15 (34.1%) |
| General disorders and administration site conditions | 6 (15.8%) | 23 (23.5%) | 11 (25.0%) |
| Metabolism and nutrition disorders | 4 (10.5%) | 14 (14.3%) | 4 (9.1%) |
| Investigations | 7 (18.4%) | 12 (12.2%) | 2 (4.5%) |
| Nervous system disorders | 2 (5.3%) | 12 (12.2%) | 0 |
| Blood and lymphatic system disorders | 1 (2.6%) | 11 (11.2%) | 4 (9.1%) |
| Skin and subcutaneous tissue disorders | 6 (15.8%) | 9 (9.2%) | 5 (11.4%) |
| Respiratory, thoracic and mediastinal disorders | 5 (13.2%) | 9 (9.2%) | 4 (9.1%) |
| Psychiatric disorders | | 6 (6.1%) | 1 (2.3%) |
| Injury, poisoning and procedural complications | 3 (7.9%) | 5 (5.1%) | 2 (4.5%) |
| Renal and urinary disorders | 1 (2.6%) | 4 (4.1%) | 3 (6.8%) |
| Musculoskeletal and connective tissue disorders | 0 | 4 (4.1%) | 3 (6.8%) |
| Immune system disorders | 1 (2.6%) | 4 (4.1%) | 0 |
| Vascular disorders | 2 (5.3%) | 3 (3.1%) | 1 (2.3%) |
| Surgical and medical procedures | 0 | 3 (3.1%) | 1 (2.3%) |
| Cardiac disorders | 1 (2.6%) | 3 (3.1%) | 0 |
| Eye disorders | 2 (5.3%) | 2 (2.0%) | 2 (4.5%) |
| Neoplasms benign, malignant and unspecified | 0 | 2 (2.0%) | 1 (2.3%) |

| | | | |
|---|---|---|---|
| Hepatobiliary disorders | 1 (2.6%) | 2 (2.0%) | 0 |
| Congenital, familial and genetic disorders | 0 | 1 (1.0%) | 0 |
| Endocrine disorders | 0 | 1 (1.0%) | 0 |

Source: Reviewer's analysis

Most common TEAEs by preferred term is summarized in Table 8-35 and Table 8-36 for OPT-80-206 and the SUNSHINE study, respectively.

**Table 8-35. TEAEs by Preferred Term Reported for at Least 5% of Patients in OPT-80-206 Study (SAF)**

| Preferred Term | Fidaxomicin (n=38) |
|---|---|
| **Any TEAEs** | **28 (73.7%)** |
| Pyrexia | 4 (10.5%) |
| Vomiting | 4 (10.5%) |
| Abdominal pain upper | 3 (7.9%) |
| *Clostridium difficile* colitis | 3 (7.9%) |
| Headache | 2 (5.3%) |
| Diarrhea | 2 (5.3%) |
| Constipation | 2 (5.3%) |
| Nasopharyngitis | 2 (5.3%) |
| Dehydration | 2 (5.3%) |
| Urticaria | 2 (5.3%) |
| Hypertension | 2 (5.3%) |
| Nausea | 2 (5.3%) |
| Chest pain | 2 (5.3%) |
| Esophagitis | 2 (5.3%) |

Source: Reviewer's analysis

**Table 8-36. TEAEs by Preferred Term Reported for at Least 5% of Patients in the SUNSHINE Study (SAF)**

| Preferred Term | Fidaxomicin (n=98) | Vancomycin (n=44) |
|---|---|---|
| Any TEAEs | 72 (73.5%) | 33 (75.0%) |
| Pyrexia | 13 (13.3%) | 10 (22.7%) |
| Headache | 8 (8.2%) | 0 |
| Vomiting | 7 (7.1%) | 6 (13.6%) |
| Diarrhea | 7 (7.1%) | 5 (11.4%) |
| Abdominal pain* | 7 (7.1%) | 9 (20.5%) |
| Aminotransferases increased | 7 (7.1%) | 1 (2.3%) |
| Constipation | 5 (5.1%) | 1 (2.3%) |

*Includes adverse reactions preferred terms "abdominal pain", "abdominal pain lower"
Source: Reviewer's analysis

*Clinical Reviewer's Comment: The only notable differences between the treatment arms in the SUNSHINE study were found in the SOC of "Nervous system disorders," and "Investigations". All adverse events from the SOC of "Nervous system disorders" were "headache" and this event was observed only in the fidaxomicin arm. In OPT-80-206 study headache was also the only*

*event reported in this SOC. In the adult fidaxomicin trials headache was reported in 0.5% and 0.7% of patients in the fidaxomicin and vancomycin arm, respectively. The reason for a higher incidence of headache in pediatric fidaxomicin patients is uncertain.*

*Most common AEs by preferred term from SOC of "Investigations "were AST/ALT/ or LFT abnormal, which were evaluated as AEs of special interest and already discussed in section above.*

*In general, common treatment emergent adverse events in the fidaxomicin pediatric studies were similar to those in adults, except for "elevated transaminases" which were seen at a slightly higher frequency in fidaxomicin patients in the pediatric studies, whereas, neutropenia and gastrointestinal hemorrhage were reported at higher frequencies in the fidaxomicin arm in the adult trials.*

## Laboratory Findings

**Hematology**

In adult trials, shifts in white blood cell (WBC) from normal to low were reported 2-times more frequently in the fidaxomicin as compared to vancomycin treatment arm. In study OPT-80-206, a shift from normal at baseline to low at EOT was observed in 10.5% of patients for lymphocytes and in 7.9% of patients for leukocytes and neutrophils. In the SUNSHINE study, hematological adverse events were evaluated as AEs of special interest and have already been discussed.

**Chemistry**

Changes in liver and renal laboratory tests have been discussed as adverse events of special interest.

## Vital Signs

There were no clinically relevant changes in vital signs from baseline to EOT in either trials in fidaxomicin treatment population, and there were no relevant differences between the fidaxomicin and vancomycin arms in the SUNSHINE study.

## Electrocardiograms (ECGs) and QT

Two ECGs were performed, one at screening prior to the first dose of study drug and another between 1 to 5 hours post dose. No differences in ECG parameters were observed between treatment arms which may be expected as the two drugs are minimally absorbed.

**Immunogenicity**

No specific immunogenicity studies for fidaxomicin have been conducted. Hypersensitivity reactions in fidaxomicin treated patients are discussed in section 8.2.4. of this review.

### 8.2.5. Safety Analyses by Demographic Subgroups

Safety analyses by age subgroups are discussed in section 8.2.4.

### 8.2.6. Additional Clinical Outcome Assessment Analyses

Relevant clinical outcome assessments have been discussed in prior sections of this review.

### 8.2.7. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

Carcinogenicity studies were not conducted for fidaxomicin. Given the short-expected duration of treatment in humans (10 days) and minimal systemic absorption, the carcinogenic risk is considered minimal.

**Human Reproduction and Pregnancy**

No adequate and well-controlled studies with fidaxomicin have been conducted in pregnant women. Studies in rats did not reveal changes in reproductive or fertility parameters and no maternal and development toxicity was observed. No pediatric patient of child-bearing potential became pregnant during either OPT-80-206 or SUNSHINE study.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

There were no overdoses reported in the fidaxomicin adult or pediatric trials or during post marketing safety surveillance. No drug-related adverse effects were seen in dogs dosed with fidaxomicin tablets at 9600 mg/day (over 100 times the human dose, scaled by weight) for 3 months.

### 8.2.8. Safety in the Post Market Setting

**Safety Concerns Identified Through Post Market Experience**

Adverse events of “Hypersensitivity” was identified as an important risk based on post marketing reports and had been added to the product label.

### 8.2.9. Integrated Assessment of Safety

The safety of the fidaxomicin suspension and tablet formulations for the treatment of CDAD was evaluated in 136 pediatric patients aged 1 months to less than 18 years, treated with fidaxomicin (38 patients in the Phase 2 trial (OPT-80-206), and 98 patients in the Phase 3 trial (SUNSHINE study). The mean duration of exposure to fidaxomicin was 9.6 days in OPT-80-206,

and 10.6 days in the SUNSHINE study.

Approximately two-thirds of patients in the SUNSHINE and OPT-80-206 study received oral suspension, 68% and 63%, respectively. The remainder of patients received tablets. The number of patients who received the oral suspension decreased with age.

In the SUNSHINE study there were no significant differences among the treatment arms in terms of gender, race, or weight. The majority of patients were (~60%) and white (~85%). Patients were stratified by age group in both trials. Slightly higher proportion of patients in the fidaxomicin as compared to vancomycin arm had a history of prior CDAD, 28.6% and 22.7%, respectively.

Overall, treatment emergent adverse events, adverse events related to study drug, or adverse events leading to discontinuation from study drug or from study were similar between the treatment arms. The non-fatal severe adverse events and common adverse reactions were in general, similar between treatment arms. Most adverse reactions were mild to moderate in severity. There were total of 3 patients that discontinued study drug due to adverse reaction in the Phase 2 trial. In the Phase 3 trial, 1 patient from each treatment arm discontinued study drug due to an adverse reaction.

Most common adverse reactions seen in > 5% of patients receiving fidaxomicin were pyrexia, headache, vomiting, diarrhea, abdominal pain, and increased aminotransferases. Adverse reactions were similar to that observed in adult trials.

There were 4 deaths in the fidaxomicin arm during the study follow-up period in the two pediatric trials combined. One patient died in the Phase 2 and 3 patients died in the Phase 3 trial. Notably, all deaths in fidaxomicin treated patients occurred in < 2 years age group. Reported adverse events leading to death were 'sepsis or septic shock' for 3 patients and 'refractory leukemia' for 1 patient. All patients who died received the suspension formulation of fidaxomicin (powder for suspension in the Phase 2 trial, and to be marketed granules for suspension in the Phase 3 trial. Analysis of deaths did not reveal fidaxomicin related toxicity. Results from pharmacokinetic studies in pediatric patients indicated pharmacokinetic profiles similar to adults with minimal systemic absorption across all age groups. The deaths of all 4 patients appeared to be related to underlying comorbidities.

As discussed earlier, in the SUNSHINE study a lower confirmed clinical response was observed in patients < 2 years old in the fidaxomicin as compared to vancomycin arm. However, about 60% of the patients in both treatment arms were coinfected with other diarrheal pathogens, which makes the diagnosis of CDAD in this age group and, subsequently, efficacy assessments less certain. Additionally, interpretation of this finding is limited by a small sample size in this age group.

In conclusion, the fidaxomicin tablets and oral suspension have demonstrated an acceptable

safety profile in pediatric patients from 6 months to less than 18 years.

# 9 Pediatrics

NDA 201699 for fidaxomicin tablets did not include studies of pediatric patients. The Applicant requested (b) (4) The NDA was discussed at a meeting of the Pediatric Review Committee (PeRC) on April 20, 2011. (b) (4)

At the time of approval of NDA 201699, on May 27, 2011, the pediatric study requirement for ages 0 to less than 6 months was waived because necessary studies were determined to be impossible or highly impractical since the disease does not exist in this population. The approval letter listed two PMRs for pediatric studies:

- **PMR 1757-001**: Conduct a prospective clinical trial of 10 days of DIFICID (fidaxomicin) in at least 32 pediatric patients (6 months to less than 18 years of age) with *C. difficile*-associated diarrhea to evaluate the safety and pharmacokinetics (including serum and fecal concentrations) of DIFICID (fidaxomicin).
- **PMR 1757-002**: Conduct a prospective, randomized clinical trial to demonstrate safety and effectiveness of DIFICID (fidaxomicin) compared to vancomycin in pediatric patients (6 months to less than 18 years of age) with *C. difficile*-associated diarrhea.

The final study report for OPT-80-206 was submitted on November 13, 2014, and on February 24, 2015, FDA issued a PMR fulfilled letter.

On May 16, 2018, FDA issued a Pediatric Written Request.

The SUNSHINE study (Protocol 2819-CL-0202) was designed to fulfill PMR 1757-002. The final study report for the SUNSHINE study was included in sNDA-201699/S-012 for fidaxomicin tablets and NDA 213138 for fidaxomicin oral suspension. The results of the SUNSHINE study were discussed at a PeRC meeting on December 10, 2019. The PeRC agreed that the submission fulfilled PMR 1757-002.

The results of the SUNSHINE study were discussed at the Pediatric Exclusivity Board. The Board concluded that the study met the terms of the Written Request and fidaxomicin was granted pediatric exclusivity, effective December 13, 2019. For additional details on regulatory activities related to the fidaxomicin pediatric development, please refer to Section 3 of this review.

# 10 Labeling Recommendations

Draft prescribing information was provided with the application. The notable changes to the proposed labeling are provided in Table 10-1.

**Table 10-1. Significant Changes to Applicant's Proposed Labeling**

| Labeling Section | Addition / Modifications |
|---|---|
| Indications and Usage | The indication proposed by the Applicant was revised from (b) (4) to the treatment of *Clostridioides difficile*-associated diarrhea (CDAD). The latter indication more accurately describes the disease studied in the DIFICID clinical program where patients with the most severe forms of *C. difficile* infection, such as fulminant infection or toxic megacolon were excluded. Also, the CDAD indication is consistent with the indication in the prescribing information of other products, including fidaxomicin, approved for the treatment of this infection, and with the warning on the risk of *Clostridioides difficile*-Associated Diarrhea (CDAD) included in the prescribing information of antimicrobial products. |
| Warnings and Precautions | Warning 5.2 'Hypersensitivity Reactions' was assigned number 5.1 to make the information on the possibility of hypersensitivity reactions related to fidaxomicin use more prominent as fidaxomicin is minimally absorbed and hypersensitivity reactions following its administration may not be expected and result in significant health hazard.<br><br>Warning 5.1 '(b) (4) was assigned number 5.2 and its title was changed to 'Not for Use in Infections Other than *C. difficile*-Associated Diarrhea.' The revision was made as the prior title may have implied (b) (4) The text of the warning was also revised to clarify that fidaxomicin was not studied for the treatment of infections other than CDAD. |
| Adverse Reactions | Addition of detailed information on safety findings in the fidaxomicin trials including the information on deaths that occurred in DIFICID-treated patients less than 2 years of age. |
| Clinical Studies | A table providing clinical response results by age groups was included to provide the information on the lower clinical response in fidaxomicin as compared to vancomycin treated patients aged less than 2 years. |

# 11 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held for these applications as external input was not considered necessary.

# 12 Risk Evaluation and Mitigation Strategies (REMS)

There are no specific risks that warrant consideration of a REMS.

# 13 Post marketing Requirements and Commitment

None.

# 14 Deputy Division Director (Clinical) Comments

I concur with the review team's comments and assessments.

# 15 Appendices

## 15.1. References

References are included as footnotes throughout the review.

## 15.2. Financial Disclosure

Financial disclosure for SUNSHINE Study
**Covered Clinical Study (Name and/or Number):** SUNSHINE

| | | |
|---|---|---|
| Was a list of clinical investigators provided? | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 129 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): | | |

| | | |
|---|---|---|
| 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements? | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided? | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ | | |
| Is an attachment provided with the reason? | Yes ☐ | No ☐ (Request explanation from Applicant) |

## 15.3. Nonclinical Pharmacology/Toxicology

**Study title/ number: A 7-day comparative toxicokinetic study of fidaxomicin (OPT-80, PAR-101) in beagle dogs upon oral (gavage and capsule) administration; (Study No. WIL-609011; GLP; 7/2010)**
Sponsor: Optimer Pharmaceuticals, Inc. San Diego, CA, USA
Study Initiation Date: 10/9/2009
Conducting facility: (b) (4)

A GLP 7-day repeat-dose toxicokinetic study was conducted in beagle dogs (~5 months old; Males: 6.6-7.9 kg; Females: 5.3-6.9 kg) to compare the toxicokinetic profile of fidaxomicin (OPT-80) and its metabolite (OP-1118) for tablet and suspension formulations when administered orally, once daily by gavage (suspension, 5 mL/kg) or by capsule (5-8 tablets) at 0 or 200 mg/kg/day. Two dogs/sex/group (control) and 4 dogs/sex/group (fidaxomicin suspension or tablets) were assessed for both fecal and plasma exposure of OPT-80 and its metabolite, OP-1118. The composition of the vehicle for suspension is presented in the table below.

**Table 15-1. Composition of Vehicle for Suspension in Study WIL-609011**

| Excipient | mg/mL (b) (4) |
|---|---|
| [redacted] | |

*(Text table on page 458 of study report)*

Study parameters included assessments of mortality (2x daily), clinical signs (during dosing, 0.5 h and 2 hours after dosing); detailed clinical observations (1x weekly); body weight (daily); food consumption (daily); fecal sample collection (Day 5); and TK blood collection (5, 15, 30 minutes, 1, 2, 4, 6, 8,12, and 24 hours after dosing on Day 6 of dosing). No clinical pathology or gross or histopathological evaluations were conducted.

Seven consecutive days of daily dosing with both oral formulations of OPT-80 (up to 200 mg/kg/day) to male and female beagle dogs appeared to be generally well tolerated, with no treatment related adverse effects noted on any study parameters evaluated.

Mean fecal concentrations of OPT-80 and OP-1118 observed in the 200 mg/kg/day suspension and capsule dose groups are described in the table below. Higher fecal concentrations of both OPT-80 and OP-1118 were observed in dogs administered tablets compared to dogs administered the suspension formulation.

**Table 15-2. Fecal Concentrations of OPT-80 and OP-1118 in Beagle Dogs after Dosing with the Oral Suspension or Tablet Formulations**

| | Fidaxomicin Suspension (200 mg/kg/day) | | Fidaxomicin Tablet (200 mg/kg/day) | |
|---|---|---|---|---|
| | Mean Fecal Concentration (µg/g) [a] – Study Day 5 | | | |
| Sex | Fidaxomicin | OP-1118 | Fidaxomicin | OP-1118 |
| Males | 9390 | 92.1 | 15500 | 219 |
| Females | 4740 | 39.2 | 21300 | 166 |

LLOQ = Lower limit of quantitation

a Fecal samples (approximately 20 g) for analysis of fidaxomicin and OP-1118 were collected from solid stool on Study Day 5. Fecal concentrations of fidaxomicin and OP-1118 from all control group animals were below the LLOQ (< 10.0 ng/mL fidaxomicin; < 50.0 ng/mL OP-1118).

*(Table 2.6.6:10 on page 14 of the Toxicology Written Summary)*

Mean toxicokinetic parameters for OPT-80 and OP-1118 are described in the table below. Limited systemic exposure to OPT-80 and OP-1118 were noted in 1 male and 1 female dog administered the suspension and in 4 males and 3 females administered tablets. Inter-animal variability was generally high due to low systemic absorption of orally administered formulations, precluding reliable comparisons between genders and dosage forms. However, mean exposure to OPT-80 and OP-1118 trended higher in dogs administered tablets compared to dogs administered the suspension. Where reportable, Tmax ranged between 0.5 to 4 hours post-dosing and plasma half-life for OPT-80 ranged from 0.4-5 hours for both formulations. Half-life was not calculable for OP-1118. Systemic exposure to OP-1118 (AUClast) was < 10% of the exposure to the parent for both formulations. Cmax values also appeared lower for OP-1118 compared to the parent compound, OPT-80.

**Table 15-3. Mean Toxicokinetic Results for OPT-80 and OP-1118 in Dogs***

| Sex/Group | $AUC_{last}$ (ng·h/mL) | Metabolite/ Parent Ratio** | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $T_{1/2}$ (h) |
|---|---|---|---|---|---|
| | | Fidaxomicin | | | |
| Males | | | | | |
| Group 2, Gavage | 147 (19.0-269) | NA | 223 (31.3-451) | 0.63 (0.5-1) | 0.43†2 |
| Group 3, Capsule | 1921 (331-3408) | NA | 916 (296-2130) | 2.0 (1-4) | 0.60†2 |
| Females | | | | | |
| Group 2, Gavage | 801 (65.0-1648) | NA | 198 (74.3-519) | 3.4 (0.5-12) | 0.61†1 |
| Group 3, Capsule | 742 (110-1516) | NA | 748 (149-1760) | 1.3 (1-2) | NC |
| | | OP-1118 | | | |
| Males | | | | | |
| Group 2, Gavage | NA | NA | NA | NA | NA |
| Group 3, Capsule | 129†2 (86.3-172) | 0.046†2 (0.025-0.067) | 75.5 (24.0-127) | 2.0†2 | NC |
| Females | | | | | |
| Group 2, Gavage | 40.9†1 | 0.025†1 | 14.5†1 | 8†1 | NC |
| Group 3, Capsule | 34.2†1 | 0.023†1 | 25.5†1 | 1†1 | NC |

N = 4 except where reported as †n where n = number of values used to calculate mean.
NA = Not applicable; NC = Not calculable.
* Due to high inter-animal variability, mean and range are reported for $AUC_{last}$, metabolite/parent ratio, $C_{max}$ and $T_{max}$ (unless all data points are equal)
**Ratio of OP-1118 $AUC_{last}$/Fidaxomicin $AUC_{last}$.

*(Text Table 1 on page 27 of the Study Report)*

**Study title/ number: A 14-day Dose Range Finding Study by Oral Gavage Administration of Fidaxomicin (OPT-80) in the Juvenile Beagle Dog**

Study no.: 902517

| | |
|---|---|
| Study report location: | EDR |
| Conducting laboratory and location: | (b) (4) [redacted] |
| Date of study initiation: | July 24, 2012 |
| Duration: | 14 days (dosing commencing on day 4 post-partum) |
| Duration Units: | days |
| GLP compliance: | N |
| QA statement: | N |
| Drug, lot #, and % purity: | Fidaxomicin, batch no. EH-B09-01-001635; Lot No. 1024-12-17; 94.1% purity |

## Methods

| | |
|---|---|
| Doses: | 0, 50 100, 200 mg/kg (See Table below) |
| Frequency of dosing: | Once daily |
| Route of administration: | ORAL GAVAGE |
| Dose volume: | 5 mL/kg |
| Formulation/Vehicle: | Fidaxomicin (OPT-80) OS Excipient Blend: (b) (4) [redacted] |
| Species: | DOG |
| Strain: | BEAGLE |
| Dedicated Juvenile Animal Study: | Y |
| Number/Sex/Group: | 4/sex/group |
| Age: | 4 days at the initiation of dosing |
| Weight: | 367 to 561 g for males and from 367 to 566 g for females. |
| Deviation from study protocol: | None that was noteworthy |

**Table 15-4. Design of a 14-Day Dose Range Finding Study in Juvenile Beagle Dogs**

| Group No. | Dose Level (mg/kg/dose) | Dose Volume (mL/kg) | Dose Concentration (mg/mL) | Minimum No. of Litters | No. of Animals Main Study | |
|---|---|---|---|---|---|---|
| | | | | | Males | Females |
| 1/ Control | 0 | 5 | 0 | 2 | 4 | 4 |
| 2/ Fidaxomicin (OPT-80) | 50 | 5 | 10 | 2 | 4 | 4 |
| 3/ Fidaxomicin (OPT-80) | 100 | 5 | 20 | 2 | 4 | 4 |
| 4/ Fidaxomicin (OPT-80) | 200 | 5 | 40 | 2 | 4 | 4 |

*(Text table 1, page 12 of the final report)*

The objectives of this study were to evaluate the toxicokinetics and tolerability of fidaxomicin and its metabolite (OP-1118) administered by the oral route once a day to juvenile Beagle dogs for 14 days, commencing at Day 4 post-partum (pp), and to determine the dose levels for the subsequent pivotal toxicity study in juvenile dogs. A total of 9 gravid dogs were received (2.5-5 years old) and allowed to deliver normally. Young, nursing pups were administered control or OPT-80 from days 4-17 pp (inclusive, dose volume of 5mL/kg) by oral gavage. The dose of 200 mg/kg/day was selected as the high dose since it was considered the maximum practicable dose that could be administered by oral gavage.

The parameters evaluated included: mortality, clinical signs, body weights, and pharmacokinetic parameters in plasma and feces.

**Key Study Findings**

- There were no OPT-80 or P-1118 treatment related deaths.
- For some of the treated animals (both males and females) in the 200 mg/kg/day group, overall weight gains were reduced (5-16 percent) when compared to controls.

The observations, although mild, were considered treatment related.

***Summary of pharmacokinetics results***

Parent (OPT-80)

**Table 15-5. Toxicokinetic Parameters of Fidaxomicin (OPT-80) in Juvenile Beagle Dog Plasma Day 4 pp (Dosing Day 1)**

| Toxicokinetic Parameter | Daily Dose (mg/kg) | | | | | |
|---|---|---|---|---|---|---|
| | 50 | | 100 | | 200 | |
| | Males | Females | Males | Females | Males | Females |
| $T_{max}$ (h) | 4.0 | 4.0 | 0.5 | 2.0 | 2.0 | 1.0 |
| $C_{max}$ (ng/mL) | 323 | 487 | 459 | 1020 | 829 | 1100 |
| $AUC_{(0-t)}$ (ng•h/mL) | 1650 | 1830 | 2620 | 4870 | 3690 | 3600 |
| $AUC_{(0-inf)}$ (ng•h/mL) | 1670 | 1850 | 2650 | 4900 | NC | 3620 |
| $AUC_{(0-12)}$ (ng•h/mL) | 1650 | 1830 | 2440 | 4470 | 3690 | 3600 |
| $AUC_{(12-24)}$ (ng•h/mL) | 65.5 | 47.3 | 178 | 400 | 300 | 63.6 |
| $T_{1/2}$ (h) | 1.51 | 1.47 | 4.35 | 3.73 | NC | 1.58 |

*(Text Table 10, page 32 of the final report)*

**Table 15-6. Parameters of Fidaxomicin (OPT-80) in Juvenile Beagle Dog Plasma Day 10 pp (Dosing Day 7)**

| Toxicokinetic Parameter | Daily Dose (mg/kg) | | | | | |
|---|---|---|---|---|---|---|
| | 50 | | 100 | | 200 | |
| | Males | Females | Males | Females | Males | Females |
| $T_{max}$ (h)[a] | 4.0 | 1.0 | 1.5 | 1.0 | 1.5 | 1.0 |
| $C_{max}$ (ng/mL) | 295 | 266 | 639 | 487 | 1200 | 1370 |
| $AUC_{(0-t)}$ (ng•h/mL) | 1730 | 1090 | 3100 | 2520 | 4730 | 4610 |
| $AUC_{(0-inf)}$ (ng•h/mL) | 1860 | 1310 | 3060 | 2980 | 5420 | 4660 |
| $AUC_{(0-12)}$ (ng•h/mL) | 1730 | 1190 | 3040 | 2470 | 4520 | 4420 |
| $AUC_{(12-24)}$ (ng•h/mL) | 140 | 40.0 | 226 | 133 | 308 | 248 |
| $T_{1/2}$ (h) | 2.23 | 2.17 | 2.53 | 2.78 | 1.90 | 2.21 |

NC = Not calculated [a] = Median.

*(Text Table 11, page 32 of the final report)*

**Table 15-7. Toxicokinetic Parameters of Fidaxomicin (OPT-80) in Juvenile Beagle Dog Plasma Day 17 pp (Dosing Day 14)**

| Toxicokinetic Parameter | Daily Dose (mg/kg) | | | | | |
|---|---|---|---|---|---|---|
| | 50 | | 100 | | 200 | |
| | Males | Females | Males | Females | Males | Females |
| $T_{max}$ (h)[a] | 4.0 | 1.5 | 1.0 | 1.5 | 0.5 | 1.0 |
| $C_{max}$ (ng/mL) | 242 | 188 | 843 | 373 | 940 | 753 |
| $AUC_{(0-t)}$ (ng•h/mL) | 1500 | 987 | 3140 | 1410 | 2790 | 2690 |
| $AUC_{(0-inf)}$ (ng•h/mL) | 1490 | 987 | 3290 | 1580 | 2870 | 2820 |
| $AUC_{(0-12)}$ (ng•h/mL) | 1580 | 955 | 3130 | 1550 | 2850 | 2750 |
| $AUC_{(12-24)}$ (ng•h/mL) | 77.0 | 112 | 89.7 | 83.3 | 84.8 | 135 |
| $T_{1/2}$ (h) | 2.40 | 2.67 | 1.88 | 2.39 | 1.89 | 2.20 |

NC = Not calculated [a] = Median

*(Text Table 12, page 33 of the final report)*

Metabolite (OP-1118)

**Table 15-8. Toxicokinetic Parameters of OP-1118 in Juvenile Beagle Dog Plasma Day 4 pp (Dosing Day 1)**

| Toxicokinetic Parameter | Daily Dose (mg/kg) | | | | | |
|---|---|---|---|---|---|---|
| | 50 | | 100 | | 200 | |
| | Males | Females | Males | Females | Males | Females |
| $T_{max}$ (h) | 4.0 | 4.0 | 2.0 | 6.0 | 2.0 | 2.0 |
| $C_{max}$ (ng/mL) | 30.1 | 48.6 | 36.9 | 230 | 197 | 114 |
| $AUC_{(0-t)}$ (ng•h/mL) | 135 | 137 | 166 | 744 | 657 | 371 |
| $AUC_{(0-12)}$ (ng•h/mL) | 173 | 178 | 190 | 744 | 657 | 454 |
| $AUC_{(12-24)}$ (ng•h/mL) | 0.0 | 0.0 | 0.0 | 115 | 91.4 | 0.0 |

*(Text Table 13, page 33 of the final report)*

**Table 15-9. Toxicokinetic Parameters of OP-1118 in Juvenile Beagle Dog Plasma Day 10 pp (Dosing Day 7)**

| Toxicokinetic Parameter | Daily Dose (mg/kg) | | | | | |
|---|---|---|---|---|---|---|
| | 50 | | 100 | | 200 | |
| | Males | Females | Males | Females | Males | Females |
| $T_{max}$ (h)[a] | 4.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| $C_{max}$ (ng/mL) | 30.9 | 26.8 | 80.1 | 88.7 | 278 | 193 |
| $AUC_{(0-t)}$ (ng•h/mL) | 151 | 155 | 390 | 495 | 1300 | 872 |
| $AUC_{(0-inf)}$ (ng•h/mL) | NC | NC | 553 | 872 | 1680 | 978 |
| $T_{1/2}$ (h) | NC | NC | 2.40 | 3.10 | 2.53 | 2.75 |

NC = Not calculated [a] = Median

*(Text Table 14, page 33 of the final report)*

**Table 15-10. Toxicokinetic Parameters of OP-1118) in Juvenile Beagle Dog Plasma Day 17 pp (Dosing Day 14)**

| Toxicokinetic Parameter | Daily Dose (mg/kg) | | | | | |
|---|---|---|---|---|---|---|
| | 50 | | 100 | | 200 | |
| | Males | Females | Males | Females | Males | Females |
| $T_{max}$ (h)[a] | 5.0 | 2.0 | 2.0 | 3.0 | 3.0 | 3.0 |
| $C_{max}$ (ng/mL) | 33.1 | 30.6 | 155 | 64.9 | 177 | 115 |
| $AUC_{(0-t)}$ (ng•h/mL) | 169 | 107 | 538 | 313 | 1010 | 583 |
| $T_{1/2}$ (h) | NC | NC | 1.37 | 1.91 | 2.43 | 2.43 |

NC = Not calculated [a] = Median.

*(Text Table 15, page 34 of the final report)*

**TK summary**

The time to reach maximum concentrations of OPT-80 across all groups and dosing days ranged from 0.5 and 4 hours post dose. There was varied dose proportionality (from slightly less than proportional to proportional) in the AUC of males and females in the groups treated with OPT-80 at 50 to 100 mg/kg, and consistently less than dose proportional increase from 100 to 200 mg/kg across all treatment groups. Overall, the AUC levels (i.e., exposure) appeared to be higher in the 200 mg/kg pups dosed on Day 1 and Day 7 when compared to pups dosed on Day 14.

The time to reach maximum concentrations of OP-1118 80 across all groups and dosing days ranged from 0.5 and 5 hours post dose. There was dose proportionality in the AUC of males and females with at dosing days 7 and 14 (no clear dose proportionality observed on males or females across all test groups on dosing day 1). The highest concentrations of OP-1118 in plasma were observed at the highest dose (200 mg/kg) at dosing day 14. Measurements of both the parent compound (OPT-80) and metabolite (OP-1118) were considerably higher in feces than in plasma. Based on AUC levels, OPT-80 and metabolite OP-1118 plasma exposures were generally higher in the females when compared to the males on Day 1 in the 100 mg/kg group. The same treatment group appeared to have slightly lower AUCs in females when compared to males from dosing day 14. The percent metabolite-to-parent ratio ranged from 6.4 to 38.4%. OPT-80 and OP-1118 were quantifiable in the feces throughout the 24-hour sampling period. The high concentration in feces may indicate limited exposure in plasma due to lack of absorption from the GI tract. Based on the mild effects observed at the high dose tested (slightly reduced weight gain in some animals and single occurrences of yellow liquid material in the feces of some animals) doses of 50, 100 and 200 mg/kg/day were selected for the 28-day juvenile study.

**Study title/ number: A 28-day Study by Oral Gavage Administration of Fidaxomicin (OPT-80) in the Juvenile Beagle Dog with a 56-day Recovery Period**

| | |
|---|---|
| Study no.: | 902518 |
| Study report location: | SDN # |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | January 29, 2013 |
| Duration: | 28 days (dosing commencing on day 4 post-partum); 56-day recovery period |
| Duration Units: | days |
| GLP compliance: | Y |
| QA statement: | Yes |
| Drug, lot #, and % purity: | Fidaxomicin (OPT-80), batch (lot) no. EH-B09-01-001635; 94.1 % purity (as per CoA) |

**Key Study Findings**

There were no treatment related mortality or changes/observations in body weight, food consumption, clinical pathology, organ weights, gross necropsy or histopathology. The highest dose tested, 200 mg/kg was considered the study NOAEL.

*Reviewer comment: A comparison of AUCs between juvenile beagles and children were not possible because these values were not calculated in the Phase 2a or Phase 3 studies due to the low plasma levels (3-33 ng/mL).*

**Methods**

Doses: See Tables below
Frequency of dosing: Once daily
Route of administration: ORAL GAVAGE
Route of administration:
Dose volume: 5 mL/kg
Formulation/Vehicle: Fidaxomicin (OPT-80) OS Excipient Blend: pre-blended (b) (4)

Species: DOG
Strain: BEAGLE
Dedicated Juvenile Animal Study: Y
Number/Sex/Group: Control and high dose Fidaxomicin 6/sex/group; low- and mid-dose Fidaxomicin 5/sex/group
Age: 4 days at the initiation of dosing
Weight: At post-partum day 4, males weighed 283-561 g and females weighed 317-565 g.
Satellite groups: Toxicokinetics animals (see Table below)
Deviation from study protocol: None that was noteworthy

**Table 15-11. Design of a 28-Day Study in Juvenile Beagle Dogs with a 56-Day Recovery Period**

| Group No. | Dose Level (mg/kg/dose) | Dose Volume (mL/kg) | Dose Concentration (mg/mL) | Number of Litters Used | No. of Animals[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Main/TK Study | | Recovery Study | |
| | | | | | Males | Females | Males | Females |
| 1/ Control | 0 | 5 | 0 | 6 | 5[a]/2+1[b] | 5[a]/2+1[b] | 3 | 3 |
| 2/ Fidaxomicin (OPT-80) | 50 | 5 | 10 | 5 | 5/3+3[c] | 5/3+3[c] | - | - |
| 3/ Fidaxomicin (OPT-80) | 100 | 5 | 20 | 5 | 5/2+3[c,d] | 5/4+3[c,d] | - | - |
| 4/ Fidaxomicin (OPT-80) | 200 | 5 | 40 | 6 | 5/3+3[c] | 5/3+3[c] | 3 | 3 |

- Not applicable

[a] 2 main study pups/sex were used for TK blood collection on Day 31 pp

[b] 3 TK pups were used for TK blood collection on Day 4 pp and 1 TK pup was used for TK blood collection on Day 31 pp

[c] 6 TK pups/sex/group were used for TK blood collection on Day 4 pp and 3 TK pups/sex/group were used for TK blood collection on Day 31 pp. For Group 3, 5 male/7 female pups were bled on Day 4 pp and 3 male/3 female pups were bled on Day 31 pp.

[d] As the desired number of males or females was not available, the available pups were used regardless of sex

*(Text Table 3, page 24 of the final Study Report)*

**Table 15-12. Terminal Procedures for Main Study, Toxicokinetic and Recovery Animals**

| Group No. | No. of Animals | | Scheduled Euthanasia Day | Necropsy Procedures | | | Histology | Histopathology[e] |
|---|---|---|---|---|---|---|---|---|
| | M | F | | Necropsy | Tissue Collection | Organ Weights | | |
| 1 | 5[a] | 5[a] | 32 pp | X | X | X | Full Tissue | Full Tissue |
| 2 | 5[a] | 5[a] | | | | | Full Tissue | - |
| 3 | 5[a] | 5[a] | | | | | Full Tissue | - |
| 4 | 5[a] | 5[a] | | | | | Full Tissue | Full Tissue |
| 1 | 3[b] | 3[b] | 5 pp | - | - | - | - | |
| 2 | 3[b] | 3[b] | | | | | - | |
| 3 | 3[b] | 3[b] | | | | | - | |
| 4 | 3[b] | 3[b] | | | | | - | |
| 1 | 3[c] | 3[c] | 32 pp | - | - | - | - | |
| 2 | 3[c] | 3[c] | | | | | - | |
| 3 | 3[c] | 3[c] | | | | | - | |
| 4 | 3[c] | 3[c] | | | | | - | |
| 1 | 3[d] | 3[d] | 88 pp | X | X | X | Full Tissue | - |
| 4 | 3[d] | 3[d] | | | | | Full Tissue | - |
| Unscheduled Deaths | | | | X | X | - | Full Tissue | Full Tissue |

X = Procedure conducted; - = Not applicable.

[a] Main study animals

[b] 3 toxicokinetic pups/sex/group bled on Day 4 pp

[c] 3 toxicokinetic pups/sex/group bled on Day 31 pp

[d] Recovery animals

[e] See Tissue Collection and Preservation table for listing of tissues.

*(Text Table 14, page 32 of the final Study Report)*

**Observations and Results**

Mortality

All animals (F0 and F1) were checked at least twice daily for mortality and moribundity (cage side observations) throughout the study.

There were no OPT-80 related unscheduled deaths in either the main or the recovery studies.

Clinical Signs

Dams were observed each day from day 55 of gestation onward, for signs of parturition. Parturition was observed when possible and post-partum behavior and maternal performance were observed after whelping. On Day 0 (day of littering completion) pups were examined for malformations (no malformations observed). Pups were patient to a detailed examination (animals removed from the cage) once daily until weaning as part of the litter check and twice weekly thereafter. The Sponsor notes that during the study more frequent evaluations were performed as considered appropriate by the Study Director or veterinarian.

There were no OPT-80 related clinical observations except for some fur staining (paws, abdominal region) across all groups (more consistently on the 50 mg/kg/dose) including

animals in the control group. These observations appeared to be incidental and not treatment related.

Body Weights
Pups were weighed daily until day 31 post-partum, and twice weekly thereafter. A terminal body weight (fasted for recovery animals) was recorded prior to scheduled euthanasia.

There were no OPT-80 related changes in body weights or body weight gains in any of the test groups throughout the study including the recovery period animals with exception of an apparent weight gain increase in the 200 mg/kg/day group females (during and at the end of the recovery period). These apparent weight gain increases were not likely treatment related, and potentially related to allocation of heavier females in that dose group.

Feed Consumption
Food consumption for recovery animals was measured by cage starting from weaning (day 56 post-partum).

There were no OPT-80 related changes in food consumption in the male or female beagles in the main study or recovery animals.

Hematology
Blood samples for hematology and clinical chemistry (target volume 0.7 mL) were collected from the jugular vein from the main study and recovery animals.

There were no OPT-80 treatment related changes in hematology parameters in the male or female beagles in the main study or in the recovery animals.

Coagulation
Blood samples (target volume 0.9 mL) were processed for plasma.

There were no OPT-80 treatment related changes in coagulation parameters in the male or female beagles in the main or in the recovery animals

Clinical Chemistry
Blood samples (target volume 0.7 mL) were processed for serum.

There were no OPT-80 related changes in clinical chemistry parameters in the male or female beagles in the main or in the recovery animals.

Urinalysis
There were no OPT-80 related changes observed in urinalysis parameters in the male or female beagles in the main or in the recovery animals.

Gross Pathology
Animals were euthanized by exsanguination (through incision of the axillary or femoral artery) following anesthesia by either intravenous (dams) or intraperitoneal (pups) injection of sodium pentobarbital. A sedative, Ketamine HCl for Injection, U.S.P. and Xylazine were administered by intramuscular injection before animals were transported from the animal room to the necropsy area. Animals were fasted overnight before scheduled necropsy.

There were no OPT-80 related gross pathology observations in the male or female beagles in the main or in the recovery animals. There were some changes observed in some of the treated animals in the main study (more consistently in the 50 mg/kg/day group) as well as in animals in the control group (e.g., dark focus in the lung that sometimes had a histopathological correlate with inflammation or minimal lung hemorrhage). These observations were random, not dose related and considered incidental.

Organ Weights
There were no OPT-80 related changes in organ weights in the male or female beagles in the main or in the recovery animals.

Histopathology
Adequate Battery: Yes
Peer Review: No

Histological Findings
There were no OPT-80 related histopathological observations in the male or female beagles in the main or in the recovery animals

Toxicokinetics

**Table 15-13. Toxicokinetic Parameters of OPT-80 and OP-1118 in Juvenile Beagle Dogs**

| Sex | Dose (mg/kg) | Fidaxomicin | | OP-1118 | |
|---|---|---|---|---|---|
| | | Mean $C_{max}$ (ng/mL) | Mean $AUC_{0-t}$ (ng·hr/mL) | Mean $C_{max}$ (ng/mL) | Mean $AUC_{0-t}$ (ng·hr/mL) |
| | | PND4 (Dosing Day 1) [a] | | | |
| Males | 50 | 272 | 1800 | 28.8 | 117 |
| | 100 | 809 | 2960 | 77.5 | 262 |
| | 200 | 2240 | 10500 | 830 | 2460 |
| Females | 50 | 175 | 1010 | 17.1 | NC |
| | 100 | 774 | 3240 | 58.7 | 307 |
| | 200 | 1680 | 5430 | 135 | 682 |
| | | PND31 (Dosing Day 28) [a] | | | |
| Males | 50 | 68 | 311 | NC | NC |
| | 100 | 327 | 404 | 30.4 | 64.9 |
| | 200 | 646 | 1010 | 54.1 | 77.4 |
| Females | 50 | 42.7 | 144 | NC | NC |
| | 100 | 309 | 2230 | 21.9 | 369 |
| | 200 | 625 | 1270 | 34.4 | 191 |

LLOQ = Lower limit of quantitation; NC = not calculated; PND = Postnatal day

a Plasma concentrations of fidaxomicin and OP-1118 from all control group animals were below the LLOQ (10.0 ng/mL for fidaxomicin and OP-1118).

*(Table 2.6.6.6:6 on page 11 of the Toxicology-Written-Summary)*

Peak plasma concentrations of OPT-80 were observed between 0.5 and 4 hours post dose with exception of day 1 females in the 200 mg/kg group (peak at 6 hours post-dose) (Table 15-3). There was varied dose proportionality (from slightly less than proportional to proportional) in the AUC for males and females in the groups treated with OPT-80 from 50-100 mg/kg, and consistently less than dose proportional from 100-200 mg/kg across all treatment groups. Overall, higher AUC levels (i.e., exposure) were observed in 200 mg/kg pups dosed on Day 1 and Day 4 when compared to pups dosed on Day 14.

Measurements of both the parent compound (OPT-80) and metabolite (OP-1118) were considerably higher in feces than in plasma (Table 15-4). Based on AUC levels, OPT-80 and metabolite OP-1118 plasma exposures were generally higher in the females when compared to the males on Day 1 at the mid-dose tested. The percent metabolite-to-parent ratio ranged from 6.4 to 38.4%. OPT-80 and OP-1118 were quantifiable in the feces throughout the 24-hour sampling period. Based on these results, doses of 50, 100 and 200 mg/kg/day were selected for the 28-day juvenile study.

**Table 15-14. Fecal Concentration of Fidaxomicin and OP-1118 in Juvenile Beagle Dogs**

| Sex | Dose (mg/kg) | Mean Fecal Concentration (µg/g) [a] | | | |
|---|---|---|---|---|---|
| | | PND4/5 | | PND31/32 | |
| | | Fidaxomicin | OP-1118 | Fidaxomicin | OP-1118 |
| Males | 50 | 1990 | 229 | 3170 | 261 |
| | 100 | 1250 | 320 | 4030 | 160 |
| | 200 | 4390 | 402 | 4150 | 202 |
| Females | 50 | 1300 | 259 | 3020 | 93.5 |
| | 100 | 4060 | 482 | 4980 | 256 |
| | 200 | 3060 | 491 | 2980 | 174 |

LLOQ = Lower limit of quantitation; PND = Postnatal day

a Fecal samples were collected from the rectum and colon from each toxicokinetic animal at necropsy (i.e., PND4/5 and PND31/32). Fecal concentrations of fidaxomicin and OP-1118 from all control group animals were below the LLOQ (< 0.100 µg/mL (2 µg/g) fidaxomicin; < 0.500 µg/mL (10 µg/g) OP-1118), with the exception of 2 control group males (PND31 samples).

*(Table 2.6.6: 7 on page 11 of the Toxicology-Written-Summary)*

## 15.4. OCP Appendices

**Pharmacokinetic Analyses**

The PK of fidaxomicin in pediatric patients with CDAD were evaluated in one Phase 2a study (OPT-80-206) and one Phase 3 study (SUNSHINE). A powder for reconstitution formulation was investigated in the OPT-80-206 study and the to-be-marketed granules for oral suspension formulation was used in the SUNSHINE study. In both studies, the approved 200-mg fidaxomicin film-coated tablet was used for patients with a weight of ≥12.5 kg who were able to swallow tablets.

In study OPT-80-206, 36 patients contributed to the plasma pharmacokinetic analysis set and 30 patients to the fecal pharmacokinetic analysis set. In the SUNSHINE study, 82 patients contributed plasma concentrations and 74 contributed fecal concentrations to the pharmacokinetic analysis.

The plasma and fecal concentrations of fidaxomicin and its main metabolite, OP-1118, were measured in both pediatric clinical studies, using validated liquid chromatography/tandem mass spectroscopy methods (Tables 15-15, 15-16, 15-17, and 15-18).

**Table 15-15. Median Fidaxomicin Plasma Concentrations (ng/mL) from Phase 2a and Phase 3 Study**

| | ≥6 to <24 Months (n = 8) | ≥2 to <6 Years (n = 7) | ≥6 to <12 Years (n = 9) | ≥12 to <18 Years (n = 12) | All Patients (n = 36) |
|---|---|---|---|---|---|
| Fidaxomicin Plasma Concentrations from Phase 2a Study | | | | | |
| Predose | | | | | |
| | 3.310 (1.180 - 65.800) | 9.070 (4.460 - 13.200) | 8.730 (1.150 - 18.700) | 6.580 (1.750 - 31.700) | 7.095 (1.150 - 65.800) |
| 1 to 2 hours postdose | | | | | |
| | 5.695 (1.75 - 64.70) | 13.300 (7.77 - 35.00) | 8.710 (1.89 - 39.90) | 7.265 (1.86 - 22.90) | 8.795 (1.75 - 64.70) |
| 3 to 5 hours postdose | | | | | |
| | 4.925 (0.563 - 87.400) | 14.400 (7.530 - 22.400) | 14.925 (3.550 - 28.900) | 8.400 (3.130 - 22.800) | 8.725 (0.563 - 87.400) |
| Fidaxomicin Plasma Concentrations from Phase 3 Study | | | | | |
| Predose | | | | | |
| | 7.68 (2.5 - 29.0) | 9.86 (1.2 - 121.0) | 9.14 (2.1 - 93.8) | 11.10 (2.2 - 326.0) | 9.19 (1.2 - 326.0) |
| 1 to 5 hours postdose | | | | | |
| | 18.40 (3.0 - 208.0) | 14.05 (2.2 - 367.0) | 21.55 (7.0 - 154.0) | 32.65 (3.9 - 359.0) | 21.00 (2.2 - 367.0) |

**Table 15-16. Median OP-1118 Plasma Concentrations (ng/mL) from Phase 2a and Phase 3 Study**

| | ≥6 to <24 Months (n = 8) | ≥2 to <6 Years (n = 7) | ≥6 to <12 Years (n = 9) | ≥12 to <18 Years (n = 12) | All Patients (n = 36) |
|---|---|---|---|---|---|
| OP-1118 Plasma Concentrations from Phase 2a Study | | | | | |
| Predose | | | | | |
| | 15.0 (4.230 - 850.000) | 26 ((0.445 - 82.200) | 20.5 (5.540 - 106.000) | 15.2 (4.240 - 71.300) | 19.5 ((0.445 - 850.000) |
| 1 to 2 hours postdose | | | | | |
| | 17.0 (5.66 - 930.00) | 41.7 (26.70 - 96.80) | 29.0 (6.99 - 129.00) | 28.15 (4.62 - 56.90) | 27.6 (4.62 - 930.00) |
| 3 to 5 hours postdose | | | | | |
| | 4.925 (0.563 - 87.400) | 14.400 (7.530 - 22.400) | 14.925 (3.550 - 28.900) | 8.400 (3.130 - 22.800) | 8.725 (0.563 - 87.400) |
| OP-1118 Plasma Concentrations from Phase 3 Study | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Predose | | | | | |
| | 30.50 (8.8 - 81.6) | 22.70 (5.4 - 560.0) | 20.05 (6.7 - 203.0) | 29.25 (7.4 - 1410.0) | 23.90 (5.4 - 1410.0) |
| 1 to 5 hours postdose | | | | | |
| | 71.90 (9.8 - 459.0) | 33.75 (9.4 - 1720.0) | 47.65 (16.9 - 337.0) | 57.30 (11.3 - 1500.0) | 47.80 (9.4 - 1720.0) |

**Table 15-17. Median Fidaxomicin Fecal Concentrations (mcg/g) from Phase 2a and Phase 3 Study**

| | ≥6 to <24 Months (n = 8) | ≥2 to <6 Years (n = 7) | ≥6 to <12 Years (n = 9) | ≥12 to <18 Years (n = 12) | All Patients (n = 36) |
|---|---|---|---|---|---|
| Fidaxomicin Fecal Concentrations from Phase 2a Study | | | | | |
| | 4700 (848.0 - 11500) | 1040.50 (268.0 - 3270.0) | 2280 (844.0 - 6660.0) | 1950 (1010.0 - 4400.0) | 2425 (268.0 - 11500) |
| Fidaxomicin Fecal Concentrations from Phase 3 Study | | | | | |
| | 2110 (329.0 - 6240.0) | 2510 (0 - 13700.0) | 1790 (469.0 - 9050.0) | 1650 (48.1 - 5440.0) | 2100 (0 - 13700.0) |

**Table 15-18. Median OP-1118 Fecal Concentrations (mcg/g) from Phase 2a and Phase 3 Study**

| | ≥6 to <24 Months (n = 8) | ≥2 to <6 Years (n = 7) | ≥6 to <12 Years (n = 9) | ≥12 to <18 Years (n = 12) | All Patients (n = 36) |
|---|---|---|---|---|---|
| OP-1118 Fecal Concentrations from Phase 2a Study | | | | | |
| | 942.00 (75.8 - 1610.0) | 280.00 (139.0 - 333.0) | 897.00 (166.0 - 2540.0) | 743.00 (378.0 - 1490.0) | 758.00 (75.8 - 2540.0) |
| OP-1118 Fecal Concentrations from Phase 3 Study | | | | | |
| | 369.00 (29.9 - 1269.0) | 710.00 (0 - 4560.0) | 812.50 (110.0 - 3940.0) | 724.00 (16.8 - 3740.0) | 691.00 (0 - 4560.0) |

*Reviewer Comment: In Study OPT-80-206 higher fidaxomicin fecal concentrations were noted in the youngest age category, although the youngest patients also had the highest degree of variability, which may have been attributable to the sample collection method (diapers), leading to a bias towards higher measured concentrations.*

The 200-mg fidaxomicin film-coated tablet has been approved for use in adults and this tablet formulation is considered adequate for the treatment of pediatric patients with a weight of ≥ 12.5 kg who are able to swallow tablets, as evaluated in the OPT- 80-206 and SUNSHINE studies. Fidaxomicin and OP-1118 plasma and fecal concentrations were similar between the tablet and the to be marketed suspension as highlighted in Tables 15-19 and 15-20, respectively.

**Table 15-19. SUNSHINE Study: Observed Plasma Concentrations of Fidaxomicin and Metabolite OP-1118 on Days 5 to 10 by Formulation**

| | Plasma Concentration (ng/mL) | |
|---|---|---|
| | Oral Suspension (Granules) | Tablets |
| Fidaxomicin | | |
| Predose | | |
| n | 55 | 27 |
| Median (min-max) | 9.05 (1.2-121.0) | 9.26 (2.5 – 326.0) |
| 1 to 5 hours postdose | | |
| n | 53 | 28 |
| Median (min-max) | 15.3 (2.2 – 367.0) | 26.75 (3.9 – 359.0) |
| OP-1118 | | |
| Predose | | |
| n | 55 | 27 |
| Median (min-max) | 24.30 (5.4 – 560.0) | 22.9 (6.7 – 1410.0) |
| 1 to 5 hours post dose | | |
| n | 53 | 28 |
| Median (min-max) | 47.20 (9.4 – 1720) | 57.25 (11.3 – 1500) |

**Table 15-20. SUNSHINE Study: Observed Fecal Concentrations of Fidaxomicin and Metabolite OP-1118 Within 24 Hours Postdose on Days 5 to 10 by Formulation**

| Statistic | Fecal Concentration (mcg/g) | |
|---|---|---|
| | Oral Suspension (Granules) | Tablets |
| Fidaxomicin | | |
| n | 47 | 27 |
| Median (min-max) | 2250.0 (0 – 13700) | 1770.0 (48.1 – 9050.0) |
| OP-1118 | | |
| n | 46 | 27 |
| Median (min-max) | 635.0 (0 – 4560.0) | 876.0 (16.8 – 3940) |

Overall, plasma concentrations in pediatric patients were similar (ng/mL range) to adults (Table 15-21).

**Table 15-21. Plasma concentrations at 1-5 h following fidaxomicin 200 mg Q12h for 10 days in Phase 3 adult patients (NDA 201699)**

| | Concentration at 1-5 h (Tmax window) (ng/mL) | | | |
|---|---|---|---|---|
| | Fidaxomicin | | OP-1118 | |
| | Day 1 | End of Therapy | Day 1 | End of Therapy |
| N >LLOQ [a] | 347/430 (80.7%) | 130/160 (81.3%) | 354/420 (82.3%) | 133/160 (83.1%) |
| Median (min-max) | 13.2 (0.26 – 237) | 15.7 (0.31 – 191) | 25.9 (0.24 – 406) | 40 (1.09 – 871) |

Source: NDA 201699, Clinical Pharmacology Review; Table 1.3.2-2 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201699Orig1s000ClinPharmR.pdf)

[a] Lower limit of quantification (LLOQ) of fidaxomicin and OP-1118 in plasma was 0.2 ng/mL

*Reviewer Comment: Pediatric fecal concentrations could not be compared to adult values due to unsatisfactory storage duration of fecal samples and missing accuracy and precision information in the original application, which limited pharmacokinetic data of fidaxomicin and OP-1118 in feces to descriptive terms for the original labeling in the adults.*

## 15.5. Selected Underlying Conditions in the SUNSHINE Study

**Table 15-22. Underlying Conditions from the SOC "Neoplasms benign, malignant, and unspecified" in the SUNSHINE Study (SAF)**

| | **Fidaxomicin (n = 98)** | **Vancomycin (n = 44)** |
|---|---|---|
| **Neoplasms benign, malignant and unspecified** | **44 (45%)** | **19 (43%)** |
| **Hematological malignancies** | | |
| Acute lymphocytic leukemia | 14 (14%) | 5 (11%) |
| Acute lymphocytic leukemia (in remission) | 1 (1%) | 1 (2%) |
| Acute megakaryocytic leukemia | 1 (1%) | 0 |
| Acute myeloid leukemia | 3 (3%) | 1 (2%) |
| Acute myeloid leukemia recurrent | 1 (1%) | 0 |
| Astrocytoma | 0 | 1 (2%) |
| B precursor type acute leukemia | 0 | 1 (2%) |
| B-cell type acute leukemia | 1 (1%) | 0 |
| Diffuse large b-cell lymphoma | 2 (2%) | 0 |
| Leukemia | 0 | 1 (2%) |
| Lymphoma | 3 (3%) | 0 |
| Hodgkin's disease | 0 | 1 (2%) |
| Langerhans' cell histiocytosis | 1 (1%) | 0 |
| Myelodysplastic syndrome | 0 | 1 (2%) |
| T-cell lymphoma | 1 (1%) | 0 |
| **Other Malignancies** | | |

| | **Fidaxomicin (n = 98)** | **Vancomycin (n = 44)** |
|---|---|---|
| Benign lung neoplasm | 1 (1%) | 0 |
| Benign neoplasm of thyroid gland | 1 (1%) | 0 |
| Desmoplastic small round cell tumor malignant | 0 | 1 (2%) |
| Diffuse large b-cell lymphoma | 2 (2%) | 0 |
| Embryonal rhabdomyosarcoma | 1 (1%) | 0 |
| Ependymoma | 2 (2%) | 0 |
| Ewing's sarcoma | 4 (4%) | 1 (2%) |
| Ganglioneuroblastoma malignant | 0 | 1 (2%) |
| Hepatoblastoma malignant | 0 | 1 (2%) |
| Malignant ascites | 0 | 1 (2%) |
| Malignant glioma | 0 | 1 (2%) |
| Medulloblastoma | 3 (3%) | 0 |
| Neoplasm unspecified | 1 (1%) | 0 |
| Nephroblastoma | 1 (1%) | 0 |
| Neuroblastoma | 1 (1%) | 1 (2%) |
| Osteosarcoma | 0 | 1 (2%) |
| Rhabdomyosarcoma | 1 (1%) | 0 |
| Testicular germ cell cancer | 1 (1%) | 0 |

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