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# Anti-Infective Drugs Advisory Committee Meeting
# Briefing Document

## Dificid™ (fidaxomicin tablets) for the treatment of *Clostridium difficile* infection (CDI), also known as *Clostridium difficile*-associated diarrhea (CDAD), and for reducing the risk of recurrence when used for treatment of initial CDI

## NDA 201699

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ADME | Absorption, distribution, metabolism and excretion |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ASHP | American Society of Health System Pharmacists |
| AST | Aspartate aminotransferase |
| $AUC_{0\text{-}inf}$ | Area under the curve |
| $AUC_{0\text{-}t}$ | Area under the curve from zero up to time t |
| $AUC_{0\text{-}\infty}$ | Area under the curve from zero up to infinite time |
| BI | An epidemic hypervirulent *C. difficile* strain |
| BMI | Body mass index |
| CDAD | *Clostridium difficile*-associated diarrhea |
| CDC | Centers for Disease Control and Prevention |
| CDI | *Clostridium difficile* infection |
| CFU | Colony forming units |
| CHO | Chinese hamster ovary |
| CI | Confidence interval |
| CLSI | Clinical and Laboratory Standards Institute |
| $C_{max}$ | Maximum plasma concentration |
| CNS | Central nervous system |
| CYP | Cytochrome |
| eCCL | Estimated creatinine clearance |
| ECG | Electrocardiogram |
| EOT | End of therapy |
| ESCMID | European Society of Clinical Microbiology and Infectious Diseases |
| EU | European Union |
| FDA | Food and Drug Administration |
| FSR | Frequency of spontaneous resistance |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| GLP | Good laboratory practice |
| hERG | Human ether-à-go-go related gene |
| HICPAC | Hospital Infection Control Practices Advisory Committee |
| $^{3}$H-UTP | Radiolabeled uridine triphosphate |

| | |
|---|---|
| $IC_{50}$ | Half maximal inhibitory concentration |
| IDSA | Infectious Disease Society of America |
| ITT | Intent-to-Treat |
| IUD | Intrauterine device |
| i.v. | Intravenously |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LC-MS/MS | Liquid chromatography tandem mass spectrometry |
| LFT | Liver function test |
| LLOQ | Lower limit of quantification |
| MIC | Minimum inhibitory concentration |
| $MIC_{90}$ | Minimum inhibitory concentration required to inhibit the growth of 90% of organisms |
| mITT | Modified Intent-to-Treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| NA | Not applicable |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| NAP1 | North America PFGE pulsotype 1 |
| NC | Not calculated |
| ND | Not determined |
| NDA | New Drug Application |
| NOAEL | No observed adverse effect level |
| NOEL | No observed effect level |
| OP-1118 | Metabolite of fidaxomicin |
| OPT-80 | Code name for fidaxomicin drug product |
| PAE | Post-antibiotic effect |
| PAR-101 | Previous code name for fidaxomicin drug product |
| PCR | Polymerase chain reaction |
| PE | Point estimate |
| PFGE | Pulsed Field Gel Electrophoresis |
| P-gp | P-glycoprotein |
| pH | A measure of the acidity or alkalinity of a solution |
| PK | Pharmacokinetic |
| PP | Per protocol |

| | |
|---|---|
| PT | MedDRA preferred term |
| q6h | Every 6 hours |
| q12h | Every 12 hours |
| QTcB | Bazett's corrected QT interval |
| QTcF | Fridericia corrected QT interval |
| REA | Restriction endonuclease analysis |
| RBC | Red blood cell |
| RNA | Ribonucleic acid |
| RTI | Respiratory tract infection |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SHEA | Society for Healthcare Epidemiology of America |
| SOC | MedDRA System Organ Class |
| $t_{1/2}$ | Terminal half-life |
| TEAE | Treatment-emergent adverse event |
| $T_{max}$ | Time to maximum plasma concentration |
| TTROD | Time-to-resolution of diarrhea |
| UBM | Unformed bowel movements |
| UTI | Urinary tract infection |
| VISA | Vancomycin-intermediate *Staphylococcus aureus* |
| VRE | Vancomycin-resistant *Enterococcus* |
| VRSA | Vancomycin-resistant *Staphylococcus aureus* |
| WBC | White blood cells |
| $\lambda_z$ | Terminal rate constant |

# 1 EXECUTIVE SUMMARY

Fidaxomicin (also known as OPT-80 and PAR-101) is a novel antibiotic agent and the first representative of a new class of antibacterials referred to as macrocycles, which are characterized by an 18-membered macrocyclic ester structure and inhibitory activity against bacterial RNA polymerase. Fidaxomicin has a narrow spectrum antibacterial profile and potent, bactericidal activity against *Clostridium difficile*. In addition, it is minimally absorbed (<1% of the drug is excreted in the urine) and exerts its activity in the gastrointestinal (GI) tract. Therefore, fidaxomicin has an optimal profile to treat *C. difficile* infection (CDI) (also known as *C. difficile*-associated disease or diarrhea [CDAD]), and has been developed by Optimer Pharmaceuticals, Inc. for the indication of the treatment of CDI and for reducing the risk of recurrence when used for treatment of initial CDI. This potential new therapeutic option addresses an urgent medical need, in particular the high level of CDI recurrences observed after treatment with vancomycin or metronidazole, the two most common treatments for CDI; approximately 20% to 30% of subjects who initially respond to metronidazole or vancomycin suffer a clinical recurrence following the cessation of therapy [Fekety, 1997; Aslam, 2005; Kuijper, 2007].

*C. difficile* is a spore-forming, anaerobic, gram-positive bacillus. CDI is caused by an overgrowth of *C. difficile* in the colon. Once overgrown, *C. difficile* produces harmful toxins that cause a variety of complications, including pseudomembranous colitis, toxic megacolon, perforations of the colon, sepsis and in some cases death, particularly if pseudomembranes are present [Kuijper, 2006]. Extrapolating from recent Centers for Disease Control and Prevention (CDC) data, the CDI incidence in the United States (US) is currently estimated at 700,000 cases per year. Most cases of CDI are associated with antibiotic use, which eradicates the beneficial bacteria found in the gut flora, allowing *C. difficile* to proliferate. The rising incidence of CDI has been attributed to the frequent prescription of broad-spectrum antibiotics to hospitalized patients [Wilcox, 1996; Fowler, 2007]. Although typically associated with hospitals and long-term care facilities, CDI has now also spread into the community. While not as common as hospital-acquired CDI, community-acquired CDI is afflicting otherwise healthy people with no recent history of hospital admission or antibiotic use [Mylonakis, 2001; Bartlett, 2006; Kuijper, 2006; Monaghan, 2008]. In addition, there is also growing concern that CDI is developing into a more serious disease as a result of the emergence of hypervirulent strains [Kuijper, 2006; Blanckaert, 2008; Calfee, 2008]. It is also of note that the elderly are disproportionately affected by CDI, probably due to increased exposure to health care facilities, pre-existing co-morbidities and weakened immune systems [Wistrom, 2001; Calfee, 2008]. Given that the proportion of the US population over 65 years old continues to rise, the impact of CDI is a major healthcare issue [Kuijper, 2006].

The results from non-clinical studies demonstrated that fidaxomicin is minimally absorbed, with <1% excreted in the urine following oral administration, with most of the dose remaining in the GI tract. In dogs dosed orally with radiolabeled fidaxomicin, over 99% of recovered radioactivity was passed out in the feces, predominantly as the parent compound, but with some converted to the metabolite OP-1118. These results were confirmed in clinical pharmacology studies in humans, where systemic and urinary concentrations of fidaxomicin and its main metabolite were found to be in the low ng/mL range. There was no evidence of

accumulation of fidaxomicin or OP-1118 following multiple dosing and systemic levels of fidaxomicin and OP-1118 were largely unchanged when fidaxomicin tablets were taken with a high-fat meal. As the large intestine is the site of antibacterial action, these pharmacokinetic (PK) properties are appropriate for the planned indication.

Fidaxomicin exposure levels in the µg/mL (plasma) or mg/g (feces) range were shown to be well tolerated in preclinical studies, as were its main metabolite OP-1118 and minor metabolite tiacumicin F at exposures in excess of those observed in humans. Evaluation of fidaxomicin in genotoxicity, safety pharmacology, general toxicology (up to 3 months in the dog) and reproductive toxicity studies also demonstrated the safety of fidaxomicin for human use.

Fidaxomicin demonstrated no clinically meaningful impact on the pharmacokinetics of drugs that were substrates for cytochrome P (CYP) enzymes (warfarin, CYP2C9; omeprazole, CYP2C19; midazolam, CYP3A4/5) or P-glycoprotein (P-gp) mediated efflux (digoxin) and no dose adjustment is considered necessary when these drugs are coadministered with fidaxomicin. While co-administration of fidaxomicin with the P-gp inhibitor cyclosporine increased plasma concentrations of fidaxomicin and its metabolite OP-1118, the plasma concentrations measured were still in the low ng/mL range and therefore this pharmacokinetic interaction is unlikely to be clinically meaningful. Thus, no dose adjustment is considered necessary for fidaxomicin when administered with P-gp inhibitors.

The target organism of fidaxomicin, *C. difficile*, is susceptible at concentrations far below the concentrations observed in the feces in subjects from the Phase 3 studies, with fecal concentrations of fidaxomicin being more than 5000 times the minimum inhibitory concentration $(MIC)_{90}$ in clinical isolates from both Phase 3 studies. Microbiology data from the *in vitro* profiling studies and from clinical isolates are consistent, and demonstrated a high degree of susceptibility among all *C. difficile* isolates (typical $MIC_{90}$ values ranged between 0.125 to 0.25 µg/mL). These data clearly provide the microbiological background information to explain the positive clinical response rates. Samples collected in the Phase 2 and 3 studies showed that *C. difficile* has a unimodal distribution of susceptibilities to fidaxomicin, consistent with those observed by other investigators for a naïve wild type population. A wide range of REA groups were observed, the most common group being the BI strain – a hypervirulent strain, with fidaxomicin showing activity against all these strain types, albeit with some differences in activity between strains. However, treatment outcomes did not appear to be dependent on MIC.

The efficacy of fidaxomicin was evaluated in one Phase 2A dose-finding study (OPT-80 Phase 2A) and two Phase 3 studies (101.1.C.003 and 101.1.C.004). The Phase 2A study demonstrated a dose-response and indicated that the most effective dose was 200 mg q12h, and this was the dose used in the subsequent Phase 3 studies. The Phase 3 studies were randomized, double-blind, comparator controlled (vancomycin 125 mg q6h) studies with participating sites from the US, Canada and Europe. Clinical cure rates at the end of therapy (EOT) visit demonstrated the non-inferiority of fidaxomicin compared with vancomycin, with the robustness of the results supported by a sensitivity analysis of the cure rate using a cure definition based solely on objective criteria. Recurrence rates among those subjects who were initially cured were statistically significantly lower in subjects treated with fidaxomicin.

Subjects treated with fidaxomicin also recurred later compared to subjects treated with vancomycin, with these differences being statistically significant as well as clinically relevant.

The advantage of fidaxomicin treatment over vancomycin treatment in higher global cure rates (a composite endpoint encompassing clinical cure and absence of recurrence) and lower recurrence rates was also consistent between treatments within study population subgroups and baseline characteristics, supporting the claim that fidaxomicin is indicated for the treatment of CDI and for reducing the risk of recurrence when used for treatment of initial CDI in all categories of subjects studied. As expected with compounds that have very low systemic bioavailability, fidaxomicin and vancomycin both showed a similarly low incidence of treatment-related adverse events (AEs) of approximately 10%. Most of the AEs reported during the course of the two large Phase 3 trials are compatible with the signs and symptoms of the disease; indeed, the most frequent observed events (diarrhea, nausea, vomiting, infection, pseudomembranous colitis, abdominal pain) are commonly seen in CDI subjects.

No signal of QT prolongation associated with fidaxomicin was identified in clinical or nonclinical studies and QTc parameters were similar between treatment groups, both in terms of the number of subjects with changes in QTc values meeting threshold levels and the mean and range of QTc interval changes from baseline to EOT. While some subjects in both groups did have abnormal QT prolongation (5.8% of subjects in the fidaxomicin group and 9.6% in the vancomycin group), it is considered that any observed QTc prolongation with fidaxomicin or vancomycin is likely to have resulted from fluid and electrolyte disturbances as a result of the diarrhea or to be related to underlying medications.

Approximately half of the subjects in the two Phase 3 trials were elderly, and the use of fidaxomicin treatment in subjects aged ≥65 years revealed no particular safety issues in this age group. No consistent trends were noted in plasma levels of fidaxomicin and OP-1118 in patients with impaired renal or hepatic function and therefore no dosage adjustment was considered necessary in these patients.

Thus, these data support the conclusion that fidaxomicin is effective and safe in treating CDI, and most notably has an advantage in reducing the risk of recurrence of infection. It therefore meets the need for a new treatment option in this therapeutic area and should be considered as first-line treatment for patients presenting with *C. difficile* infection.

# 2 INTRODUCTION

## 2.1 Disease Burden of CDI

*Clostridium difficile* is a spore-forming, anaerobic, gram-positive bacillus. *Clostridium difficile* infection (CDI) is caused by an overgrowth of *C. difficile* in the colon. Extrapolating from recent CDC data, the CDI incidence in the US is currently estimated at 700,000 cases per year. Most cases are associated with previous antibiotic use which eradicates or disrupts the gut flora, allowing *C. difficile* to proliferate, and not surprisingly, the rising incidence of CDI has been attributed to the frequent prescription of broad-spectrum antibiotics to hospitalized patients [Wilcox, 1996; Fowler, 2007]. Antibiotics commonly linked to CDI include cephalosporins, fluoroquinolones, clindamycin, ampicillin, and amoxicillin [Fekety, 1997; Wistrom, 2001], but almost any antibiotic can cause CDI. Proliferating *C. difficile* produce harmful toxins that can result in diarrhea, fever, leukocytosis, or lead to a variety of complications, including pseudomembranous colitis, toxic megacolon, perforations of the colon, and sepsis, with death occurring in 6% to 30% of subjects (the higher figure corresponding to when pseudomembranous colitis is present) [Kuijper, 2006].

Unquestionably, one of the most challenging complications of CDI is recurrences. Since *C. difficile* spores persist in the environment and in the stools of 10-40% of subjects with CDI [Kuijper, 2006], the slow resolution of the associated disruption of the gut ecology that fostered the initial development of CDI can facilitate re-infection with a new strain or relapse with the original strain, leading to recurrence of disease [Fekety, 1997; Barbut, 2000; Bartlett, 2002]. Up to 30% of CDI patients develop recurrence of infection within 2 months of initial diagnosis and the recurrence rate increases to 50-65% if the patient has had two or more episodes of prior CDI. Repeated antibiotic treatments can last months or years before the patient is cured [McFarland, 2005].

CDI is the most common cause of hospital-associated diarrhea in developed countries [Guerrant, 1990; Kelly, 1994; McFarland, 1995]. The disease accounts for approximately 15-35% of cases of antibiotic-associated diarrhea, and for 95% of cases of antibiotic-associated pseudomembranous colitis [Wistrom, 2001; Blanckaert, 2008; Calfee, 2008; Monaghan, 2008]. Although typically associated with hospitals, CDI is moving into the community. While not as common as hospital-acquired CDI, community-acquired CDI is afflicting otherwise healthy people with no recent history of hospital admission or antibiotic use [Mylonakis, 2001; Bartlett, 2006; Kuijper, 2006; Monaghan, 2008].

Recent reports suggest that CDI may be evolving into a more severe disease; outbreaks of CDI with increased morbidity and mortality have been described. These outbreaks were associated with the emergence and dissemination of hypervirulent strains, including the epidemic strain, characterized variously as restriction endonuclease analysis (REA) type BI, North America PFGE pulsotype 1 (NAP1), PCR ribotype 027, and toxinotype III, which was first identified in 2003 in Canada . This NAP1/BI/027 strain along with a few other emerging ribotype strains (e.g., 001, 078) are known to be resistant to the fluoroquinolone-class of antibiotics and may produce large amounts of toxins A and B (16-23 times greater than those produced by control strains from toxinotype 0, Warny, 2005) and the toxin itself may be more cytotoxic compared to historical isolates [Lanis et al, 2010]. The NAP1/BI/027 strain

also produces binary toxin [Cloud, 2007; Monaghan, 2008], however, the role of binary toxin in pathogenicity has not been identified. Infection by this organism has been associated with poor response to standard CDI therapy and clinical deterioration. To date, these hypervirulent strains of *C. difficile* have been identified in the US, Canada, and 16 European Union (EU) countries, as well as Switzerland [Kuijper, 2008]. There is increasing evidence that multiple mechanisms of genetic modification may be involved in continuing evolution of these hypervirulent strains [Stabler, 2010]. Further dissemination of hypervirulent strains throughout the US could lead to important changes in the epidemiology of CDI and demonstrates the need for ongoing clinical and molecular surveillance.

The elderly are disproportionately affected by CDI, probably due to increased exposure to health care facilities and weakened immune systems [Wistrom, 2001; Calfee, 2008]. Patients 65 years of age and older have an incidence of CDI that is nearly 5-fold higher than that of individuals 45-64 years of age, and 20-fold higher than that of individuals 15-45 years of age [Calfee, 2008]. Also, the death rate directly attributable to CDI is up to 15% in frail elderly individuals [Miller, 2010]. Given that the proportion of the US population over 65 years old continues to rise, the impact of CDI is a major healthcare issue [Kuijper, 2006].

CDI-associated mortality rates are rising [Redelings, 2007; Loo, 2005; Zilberberg, 2008], and CDI is occurring in populations previously considered low risk such as young, healthy persons living in the community and peripartum women [CDC, 2005; Rouphael, 2008]. Compared with prior observations [Gerding, 1995], clinical response and recurrence rates have become more problematic in recent studies [Musher, 2005; Pepin, 2005; Maroo, 2006; Pepin, 2007].

## 2.2 Current Treatments

The initial therapeutic approach to a diagnosed CDI case is to stop the causative antibiotic, but this is frequently not successful; symptoms may persist and even escalate, or continuation of the antibiotic might be necessary to treat the coexistent infection. In addition, as many as 42% of subjects develop CDI without a recent history of antibiotic use [Kelly, 2008; Calfee, 2008; Bauer, 2009a]. CDI can then be treated, as appropriate, with the two most commonly utilized therapies being oral vancomycin and metronidazole [Kuipers, 2008], although it should be noted that only vancomycin is approved for the treatment of CDI in the US.

Both agents are in most cases effective in treating CDI, but approximately 20% to 30% of subjects who initially respond to metronidazole or vancomycin suffer a clinical recurrence following the cessation of therapy [Fekety, 1997; Aslam, 2005; Kuijper, 2007]. This is probably due to disruption of the normal gut flora by these agents and persistence of the spore form of *C. difficile* [Kyne, 1999; Kyne, 2001]. In addition, metronidazole and vancomycin have several drawbacks with their use:

- Both metronidazole and vancomycin are themselves capable of inducing CDI [Fekety, 1997].
- The spectrum of activity of metronidazole is quite broad and includes the following: anaerobic gram-negative bacilli, including most *Bacteroides* species, *Fusobacterium*, and

*Veillonella*; and anaerobic gram-positive cocci including *Clostridium*, *Eubacterium*, and *Peptostreptococcus* [Finegold, 2004; Credito, 2004].

- Vancomycin's spectrum is also broad and includes almost all gram positive aerobes and anaerobes and even gram negative anaerobes such as *Bacteroides fragilis* at elevated concentrations ($MIC_{90}$, 128 µg/mL) [Finegold, 2004; Credito, 2004].
- Metronidazole is effective particularly in mild CDI cases, is less expensive than vancomycin and can be used either orally or intravenously (i.v.) and so is usually used as first-line treatment for subjects experiencing their first episode of CDI [ASHP position statement, 1998]. However, it is near-fully absorbed in the absence of diarrhea and oral absorption is associated with significant adverse effects, including nausea, zinc-like taste in the mouth, neuropathy, leucopenia, seizures and a toxic reaction to alcohol [Kelly, 1994; Fekety, 1984]. In addition, the current treatment regime is burdensome, comprising either 250 mg four times daily (q6h) or 500 mg three times daily (q8h) for 10 days or longer, which can lead to compliance issues. Furthermore, recent studies have shown that metronidazole treatment is associated with more failures and higher recurrence rates compared to vancomycin, especially in severely ill patients [Zar, 2007; Bartlett, 2008].
- There is an urgent need for new, innovative treatment in light of the evidence of emerging resistance to vancomycin among various important pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) [Pelaez, 2002; Freeman, 2005] and vancomycin is the only antibiotic available to treat certain serious life-threatening multi-drug resistant bacteria. Both vancomycin and metronidazole also encourage intestinal colonization and systemic infection with VRE [Al-Nassir, 2008]. Therefore, in an effort to slow the continuing emergence of MRSA, vancomycin-intermediate/resistant *S. aureus* (VISA/VRSA) and VRE, the medical community discourages the use of vancomycin except when strictly necessary [Hospital Infection Control Practices Advisory Committee (HICPAC) Recommendations, 1995; Watanabe, 1997; American Society of Health System Pharmacists (ASHP) position statement, 1998; Werner, 2008].

Other agents, such as fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin and bacitracin have all been reported as potential treatments for patients with CDI [Nelson, 2008], but none are approved in this indication. Also very few of the trials were well conducted or adequately controlled, and none of the tested agents offer a significant advantage over vancomycin or metronidazole. Anion exchange resins or cholestyramine can bind *C. difficile* toxins, but neither have been conclusively proved to be effective in the clinical setting [Kreutzer, 1978; Taylor, 1980; Ariano, 1990]. A non-pathogenic yeast, *Saccharomyces boulardii*, has been evaluated in conjunction with standard therapy for the treatment and prophylaxis of CDI and has shown some efficacy in patients with recurrent CDI. However, it has no benefit in patients in their first episode [McFarland, 1994; Surawicz, 2000]. A novel toxin binding polymer, tolevamer, has been tested in controlled clinical studies as a treatment for CDI. However, the development of this drug has been halted after two Phase 3 studies demonstrated tolevamer was less effective than oral vancomycin or metronidazole for the treatment of CDI [Louie, 2007].

Recurrent CDI is one of the biggest challenges of this illness. After successful initial treatment with either metronidazole or vancomycin, up to 30% of individuals have a recurrence of illness within 2 months post-therapy [Johnson, 1989], with the recurrence rates being even higher in the elderly. Retreatment with metronidazole or vancomycin resolves the condition in most patients but in about one third of patients the disease can recur again, with recurrence rate up to 65% in patients with two or more episodes of prior CDI. Recurrences can continue for months or even years, resulting in frequent hospitalizations and severe illness. Even deaths have been reported with relapses at approximately the same rate as for the primary event [McFarland, 2005].

The treatment of CDI recurrences is variable, with no single approach showing consistently successful results. Oral vancomycin is often used in repeated courses, as long tapering courses, or even as "pulsed" doses. Off-label use of rifaximin has also been tried, as has administration of intravenous immunoglobulins, but with limited success. The lack of effective treatments has pushed clinicians to treat refractory or recurrent *C. difficile* infection by such techniques as donated stool transplanted via colonoscopy [Yoon, 2010].

## 2.3 Rationale for a New Treatment

A new treatment for CDI is therefore urgently needed and it would be desirable to have the following characteristics:

- Safe and well-tolerated oral therapy
- Rapid resolution of CDI symptoms
- Non-absorbable, working directly in the GI tract
- Narrow spectrum, potent, bactericidal activity against *C. difficile*
- Minimum disruption of normal gut flora
- Low potential of resistance development
- A high rate of clinical cure equivalent or better than the currently available treatments
- Low frequency of clinical recurrence (significantly less than 20%)
- Low risk of inducing intestinal colonization with VRE
- Continued efficacy in the presence of concomitant antibacterials
- Convenient treatment regime, e.g., taken twice a day
- Long post-antibiotic effect

The clinical development program for fidaxomicin has successfully demonstrated these characteristics, as shown in Section 2.4.

## 2.4 Fidaxomicin

Fidaxomicin (also known as OPT-80 and PAR-101) is a novel antibiotic agent and the first representative of a new class of RNA polymerase inhibiting antibacterials called macrocycles. It has a narrow spectrum antibacterial profile and potent, bactericidal activity against *Clostridium difficile*. In addition, it is poorly absorbed and exerts its activity in the GI tract, thus giving it the optimal profile to treat CDI. Fidaxomicin has been developed as a therapeutic treatment for CDI by Optimer Pharmaceuticals, Inc. to provide an important therapeutic option to meet the urgent medical need for an alternative to the current treatment regimens of oral vancomycin or metronidazole (see Section 2.2). Fidaxomicin tablets will be marketed under the planned trade name Dificid™ in the US, pending approval of this name by the FDA.

Fidaxomicin, the drug substance, is derived as a fermentation product of *Dactylosporangium aurantiacum*. Fidaxomicin has a molecular weight of 1058 g/mol and a chemical formula of $C_{52}H_{74}Cl_2O_{18}$ (Figure 1). Its chemical name is Oxacyclooctadeca-3,5,9,13,15-pentaen-2-one, 3-[[[6-deoxy-4-*O*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*O*-methyl-β-D-mannopyranosyl]oxy]methyl]-12-[[6-deoxy-5-*C*-methyl-4-*O*-(2-methyl-1-oxopropyl)-β-D-*lyxo*-hexopyranosyl]oxy]-11-ethyl-8-hydroxy-18-[(1*R*)-1-hydroxyethyl]-9,13,15-trimethyl-, (3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*).

Fidaxomicin tablets are supplied as film-coated, white to off-white, modified capsule-shaped tablets containing 200 mg fidaxomicin, for oral administration. The recommended dose is one 200 mg tablet every 12 hours (400 mg per day) orally for 10 days.

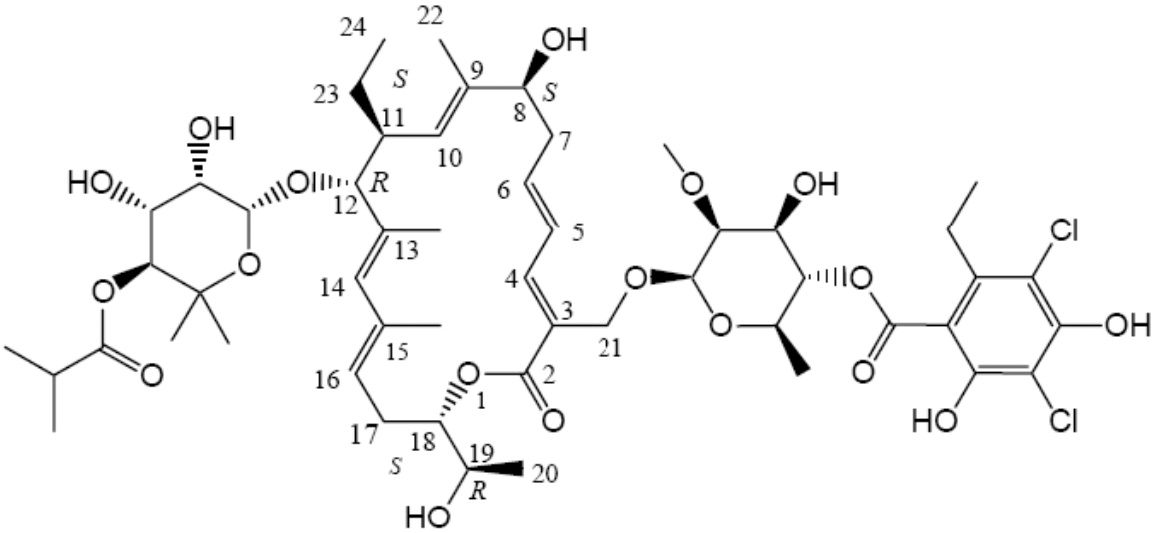


**Figure 1. Structure of Fidaxomicin**

The characteristics of fidaxomicin that make it a potentially excellent treatment for CDI are shown in Table 1.

**Table 1. Characteristics of Fidaxomicin for the Treatment of CDI**

| Desirable profile of a new antimicrobial agent for the treatment of CDI | Profile of Fidaxomicin |
|---|---|
| Safe and well-tolerated | The results of all the clinical studies indicated that fidaxomicin is safe and well tolerated. The safety profile of fidaxomicin was shown to be similar to vancomycin in the Phase 3 studies. |
| Rapid resolution of CDI symptoms | The median time to resolution of diarrhea in study 101.1.C.003 was 73 hours in the fidaxomicin group compared with 82 hours in the vancomycin group (mITT population). In study 101.1.C.004, the median time to resolution of diarrhea was 78 hours in the fidaxomicin group compared with 80 hours in the vancomycin group. |
| Non-absorbable, working directly in the GI tract | Non-clinical studies demonstrated that <1% of fidaxomicin was excreted in the urine following oral administration, with most of the dose remaining in the GI tract. In dogs dosed orally with radiolabeled fidaxomicin, over 99% of recovered radioactivity was passed out in the feces. These results were confirmed in clinical pharmacology studies in humans, where systemic and urinary concentrations of fidaxomicin and its main metabolite were found to be in the low ng/mL range. |
| Narrow spectrum of activity | Fidaxomicin displays a narrow spectrum of activity with very potent, bactericidal activity against *C. difficile*, moderate activity against other gram-positive organisms and no activity against gram-negative species and yeast. |
| Potent, bactericidal activity against *C. difficile* | The $MIC_{90}$ for fidaxomicin against *C. difficile* is 0.25 µg/mL, which is 4- and 8-fold more potent than metronidazole and vancomycin, respectively, against this species ($MIC_{90}$ values for metronidazole and vancomycin are 1 µg/mL and 2 µg/mL, respectively). |
| Minimal disruption of normal gut flora | In humans treated with fidaxomicin, fecal concentrations of *Bacteroides fragilis*, clostridial clusters IV and XIV, bifidobacteria, and other major components of the anaerobic gut flora were preserved while case-matched subjects treated with vancomycin showed a reduction in concentrations of these organisms and an increase in overgrowth of enterobacteria [Louie, 2009; Tannock 2010]. |
| Low potential of resistance development | The frequency of development of spontaneous resistance with fidaxomicin was very low ($<4 \times 10^{-9}$ at 8× MIC) and was similar to that seen with vancomycin and metronidazole. |
| A high rate of clinical cure equivalent or better than the currently available treatments | The rate of clinical cure for patients in the per protocol (PP) population of the Phase 3 studies treated with 200 mg q12h fidaxomicin tablets versus patients treated with 125 mg q6h vancomycin capsules was 92% and 90%, respectively, in study 101.1.C.003 and 92% and 91%, respectively, in study 101.1.C.004. |

| Desirable profile of a new antimicrobial agent for the treatment of CDI | Profile of Fidaxomicin |
|---|---|
| Low frequency of clinical recurrence | The rate of recurrence for patients in the modified Intention-To-Treat (mITT) population of the Phase 3 studies treated with 200 mg q12h fidaxomicin tablets versus patients treated with 125 mg q6h vancomycin capsules was 16% and 25%, respectively (p=0.008) in study 101.1.C.003 and 13% and 27%, respectively (p<0.001) in study 101.1.C.004. |
| Low risk of inducing intestinal colonization with VRE | Acquired VRE intestinal colonization among patients with CDI was lower following treatment with fidaxomicin (7%) than in patients treated with vancomycin (31%) in the 101.1.C.003 study [Nerandzic, 2009]. |
| Continued efficacy in the presence of concomitant antibacterials | Subgroup analyses of data from the Phase 3 studies showed that fidaxomicin had numerically higher cure rates compared to vancomycin in patients receiving concomitant antibacterials. |
| Convenient treatment regime | Fidaxomicin is dosed as 200 mg every12 hours compared to the recommended dosing regimen for vancomycin of 125 mg every 6 hours, thus potentially increasing compliance by making the dosing regimen easier for patients. |
| Long post-antibiotic effect | The post-antibiotic effect of fidaxomicin is exceptionally long, at approximately 10 hours, compared to less than 1 hour for vancomycin. |

## 2.5 Proposed Indication

Fidaxomicin is indicated for the treatment of *Clostridium difficile* infection (CDI), also known as *Clostridium difficile*-associated diarrhea (CDAD), and for reducing the risk of recurrence when used for treatment of initial CDI.

# 3 NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

## 3.1 Overview of Testing Strategy

The objectives of the nonclinical testing program were to determine the potential benefits of fidaxomicin in animal models of efficacy, to understand toxicological effects from excessive exposure to fidaxomicin, and to understand its pharmacokinetics (PK) and metabolism. The potential efficacy in CDI was assessed in the hamster model of infection, the earliest [Chang, 1978] and still the most common model for this disease. A standard battery of genotoxicity (bacterial reverse mutation, chromosomal aberration, and *in vivo* micronucleus), safety pharmacology (respiratory, cardiovascular including *in vitro* hERG, and central nervous system [CNS]), reproductive toxicity (fertility and embryofetal development) and general toxicity (acute and repeated dose to 3 months) studies were conducted to assess the safety of fidaxomicin. Pharmacokinetic parameters were assessed in the course of the toxicity studies, as well as in specific PK/ADME (absorption, distribution, metabolism and excretion) studies including a radiolabelled study in dogs that assessed the fate of oral fidaxomicin. *In vitro* metabolism and transport studies were conducted to characterize its metabolic profile in nonclinical species compared with humans, and to assess the potential for drug interactions with concomitantly administered drugs.

Fidaxomicin is a fermentation product with a high molecular weight (1058 g/mol) and low aqueous solubility (10-20 µg/mL at neutral pH). Absorption is consequently very low (absolute bioavailability in dogs <3%, even using vehicles to promote oral absorption), with this characteristic being appropriate for the indication of CDI, where the site of infection is the GI tract and thus high intestinal concentrations are desired but systemic exposure is unnecessary. These properties of low absorption and low solubility, though, added a challenge to the assessments of plasma PK and systemic toxicity in animal models. Multiple i.v.and oral vehicles were tested in efforts to enhance exposure to maximize the chance of achieving dose-limiting toxicity. Ultimately, an optimized i.v. vehicle was used in rats and rabbits, while a very high oral dose (9600 mg/day, ~1 g/kg) of the clinical tablet formulation was used in dog studies. The best i.v. vehicle identified and used in rats and rabbits during the course of the nonclinical program was 1% Solutol® HS15/phosphate buffered saline, which paired good tolerability with moderate solubility (dose solution concentration, 0.75 mg/mL). This typically allowed a maximal dose of 7.5 mg/kg based on the highest dosing volume generally recommended, 10 mL/kg, for rats and rabbits [Podolsky, 1999]. However, this i.v. formula was demonstrated to be poorly tolerated by dogs, therefore oral dosing, using the clinical tablet formulation, was used for the key studies in dogs. The highest oral dose used in dogs was 9600 mg fidaxomicin/dog/day (~1 g/kg/day). This dose was approximately 150 times the human daily dose by weight (based on a 60 kg human, 400 mg daily dose) and produced mean $C_{max}$ values measured in the 3 month dog study of 3010-4670 ng/mL across sexes and dosing days, which is over 300 times the human $C_{max}$ measured after a 200 mg dose.

## 3.2 ADME PK Studies

Very little fidaxomicin is absorbed after oral administration, with the majority of the drug remaining in the feces (in dogs administered a dose of radiolabelled fidaxomicin similar to

the human dose by weight, >99% of the recovered radiolabel was excreted in feces and 0.29% in urine, with no radioactivity being detected in the plasma). This is an important feature given the indication of CDI in which the infection is confined to the colon and a locally acting drug is desirable. The observation of a second plasma concentration peak in some dogs following oral dosing suggested the possibility of biliary excretion with hepatic recirculation, and a biliary cannulation study in dogs indicated that biliary excretion does occur, but accounts for <1% of the total drug administered based on quantitation of biliary excretion of fidaxomicin and its metabolite OP-1118.

The main metabolite of fidaxomicin is a hydrolysis product, OP-1118, or desisobutyryl fidaxomicin, which was observed in all species studied. The transformation is not CYP450 or nicotinamide adenine dinucleotide phosphate (NADPH) dependent, and is likely to be catalyzed via an esterase. A nonenzymatic acyl (isobutyryl) migration reaction occurs in aqueous systems including buffer resulting in the formation of minor metabolites, tiacumicin F and tiacumicin C (latter not detectable in human plasma; lower limit of quantification [LLOQ] = 0.2 ng/mL). Other minor pathways identified in vitro include monohydroxylation of fidaxomicin and OP-1118 and sulfation, and glucuronidation of OP-1118. However, few of these metabolites have been detected *in vivo*, and only in dog bile.

## 3.3 Drug-Drug Interactions

Fidaxomicin and its main metabolite OP-1118 were assessed for their ability to inhibit the activities of CYP450 isozymes in human liver microsomes at concentrations up to 10 µg/mL. These concentrations are far in excess of plasma concentrations measured in humans. At these concentrations, minimal inhibition was observed. Further escalation of OP-1118 concentrations showed that it was a time-dependent inhibitor of CYP3A4/5, although coadministration of fidaxomicin with midazolam, omeprazole, and warfarin (substrates of CYP3A4/5, CYP2C19, and CYP2C9) in a clinical drug interaction study (OPT-80-009) indicated no impact of fidaxomicin administration on the PK of these substrates. Fidaxomicin and OP-1118 were also tested for their ability to induce CYP450 expression in human hepatocytes at concentrations up to 10 µg/mL, based on the solubility of fidaxomicin. Neither compound induced CYP450 expression.

Fidaxomicin and OP-1118 were tested for P-gp interaction in Caco-2 cells. Both fidaxomicin and OP-1118 are substrates for efflux pumps, and this efflux is inhibited by cyclosporine A and ketoconazole, known inhibitors of P-gp. Fidaxomicin is also an inhibitor of P-gp, with an $IC_{50}$ (half maximal inhibitory concentration) of 2.59 µM (2.74 µg/mL), while OP-1118 is a much weaker inhibitor, causing only 43.1% inhibition at 125 µM (123 µg/mL), the highest dose tested based on cell tolerability. These findings are unlikely to have relevance systemically, due to the very low systemic concentrations of fidaxomicin. In addition, a clinical drug interaction study (OPT-80-008) with digoxin (P-gp substrate) showed no meaningful impact of fidaxomicin on the PK of digoxin. Although administration of cyclosporine (P-gp inhibitor; study OPT-80-007) did increase plasma concentrations of fidaxomicin and OP-1118, they remained in the ng/mL range, well below plasma concentrations observed at No Observed Effect Level (NOEL) doses in animals.

## 3.4 Toxicology

The toxicity of a single dose of fidaxomicin was evaluated in rats both orally, at doses up to 1000 mg/kg in a vehicle of Labrasol, and intravenously, at doses up to 200 mg/kg in an organic solvent vehicle (70% PEG-400, 20% ethanol, 10% dimethylacetamide). Oral administration of fidaxomicin produced no treatment related effects in male or female rats at doses of 1000 mg/kg (the highest dose tested). Fidaxomicin at 200 mg/kg via i.v. injection to rats in a solvent vehicle resulted in 50% mortality, likely as a result of poor solubility and precipitation of fidaxomicin in the vasculature at high plasma concentrations. Based on the lack of adverse findings in the lower dose groups, the No Observed Adverse Effect Level (NOAEL) for a single i.v. fidaxomicin dose in the rat is determined as 62.5 mg/kg. At this NOAEL dose, a peak plasma level of 3000-10,200 ng/mL fidaxomicin was noted at 30 minutes after dosing, which is at least 300-fold higher than the $C_{max}$ in humans.

The toxicity of fidaxomicin was also evaluated in a repeated-dose setting in rats and monkeys at oral doses up to 90 mg/kg for 28 days; and in dogs, at oral doses up to 9600 mg/day for 3 months (equivalent to 942 mg/kg/day in males and 1190 mg/kg/day in females, based on average body weights). Following 28 days of repeated dosing with up to 90 mg/kg fidaxomicin (in Labrasol®) in rats, there were no drug related deaths or effects on clinical observations, food consumption, hematology, clinical chemistry, urinalysis, ophthalmology, necropsy, organ weights, pathology or female body weights. Similar results were seen following 28 days of repeated dosing with up to 90 mg/kg fidaxomicin (in Labrasol®) in Cynomolgous monkeys. Thus the highest dose level (90 mg/kg/day nominal, actual 101.7 mg/kg/day) was considered to be the NOEL.

A key toxicity study, in terms of both dose and duration, was a 3-month repeated-dose study in dogs, dosed orally with fidaxomicin as the clinical tablet formulation at doses of up to 9600 mg/day. Based on average body weights, this corresponds to 942 mg/kg/day in males and 1190 mg/kg/day in females. Effects of fidaxomicin administration were limited to GI effects, with clinical observations of pale/yellow feces and white emesis. The latter occurred in all groups including capsule-only controls, but occurred most often in the highest dose fidaxomicin group. Based on the decrease in incidence over the course of the study, this was considered to be a localized effect caused by the high number of total capsules administered per day to the animals rather than an indicator of test article-related toxicity. Therefore the NOEL was determined to be 5 tablets/day (1.0 g/animal/day) and the NOAEL was 48 tablets/day. At the NOAEL dose, the lowest $C_{max}$ values measured at either time point for either sex were 3010 ng/mL for fidaxomicin and 361 ng/mL for the metabolite OP-1118, which is 305-fold and 21-fold higher than peak concentrations in healthy human volunteers at the therapeutic dose. The lowest $AUC_{0\text{-}tlast}$ values measured at either time point for either sex were 8160 ng-hr/mL for fidaxomicin and 945 ng-hr/mL, which is 117-fold and 7-fold higher than the human AUC at the therapeutic dose.

Comparative exposures for fidaxomicin and its main metabolite OP-1118 between species evaluated in the toxicity program are summarized in Table 2.

**Table 2. Summary of NOAEL and Plasma Concentrations in GLP Safety Pharmacology and Toxicology Studies Compared with Plasma Levels in Man**

| Study Type | NOAEL (Study Duration) | Plasma Exposure at NOAEL[a] | | | | Exposure Margin to Humans[b] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | FDX $C_{max}$, ng/mL | OP-1118 $C_{max}$, ng/mL | FDX $AUC_{0\text{-tlast}}$ ng-hr/mL | OP-1118 $AUC_{0\text{-tlast}}$ ng-hr/mL | FDX $C_{max}$ | OP-1118 $C_{max}$ | FDX $AUC_{0\text{-tlast}}$ | OP-1118 $AUC_{0\text{-tlast}}$ |
| Rat i.v., Fertility | 7.5 mg/kg/day (males: 28 days; females ≥1 days) | NC | ND | M = 3860<br>F = 2620 | ND | NC | ND | M = ×56<br>F = ×38 | ND |
| Rabbit i.v., Embryofetal dev. | 7.5 mg/kg/day (13 days) | NC | 54400 | 2280 | 21600 | NC | ×3091 | ×33 | ×159 |
| Dog oral, General toxicity | 9600 mg/day (3 months) | 3010 | 361 | 8160 | 945 | ×305 | ×21 | ×117 | ×7 |
| Monkey oral, General toxicity | 90 mg/kg/day (28 days) | 131 | ND | 288 | ND | ×13 | ND | ×4 | ND |
| Dog oral, Cardiovascular safety pharmacology | 9600 mg/day (single dose) | 4120 | 407 | 17000 | 1440 | ×417 | ×23 | ×245 | ×11 |
| Rat i.v., Resp. and CNS safety pharmacology | 7.5 mg/kg (single dose) | NC | 4350 | 4040 | 1380 | NC | ×247 | ×58 | ×10 |
| Human oral, Food effect | Therapeutic d ose: 200 mg | 9.88 | 17.6 | 69.5 | 136 | N/A | N/A | N/A | N/A |

F = female, FDX = fidaxomicin, GLP = Good Laboratory Practice, M = male, N/A = not applicable, NC = not calculated ($C_{max}$ of fidaxomicin not calculated for i.v. dosing), ND = not determined, NOAEL = no observed adverse effect level

[a]TK data reported as the lowest (mean) number across gender or day of dosing

[b]Margin calculated as PK metric in animals/PK metric in healthy humans (OPT-80-005, presented in the last row)

## 3.5 Genotoxicity

Genotoxicity of fidaxomicin was assessed in *in vitro* (bacterial reverse mutation and chromosomal aberration assays) and *in vivo* (rat micronucleus assay) studies, and additionally OP-1118 was evaluated for genotoxicity *in vitro* (bacterial reverse mutation and chromosomal aberration assays). Overall, the results from genotoxicity tests showed that fidaxomicin is not expected to be genotoxic in humans. Neither fidaxomicin nor OP-1118 were mutagenic in the bacterial reverse mutation assay. The metabolite OP-1118 did not show any clastogenic activity in cultured Chinese Hamster Ovary (CHO) cells. However, fidaxomicin was positive in cultured CHO cells at high concentrations, in the absence of metabolic activation only. Increased frequencies of cells with chromosomal aberrations were only observed at fidaxomicin concentrations ≥100 µg/mL, a concentration that greatly exceeds human exposure (approximately 10,000× $C_{max}$ in healthy volunteers at the 200 mg therapeutic dose, study OPT-80-005).

The clastogenic potential of fidaxomicin was tested *in vivo* by measuring the frequency of micronuclei in bone marrow red blood cells. In this study, fidaxomicin was administered to rats intravenously with the top dose selected as the maximum tolerated dose (75 mg/kg) in order to maximize systemic drug exposure and thus increase the chance of detecting fidaxomicin genotoxicity if present. There was no biologically significant increase in the frequency of cells with micronuclei even at these high fidaxomicin exposure levels. Thus the weight of evidence, based on the lack of clastogenic response *in vivo* at high exposure, support that fidaxomicin is not expected to be genotoxic in humans.

## 3.6 Reproductive Toxicity

The potential for reproductive toxicity was assessed in a fertility study in rats and embryo-fetal development studies in rats and rabbits. The maximum acceptable dosing volume of 10 mL/kg/day was generally used for rats and rabbits [Podolsky, 1999], although for the short-term dosing period used in the rat embryo-fetal development study, a dose volume of 20 mL/kg delivered as a slow bolus injection was used based on recommendation by Diehl and coworkers [Diehl, 2001]. This allowed a maximal daily dose of 15 mg/kg. Fidaxomicin at the highest dose tested in rats (15 mg/kg/day) and rabbits (7.5 mg/kg/day) had no maternal, reproductive or embryo-fetal developmental toxicity. Thus, the NOEL in these species was determined to be 15 mg/kg/day (nominal; actual, 12.6 mg/kg/day) in rats and 7.5 mg/kg/day (actual, 7.0 mg/kg/day) in rabbits.

## 3.7 Safety Pharmacology

Although plasma concentrations are low after oral dosing, the core battery of safety pharmacology studies (cardiovascular, respiratory, and CNS) were conducted for fidaxomicin. Specific safety pharmacology studies of other body systems were not conducted because general toxicity studies provided no evidence of secondary pharmacological effects on these systems, even at high multiples over the human exposure. To date, no secondary pharmacological targets for fidaxomicin have been revealed. Although transient hypotension was observed in an intravenous cardiac telemetry study in dogs immediately after dosing, the Solutol® HS 15 excipient was the probable cause of this finding [Lorenz, 1982].

A cardiovascular study of orally delivered fidaxomicin, also in dogs, at a dose which produced systemic levels in excess of those observed in the intravenous cardiovascular study, did not induce similar effects on hypotension. Studies to assess potential effects of fidaxomicin on the respiratory and CNS systems in rats were also negative for an effect. Neither fidaxomicin nor its main metabolite OP-1118 had an inhibitory effect on the hERG channel current ($IC_{50}$ greater than the highest doses tested; nominal, 10 µg/mL; actual, 7.85 µg/mL for fidaxomicin and 8.37 µg/mL for OP-1118).

## 3.8 Local Tolerance

Specific local tolerance studies were not conducted. However, as part of the nonclinical assessment of toxicity, a 3 month repeated dosing study in dogs was conducted in which dogs were administered up to 9600 mg/day of fidaxomicin, orally, which provided a considerably high level of exposure in the GI tract. Although some emesis and soft stools were observed at the highest doses, these were attributed to the very large doses delivered (5-7% of the daily food intake). They were not exacerbated with continued dosing and were not associated with changes in food consumption or weight gain between groups or with histological changes, and this indicates that high fecal levels of fidaxomicin up to mg/g levels are not associated with GI toxicity.

# 4 HUMAN PHARMACOKINETICS

Six clinical studies had a PK component to evaluate the plasma and fecal levels of fidaxomicin and its main metabolite OP-1118: two Phase 1 safety, tolerability and PK studies (OPT-80-1A-SD and OPT-80-1B-MD), a Phase 1 food effect study (OPT-80-005), a Phase 2A dose-finding study (OPT-80 Phase 2A), and two Phase 3 studies (101.1.C.003 and 101.1.C.004). In addition, three drug interaction studies were carried out to determine the effects of concomitant administration of cyclosporine on the PK of fidaxomicin (OPT-80-007), or conversely, the effect of concomitant administration of fidaxomicin on the PK of drugs metabolized by CYP450 (OPT-80-009) or effluxed by P-glycoprotein (OPT-80-008).

The results from these studies confirmed that systemic and urinary concentrations of fidaxomicin and its main metabolite are minimal, and that >90% of the drug was excreted in the feces. In addition, these studies demonstrated that fidaxomicin and OP-1118 do not notably accumulate following repeated dosing, and systemic levels of fidaxomicin and OP-1118 were largely unchanged when fidaxomicin tablets were taken with a high-fat meal. Also, no dose adjustment of fidaxomicin or concomitantly administered drugs is considered necessary for fidaxomicin when administered with P-gp inhibitors or when administered with drugs that are CYP or P-gp substrates.

## 4.1 Absorption

The physicochemical properties of fidaxomicin (Table 3) suggest it has poor permeability and poor solubility [Lipinski, 2001]. Based on a high molecular weight, a large number of hydrogen bond donors and acceptors, and poor aqueous solubility at pH values relevant to the GI tract (pH 7.0 or below), fidaxomicin was not expected to be well absorbed from the GI tract.

**Table 3. Physicochemical Properties of Fidaxomicin**

| Parameter | | Value | |
|---|---|---|---|
| Formula | | $C_{52}H_{74}Cl_2O_{18}$ | |
| Molecular Weight | | 1058.04 g/mol | |
| pKa (phenolic hydroxyl) | | 9.31 | |
| Log P | | 3.7 | |
| Solubility (1 hour) | | | |
| pH 4 | pH 6 | pH 7 | pH 8 |
| <0.06 µg/mL | <0.06 µg/mL | 18.35 µg/mL | 103.71 µg/mL |
| Number H-bond donors | | 7 (as –OH) | |
| Number H-bond acceptors | | 18 (as –O– or =O) | |

Upon administration of 200 mg fidaxomicin tablets to healthy subjects, consistently low plasma concentrations were seen. Plasma concentrations of fidaxomicin were observed as early as 15 minutes post-dose across the range of doses studied and were detectable (LLOQ 0.2 ng/mL) up to 24 hours post-dose. In healthy volunteers after a 200 mg dose (study OPT-80-005), the mean maximum plasma concentration ($C_{max}$) was 9.88 ng/mL and the area under the curve ($AUC_{0-t}$) was 69.5 ng-hr/mL (LLOQ 0.2 ng/mL). Systemic concentrations of fidaxomicin only marginally increased with increasing doses in this healthy volunteer study,

and at a dose of 400 mg (fasted), the $C_{max}$ of fidaxomicin was 10.6 ng/mL, with a corresponding $AUC_{0-t}$ of 81.2 ng-hr/mL. The plasma concentration-time curves of the metabolite OP-1118 generally mirrored those of the parent fidaxomicin, although the systemic exposure was approximately 2-fold greater (Table 4).

**Table 4. Summary of PK Parameters for Fidaxomicin Compared to OP-1118 (Representative Data from Fasted Healthy Volunteers Receiving 200 mg dose of Fidaxomicin in Study OPT-80-005)**

| Parameter | Units | Fidaxomicin Mean (SD) | OP-1118 Mean (SD) |
|---|---|---|---|
| $C_{max}$ | ng/mL | 9.88 (3.96) | 17.6 (4.73) |
| $T_{max}$[a] | hr | 1.75 (1.00, 8.00) | 1.75 (1.00, 8.00) |
| $AUC_{0-24}$ | ng-hr/mL | 69.4 (18.2) | 136 (26.1) |
| $AUC_{0-t}$ | ng-hr/mL | 69.5 (18.3) | 136 (26.2) |
| $t_{1/2}$ | hr | NC (NC) | 8.36 (2.03) |
| $\lambda_z$ | 1/hr | NC (NC) | 0.0868 (0.0242) |

[a]Median (min, max) presented for $T_{max}$, SD = standard deviation

In the Phase 3 studies, plasma concentrations were measured before and after dosing at the start and the end of therapy. Those samples collected within the specified 3-5 hour post-dose window are summarized. The range of concentrations varied greatly from subject to subject; however, there was a trend towards higher plasma levels in CDI subjects (2 to 6-fold for fidaxomicin and metabolite OP-1118) than those observed in healthy subjects. This is likely to be related to increased permeability of the inflamed GI tract in subjects with CDI, as recent studies have shown an association between intestinal inflammation and increased gut permeability [Beaurepaire, 2009]. The median concentrations in subjects with CDI were 15 ng/mL following the first dose, compared to the median concentration at the comparable timepoint in healthy volunteer studies which were 5 ng/mL after a 200 mg single dose. The highest plasma concentration measured in any subject was 197 ng/mL (Table 5).

**Table 5. Fidaxomicin Plasma Concentrations in Phase 3 Studies**

| Sample | Measurement | Study 101.1.C.003 | | Study 101.1.C.004 | |
|---|---|---|---|---|---|
| | | Fidaxomicin | OP-1118 | Fidaxomicin | OP-1118 |
| Day 1 (3-5 hours), ng/mL | N | 164 | 163 | 157 | 153 |
| | Mean (SD) | 22.78 (26.49) | 43.07 (51.34) | 22.95 (26.85) | 46.01 (49.53) |
| | Range | [0.4, 185] | [0.3, 363] | [0.4, 197.0] | [0.5, 343.0] |
| Day 10 (3-5 hours), ng/mL | N | 59 | 59 | 59 | 60 |
| | Mean (SD) | 26.39 (31.01) | 70.30 (80.45) | 29.66 (38.03) | 98.64 (171.63) |
| | Range | [1.9, 191] | [3.0, 370] | [0.3, 187.0] | [1.1, 871.0] |

No evidence of notable accumulation of fidaxomicin was observed, based on the similarity between the Day 1 and Day 10 plasma levels across both Phase 3 studies (Table 5). Fidaxomicin levels were similar at the start and EOT, and in subjects with CDI the mean plasma concentrations of the metabolite OP-1118 increased approximately 2-fold between Day 1 and EOT. The median values were similar and the standard deviation around the EOT mean was high, reflecting the contribution of a few high values to the higher mean at EOT. As noted with healthy volunteers, the plasma concentration of the metabolite OP-1118

generally mirrored that of the parent fidaxomicin, although the systemic exposure was approximately 2-fold greater. The very limited absorption of the drug is also fully supported by pre-clinical animal studies (see Section 3).

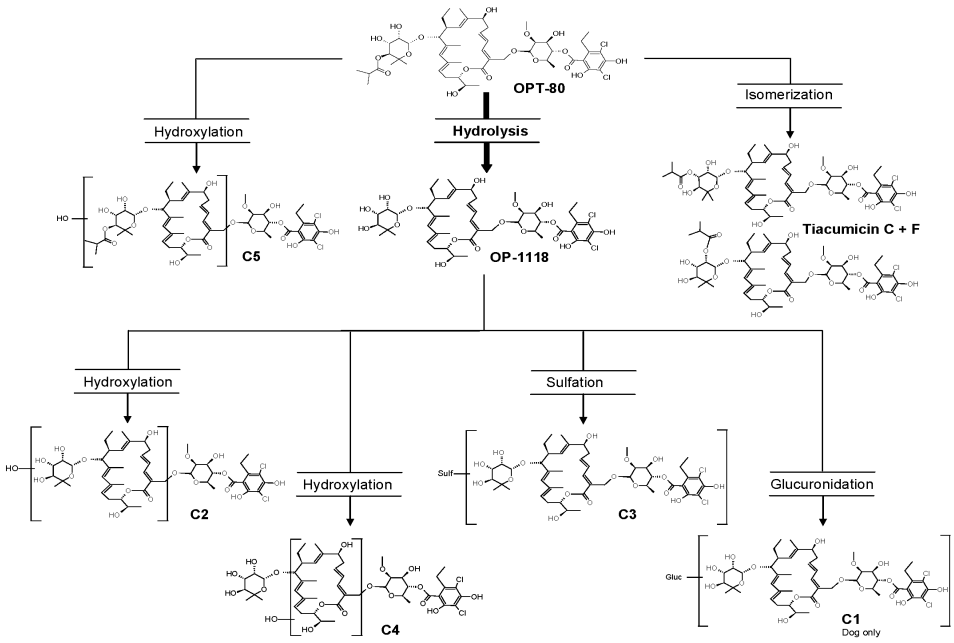
## 4.2 Distribution

Fidaxomicin is minimally absorbed after oral administration with <1% excreted in the urine and with most of the fidaxomicin remaining in the feces, thus the GI tract is the main site of exposure. Fidaxomicin has not been administered to humans intravenously as its low aqueous solubility makes it extremely difficult to solubilize in a formulation acceptable for human use, and plasma concentrations are not important for its efficacy. However, in non-clinical studies, systemic exposure was enhanced by intravenous administration of high volumes (10 mL/kg) of dilute solution, to allow the evaluation of potential systemic toxicity (see Section 3). Pharmacokinetic analyses conducted during these studies indicated that the volume of distribution at steady state was less than or equal to body water, suggesting that fidaxomicin does not extensively distribute away from body water.

## 4.3 Metabolism

The metabolism of fidaxomicin has been studied in multiple *in vitro* systems, including human intestinal and liver microsomes, human hepatocytes, and human plasma (see Section 3). Fidaxomicin is converted to OP-1118, the primary and active metabolite, by hydrolysis of the isobutyl ester located at the 4" position. This reaction has been shown to occur *in vitro* in human liver and intestinal microsomes and human plasma. This hydrolysis reaction appears to be the main route of metabolism of fidaxomicin. Additionally, *in vitro*, fidaxomicin has been shown to non-enzymatically isomerize to Tiacumicin C and Tiacumicin F. Finally, fidaxomicin and OP-1118 are 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. A summary of *in vitro* biotransformation pathways for fidaxomicin is shown in Figure 2.

Since total fecal recovery in a Phase 1 study was shown to be over 92% (when accounting for both fidaxomicin and its major metabolite, OP-1118), the contribution of oxidative and conjugative pathways in the elimination of fidaxomicin is considered to be minor. Plasma, urine, and fecal samples from healthy volunteers were reassayed via liquid chromatography mass spectrometry (LC-MS) methods for the presence of additional metabolites, and no metabolites other than OP-1118 were detectable *in vivo*, although following reanalysis using a method with picomolar detection, a very small amount ($C_{max}$ less than 1 ng/mL) of tiacumicin F was measurable in human plasma.




NOTE: C1 glucuronide metabolite was noted in dog only

**Figure 2. Summary of Fidaxomicin and OP-1118 *In Vitro* Biotransformation**

The hydrolysis of fidaxomicin is likely to be catalyzed by esterase enzymes because this reaction is time-dependent and is also dependent on the presence of enzymes (e.g., human liver microsomes) and is not dependent on NADPH. The type of esterases (e.g., Esterase A, B, and/or C) capable of this biotransformation have not been identified.

OP-1118 was characterized *in vitro* and quantified as part of the PK analyses of animal and human plasma and fecal samples. OP-1118 was also shown to have antimicrobial activity against *C. difficile*, with a higher $MIC_{90}$ (0.25 µg/mL for fidaxomicin versus 8 µg/mL for OP-1118) (see Section 5). The metabolite was shown to be present at higher levels than the parent compound in human plasma, and in very high levels in the feces. Only the levels in feces are relevant to efficacy since the drug is minimally absorbed and the site of action is the GI tract.

## 4.4 Excretion

In studies in healthy volunteers, both fidaxomicin and OP-1118 were detectable in the feces as early as the first stool passed (within hours following dosing). Peak concentrations in the feces were generally observed at least 24 hours after oral dosing and concentrations remained detectable in the feces for up to 5 days. The concentrations of fidaxomicin in the feces increased with increasing dose, with the mean concentrations in excess of the MIC for fidaxomicin versus *C. difficile* (OPT-80 1B-MD). Total fecal recovery in the OPT-80 1A-SD study was over 92% when accounting for both fidaxomicin and its major metabolite, OP-1118. The presence of high levels of fidaxomicin in the feces is consistent with the therapeutic properties required for treatment of CDI, which is a local infection of the GI tract.

Similar findings were seen in subjects with CDI, with the concentrations of fidaxomicin in the feces increasing with increasing dose, and the mean and minimum concentrations in excess of the MIC for fidaxomicin on *C. difficile* (OPT-80 Phase 2A). In the Phase 3 studies 101.1.C.003 and 101.1.C.004, fecal samples were categorized by whether the subject was cured or failed treatment, with the mean fecal concentrations at the end of therapy being presented for each category in Table 6. Although in the first pivotal study (101.1.C.003) there were lower mean fecal concentrations in the global failures compared to global cures, this finding was not confirmed in the second study (101.1.C.004). In both cases the standard deviation was very wide, with a large degree of overlap between the values for clinical cures and clinical failures. Thus fecal concentration, at the high fecal concentrations observed in these studies, did not appear to be predictive of outcome.

**Table 6. Mean (Range) Fidaxomicin and OP-1118 Fecal Concentrations in Phase 3 Studies**

| | Study 101.1.C.003 | | Study 101.1.C.004 | |
|---|---|---|---|---|
| | **Fidaxomicin** | **OP-1118** | **Fidaxomicin** | **OP-1118** |
| Fecal (Day 10), µg/g: Global cure | 1298.07 (31.7, 4640.0) | 894.08 (93.7, 4170.0) | 1636.17 (182.0, 4790.0) | 872.88 (142.0, 2440.0) |
| Fecal (Day 10), µg/g: Global failure | 906.17 (43.0, 1990.0) | 427.44 (63.4, 1350.0) | 1443.59 (5.0, 7630.0) | 704.12 (99.3, 2290.0) |

Fidaxomicin has not been detected in the urine in any of the samples taken for analysis (study OPT-80-005). While low levels of OP-1118 were detected in the urine (less than 22 ng/mL), urinary excretion represented a very small percent (<1%) of the dose.

Many subjects in the food effect study had a small secondary concentration peak approximately 6-8 hours after dosing, which may indicate biliary excretion and hepatic recirculation. A biliary cannulation study in dogs (see Section 3) indicated that biliary excretion does occur, however the magnitude is small (<1% of the administered dose was excreted in the bile). Combined with the very low plasma concentrations observed in humans, the magnitude of potential biliary excretion is likely to be minimal.

## 4.5 PK in Subpopulations

### 4.5.1 Intrinsic Factors

Subgroup analyses by age, gender, and degree of renal and hepatic impairment were carried out on the data from the Phase 3 studies 101.1.C.003 and 101.1.C.004. Plasma concentrations were not affected by gender or by degree of renal impairment. To assess the impact of renal function on fidaxomicin pharmacokinetics, plasma concentrations of fidaxomicin and OP-1118 were analyzed by baseline creatinine clearance (eCCL; Cockcroft-Gault method) (Table 7). Although no formal statistical analysis has been carried out, no consistent trends with respect to renal function were noted in plasma levels of fidaxomicin and OP-1118 and therefore no dosage adjustment is considered necessary in these patients.

**Table 7. Fidaxomicin Plasma Concentrations in Subjects with Renal Impairment (Pooled Phase 3 Studies)**

| Sample | Measurement | Fidaxomicin | OP-1118 |
|---|---|---|---|
| **Mild Renal Impairment: eCCL 51-79 mL/min** | | | |
| Plasma (Day 1, 3-5 hours post-dose), ng/mL | N >LLOQ<br>Mean (SD)<br>Median<br>Range | 79<br>27.6 (31.1)<br>18.3<br>[1.64, 185] | 83<br>52.2 (51.9)<br>31.7<br>[2.15, 321] |
| Plasma (Day 10, 3-5 hours post-dose), ng/mL | N >LLOQ<br>Mean (SD)<br>Median<br>Range | 34<br>34.9 (40.5)<br>21.9<br>[0.305, 191] | 31<br>119 (170)<br>70.5<br>[1.09, 871] |
| **Moderate Renal Impairment: eCCL 31-50 mL/min** | | | |
| Plasma (Day 1, 3-5 hours post-dose), ng/mL | N >LLOQ<br>Mean (SD)<br>Median<br>Range | 32<br>32.6 (26.8)<br>24.5<br>[1.10, 102] | 32<br>68.0 (66.0)<br>52.5<br>[2.01, 363] |
| Plasma (Day 10, 3-5 hours post-dose), ng/mL | N >LLOQ<br>Mean (SD)<br>Median<br>Range | 9<br>31.7 (31.0)<br>23.4<br>[6.2, 97.6] | 11<br>104 (85.3)<br>50.5<br>[17.6, 248] |
| **Severe Renal Impairment: eCCL ≤30 mL/min** | | | |
| Plasma (Day 1, 3-5 hours post-dose), ng/mL | N >LLOQ<br>Mean (SD)<br>Median<br>Range | 34<br>36.7 (39.2)<br>27.2<br>[1.41, 197] | 34<br>76.8 (68.2)<br>63.1<br>[5.35, 343] |
| Plasma (Day 10, 3-5 hours post-dose), ng/mL | N >LLOQ<br>Mean (SD)<br>Median<br>Range | 6<br>32.6 (20.5)<br>30.7<br>[7.09, 56.5] | 6<br>83.5 (50.7)<br>84.9<br>[8.14, 149] |

Although no formal statistical analysis has been carried out, plasma levels appeared to be slightly elevated in the elderly (age ≥65 years) (Table 8). However, values were still in the low ng/mL range and this slight increase in plasma levels is not thought to be clinically meaningful. Consequently no dose adjustment is considered necessary in the elderly.

**Table 8. Fidaxomicin Plasma Concentrations in Young and Elderly (pooled Phase 3 Studies)**

| Sample | Measurement | Age <65 years | | Age ≥65 years | |
|---|---|---|---|---|---|
| | | Fidaxomicin | OP-1118 | Fidaxomicin | OP-1118 |
| Plasma (Day 1, 3-5 hours post-dose), ng/mL | N >LLOQ<br>Mean (SD)<br>Median<br>Range | 167<br>15.2 (20.7)<br>8.76<br>[0.364, 197] | 165<br>29.4 (33.6)<br>15.5<br>[0.283, 173] | 145<br>31.6 (29.9)<br>24.3<br>[0.898, 185] | 151<br>61.0 (59.8)<br>46.5<br>[0.982, 363] |
| Plasma (Day 10, 3-5 hours post-dose), ng/mL | N >LLOQ<br>Mean (SD)<br>Median<br>Range | 42<br>18.0 (19.4)<br>9.22<br>[1.90, 86.9] | 45<br>56.4 (130)<br>19.4<br>[3.01, 871] | 58<br>36.2 (39.0)<br>22.2<br>[0.305, 191] | 58<br>108 (129)<br>68.7<br>[1.09, 829] |

No special subgroup analyses by race were conducted since the majority of subjects were White; however, there is no evidence to suggest that subjects of different ethnicities would respond differently to treatment since infection with *C. difficile* has the same clinical profile, regardless of race.

In the two Phase 3 clinical studies in subjects with CDI, PK data were available in 12 subjects with hepatic impairment, as determined by the finding of at least one liver function test at baseline of toxicity Grade 2 or higher. PK data from these subjects at Day 1 and Day 10, 3-5 hours post dose, show mean fidaxomicin and OP-1118 plasma levels were 1.3 to 2.5 times higher than those observed in subjects with liver function test results of toxicity Grade 1 or lower, but they were still in the low ng/mL range (Table 9). The observed increase in plasma levels appears not to be clinically meaningful, and no dosage adjustment is considered necessary in patients with hepatic impairment.

**Table 9. Fidaxomicin Plasma Concentrations in Subjects by Degree of Hepatic Impairment (Pooled Phase 3 Studies)**

| Sample | Measurement | Baseline Toxicity Grade ≤1 | | Baseline Toxicity Grade ≥2 | |
|---|---|---|---|---|---|
| | | Fidaxomicin | OP-1118 | Fidaxomicin | OP-1118 |
| Plasma (Day 1, 3-5 hours post-dose), ng/mL | N | 301 | 297 | 12 | 11 |
| | Mean (SD) | 21.6 (22.6) | 42.0 (46.5) | 39.0 (57.9) | 95.5 (101) |
| | Median | 13.6 | 26.2 | 17.9 | 89.1 |
| | Range | [0.669, 145] | [0.982, 363] | [0.364, 185] | [0.283, 321] |
| Plasma (Day 10, 3-5 hours post-dose), ng/mL | N | 114 | 115 | 4 | 4 |
| | Mean (SD) | 27.3 (34.9) | 79.2 (133) | 34.7 (27.9) | 200 (141) |
| | Median | 15.4 | 39.9 | 24.3 | 195 |
| | Range | [0.305, 191] | [1.09, 871] | [14.2, 75.9] | [40.7, 370] |

### 4.5.2 Food Effects

The pharmacokinetics following oral dosing in a fed or fasted state were compared. The presence of a high fat meal appeared to have a minimal effect on $C_{max}$ of both fidaxomicin and OP-1118 ($C_{max}$ was reduced by 21.5% and 33.4%, respectively, for fidaxomicin and OP-1118 in the fed state). However, the relative bioavailability, as estimated by a comparison of the $AUC_{0-\infty}$, remained unchanged. The small difference in $C_{max}$, particularly given the very low plasma concentrations observed after oral administration, is not clinically relevant because systemic exposure is not relevant to the efficacy in CDI, which is confined to the GI tract. As such, no limitation on the administration of fidaxomicin with or without food is considered necessary.

### 4.5.3 Drug-Drug Interaction Studies

Fidaxomicin is poorly absorbed and is metabolized primarily by esterase dependent metabolism to OP-1118 (see Section 4.3). Drug interactions are potentially possible with drugs that could increase absorption of fidaxomicin and inhibit its systemic clearance. However, there are no known drugs on the market that cause clinically relevant drug interactions by inhibiting esterases. Therefore, drug interactions by way of inhibition of metabolism of fidaxomicin are not anticipated.

Fidaxomicin and OP-1118 are weak inhibitors of CYP enzymes. However, the mean plasma concentrations of fidaxomicin measured in studies 101.1.C.003 and 101.1.C.004 are more than 200-fold below the half maximal inhibitory concentration ($IC_{50}$) of CYP2C9, the only isozyme for which fidaxomicin has a measurable $IC_{50}$; thus fidaxomicin is unlikely to cause systemic CYP mediated drug interactions. Similarly, OP-1118 is also not likely to cause systemic CYP-inhibition mediated drug interactions because it did not directly inhibit any of the CYP enzymes *in vitro* at concentrations up to 10 µg/mL. However, a drug-drug interaction study (OPT-80-009) was carried out using CYP substrates midazolam, omeprazole, and warfarin to investigate any potential interactions in more detail. The results of this study indicated that coadministration with fidaxomicin (q12h, with fidaxomicin dose co-administered with the CYP substrate cocktail) did not result in a statistically significant change in the PK of marker substrate drugs for CYP2C9 (warfarin), CYP2C19 (omeprazole) and CYP3A4/5 (midazolam).

Fidaxomicin and OP-1118 are substrates for P-gp, therefore, it is possible that absorption of fidaxomicin is primarily restricted by P-gp, and inhibition of this efflux transporter could increase systemic exposure to fidaxomicin and its metabolites. A drug-drug interaction study (OPT-80-007) in which fidaxomicin was administered with or without the P-gp inhibitor cyclosporine (given 1 hour prior to fidaxomicin) demonstrated that administration with cyclosporine could increase both the $C_{max}$ and AUC of fidaxomicin and its metabolite OP-1118. Even in the presence of cyclosporine, however, plasma concentrations remained in the low ng/mL range (mean $C_{max}$ for fidaxomicin increased from 5.20 to 26.9 ng/mL, while mean $C_{max}$ for OP-1118 increased from 12.0 to 132 ng/mL) and fidaxomicin remained well tolerated. Thus it was concluded that this PK interaction is not likely to be clinically meaningful, and no fidaxomicin dose adjustment is necessary when it is concomitantly administered with P-gp inhibitors. It is noteworthy that cyclosporine is a pleiotropic inhibitor of multiple efflux drug transporters and CYP3A4/5. Therefore, the magnitude of interaction with cyclosporine likely represents the largest possible increase in fidaxomicin exposure in presence of concomitantly administered inhibitors of drug transporters.

Fidaxomicin is also an inhibitor of P-gp, which plays a role in restricting digoxin absorption in the GI tract. As a result, a drug-drug interaction study (OPT-80-008) examined the impact of fidaxomicin administration (q12h, with most recent dose given 1 hour prior to digoxin tablets) on the PK of the P-gp substrate digoxin. This study concluded that there is no clinically meaningful PK interaction between digoxin and fidaxomicin.

Thus, in summary, fidaxomicin demonstrated no clinically meaningful impact on the PK of drugs that were substrates for CYP enzymes (warfarin, CYP2C9; omeprazole, CYP2C19;

midazolam, CYP3A4/5) or P-gp-mediated efflux (digoxin). While a P-gp inhibitor, cyclosporine, increased plasma concentrations of fidaxomicin and its metabolite OP-1118, the plasma concentrations measured were still in the low ng/mL range and thus this interaction is unlikely to be clinically meaningful. Therefore no dose adjustment is considered necessary for fidaxomicin when administered with P-gp inhibitors; likewise, no dose adjustment is considered necessary for drugs that are CYP or P-gp substrates when they are coadministered with fidaxomicin.

# 5 MICROBIOLOGY

*In vitro* microbiology studies were carried out to characterize the mode of action and susceptibility data for fidaxomicin and its metabolite OP-1118. The microbiology studies confirmed fidaxomicin's narrow spectrum antibacterial profile and potent, bactericidal activity against *C. difficile*.

## 5.1 Mode of Action

Fidaxomicin is bactericidal and acts via inhibition of RNA synthesis by bacterial RNA polymerase at a distinct site from that of rifamycins. Based on research with a related compound, lipiarmycin [Talpaert, 1975; Sergio, 1975], it is postulated that its antibacterial activity is mediated through inhibition of transcriptional initiation. Transcriptional inhibition by fidaxomicin was confirmed using RNA polymerase purified from *C. difficile* and the related *Clostridium acetobutylicum* and measuring the synthesis of acid-precipitable RNA using $^{3}$H-UTP. Inhibition of the clostridial RNA polymerase occurs at a concentration 20-fold lower than that for the *E. coli* enzyme (1 µM vs. 19.4 µM), partly explaining the species specificity of fidaxomicin activity. Mechanistic studies have shown that fidaxomicin inhibits RNA polymerase at a step following binding of the enzyme to the DNA template, but prior to the formation of the processive "open" RNA polymerase-DNA complex, in which the DNA template has begun to melt. These mechanistic studies, along with fidaxomicin's lack of cross-resistance with other classes of antimicrobials (see Section 5.3), and its synergy with rifampin and rifaximin, indicate that the mechanism is distinct from that of the rifamycins, another known class of RNA polymerase inhibitors.

## 5.2 Antimicrobial Activity

### 5.2.1 *In Vitro* Susceptibility

The antibacterial activity of fidaxomicin versus *C. difficile* has been tested in a number of independent laboratories. Typical $MIC_{90}$ values for this organism, tested via the Clinical and Laboratory Standards Institute (CLSI) methodology ranged between 0.125 to 0.25 µg/mL. Susceptibility testing of isolates from Phase 2 and 3 trials that included over 800 clinical isolates encompassing multiple strain types (Table 10) indicated an $MIC_{90}$ of 0.25.

**Table 10. Fidaxomicin Susceptibilities (µg/mL) Versus *C. difficile*, Tested Via CLSI Reference Methods**

| Organism (N) | Reference | MIC Range | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|
| *Clostridium difficile* (23) | Finegold, 2004 | 0.06-2 | 0.12 | 0.25 |
| *Clostridium difficile* (21) | Credito, 2004 | ≤0.016-0.125 | ≤0.016 | 0.125 |
| *Clostridium difficile* (110) | Hecht, 2007 | 0.015-0.25 | 0.125 | 0.125 |
| *Clostridium difficile* (208) | Karlowsky, 2008 | 0.06-1 | 0.25 | 0.5 |
| *Clostridium difficile* (38) | Citron, 2009 (Phase 2A) | ≤0.008–0.25 | NC | 0.125 |
| *Clostridium difficile* (415) | Phase 3 CSR (101.1.C.003) | 0.003-0.5 | 0.125 | 0.25 |
| *Clostridium difficile* (376) | Phase 3 CSR (101.1.C.004) | 0.007-1 | 0.125 | 0.25 |

NC = not calculated

The MIC distributions in these studies were unimodal, which is expected for a treatment-naïve wild type population. REA typing results from the Phase 3 studies showed that, while there were differences between strain types in terms of susceptibilities to fidaxomicin, all strains had $MIC_{90}$ values below 1 µg/mL. Assessment of these strain types represented in the Phase 3 studies and the susceptibilities by strain are presented in Table 11 for the mITT population. Although these were typed via the REA typing method, alignments of the REA groups with the ribotypes of recent outbreak strains are presented in the table, based on typing method alignments published by others [Killgore, 2008]. Susceptibilities toward fidaxomicin were generally similar between strains overall, although the BI group tended to have the highest MIC metrics toward all antibiotics tested as noted previously [Sears, 2008; Citron, 2008]. No differences were seen in susceptibility from different geographic locations.

**Table 11. Strain Types Represented in Pooled Phase 3 Studies and their Susceptibilities (mITT population: MIC values in µg/mL)**

| REA Group | N | Antibiotic | Geometric Mean | Range (min-max) | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|---|---|
| BI Group (ribotype 027) | 283 | Fidaxomicin | 0.18 | 0.015-1.0 | 0.25 | 0.5 |
| | | Vancomycin | 1.03 | 0.5-8.0 | 1.0 | 2.0 |
| | | Metronidazole | 0.87 | 0.125-4.0 | 1.0 | 2.0 |
| | | Rifaximin | 0.05 | 0.003-257.0 | 0.015 | 257.0 |
| BK Group (ribotype 078) | 15 | Fidaxomicin | 0.09 | 0.03-0.25 | 0.125 | 0.125 |
| | | Vancomycin | 1.10 | 0.5-2.0 | 1.0 | 2.0 |
| | | Metronidazole | 0.44 | 0.25-2.0 | 0.5 | 1.0 |
| | | Rifaximin | 0.02 | 0.003-257.0 | 0.015 | 0.015 |
| CF Group | 9 | Fidaxomicin | 0.09 | 0.015-0.25 | 0.125 | 0.25 |
| | | Vancomycin | 0.86 | 0.5-2.0 | 1.0 | 2.0 |
| | | Metronidazole | 0.31 | 0.05-1.0 | 0.5 | 1.0 |
| | | Rifaximin | 0.04 | 0.008-257.0 | 0.015 | 257.0 |
| DH Group | 6 | Fidaxomicin | 0.22 | 0.125-0.25 | 0.25 | 0.25 |
| | | Vancomycin | 1.00 | 1.0-1.0 | 1.0 | 1.0 |
| | | Metronidazole | 0.50 | 0.25-1.0 | 0.5 | 1.0 |
| | | Rifaximin | 0.01 | 0.003-0.015 | 0.009 | 0.015 |
| G Group | 58 | Fidaxomicin | 0.09 | 0.015-0.25 | 0.125 | 0.25 |
| | | Vancomycin | 0.96 | 0.5-2.0 | 1.0 | 2.0 |
| | | Metronidazole | 0.32 | 0.05-1.0 | 0.25 | 0.5 |
| | | Rifaximin | 0.01 | 0.003-0.125 | 0.008 | 0.015 |
| J Group (ribotype 001) | 47 | Fidaxomicin | 0.02 | 0.007-0.125 | 0.02 | 0.125 |
| | | Vancomycin | 1.05 | 0.5-4.0 | 1.0 | 4.0 |
| | | Metronidazole | 0.44 | 0.05-2.0 | 0.5 | 1.0 |
| | | Rifaximin | 0.02 | 0.003-257.0 | 0.008 | 0.06 |
| K Group | 17 | Fidaxomicin | 0.07 | 0.015-0.25 | 0.06 | 0.125 |
| | | Vancomycin | 1.09 | 0.5-4.0 | 1.0 | 2.0 |
| | | Metronidazole | 0.69 | 0.125-4.0 | 0.5 | 4.0 |
| | | Rifaximin | 0.09 | 0.004-257.0 | 0.015 | 257.0 |
| L Group | 1 | Fidaxomicin | 0.13 | 0.125-0.125 | 0.125 | 0.125 |
| | | Vancomycin | 0.50 | 0.5-0.5 | 0.5 | 0.5 |
| | | Metronidazole | 0.50 | 0.5-0.5 | 0.5 | 0.5 |
| | | Rifaximin | 0.13 | 0.125-0.125 | 0.125 | 0.125 |
| Non-Sp REA | 277 | Fidaxomicin | 0.08 | 0.003-0.5 | 0.06 | 0.125 |
| | | Vancomycin | 0.94 | 0.25-4.0 | 1.0 | 2.0 |
| | | Metronidazole | 0.33 | 0.02-2.0 | 0.25 | 0.5 |
| | | Rifaximin | 0.02 | 0.003-257.0 | 0.008 | 0.125 |
| Y Group | 79 | Fidaxomicin | 0.10 | 0.015-0.5 | 0.125 | 0.25 |
| | | Vancomycin | 0.84 | 0.25-2.0 | 1.0 | 2.0 |
| | | Metronidazole | 0.37 | 0.06-2.0 | 0.25 | 1.0 |
| | | Rifaximin | 0.01 | 0.003-0.125 | 0.008 | 0.015 |
| All strains | 792 | Fidaxomicin | 0.10 | 0.003-1.0 | 0.125 | 0.25 |
| | | Vancomycin | 0.97 | 0.25-8.0 | 1.0 | 2.0 |
| | | Metronidazole | 0.49 | 0.02-4.0 | 0.5 | 1.0 |
| | | Rifaximin | 0.03 | 0.003-257.0 | 0.015 | 0.125 |

Based on the pooled Phase 3 isolates, fidaxomicin was seen to be 4- to 8-fold more potent than metronidazole or vancomycin, respectively.

The activity of fidaxomicin against other bacteria has been assessed in a variety of laboratories [Ackermann, 2004; Finegold 2004; Credito 2004; Hecht 2007] (Table 12). These studies demonstrated that fidaxomicin has a narrow spectrum of activity against other bacteria, with virtually no activity against gram-negative organisms ($MIC_{50}$ and $MIC_{90}$ values universally above 100 µg/mL). This was supported *in vivo* by two separate analyses performed on stool samples from the Phase 2A study [Louie, 2009; Tannock, 2010]. Using quantitative culture methods, the effect of fidaxomicin on *Bacteroides fragilis* (as a marker of intestinal flora) counts was examined before and after treatment to demonstrate no reduction in *Bacteroides* counts during treatment with fidaxomicin (but not vancomycin) [Louie, 2009]. In a second analysis by Tannock et al, the effect of fidaxomicin on other major colonic microbiota was examined using culture-independent methods. This study demonstrated that gram-positive commensals, specifically members of clostridial clusters XIV and IV and bifidobacteria, in addition to gram negative organisms such as the enterobacteria, were also relatively unaffected, confirming the narrow spectrum activity and minimal disruption of colonic microflora during treatment with fidaxomicin (but not vancomycin) [Tannock, 2010].

Fidaxomicin has moderate to good activity against gram-positive organisms, but with marked variation between genera. Fidaxomicin has no activity against yeast. This narrow spectrum of activity, which should maintain the normal protective flora, in addition to the moderate activity versus some gram positive organisms such as *Enterococcus* ($MIC_{90}$, 8 µg/mL) may explain why Nerandzic and coworkers reported that out of 248 subjects tested for VRE colonization before and after treatment in the 101.1.C.003 trial, subjects treated with fidaxomicin had a lower likelihood of new colonization with VRE than subjects treated with vancomycin (7% for fidaxomicin versus 31% for vancomycin, $p < 0.001$) [Nerandzic, 2009].

**Table 12. MIC Values for Fidaxomicin Versus Anaerobic and Aerobic Bacteria, Tested Via CLSI Reference Methods**

| Organism (N) | Reference | MIC Range | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|
| **GRAM NEGATIVE ANAEROBES** | | | | |
| *B. fragilis* (19) | Credito, 2004 | 64 - >128 | >128 | >128 |
| Non-fragilis *B. fragilis* group (38) | Credito, 2004 | 64 - >128 | >128 | >128 |
| *Bacteroides fragilis* group (50) | Finegold, 2004 | 256 - >1024 | 256 | >1024 |
| *Prevotella*/*Porphyromonas* (42) | Credito, 2004 | 16 - >128 | >128 | >128 |
| *Fusobacterium nucleatum* (14) | Credito, 2004 | 64 - >128 | >128 | >128 |
| *Fusobacterium mortiferum* (10) | Credito, 2004 | 64 - >128 | >128 | >128 |
| *Fusobacterium* species (14) | Credito, 2004 | 16 - >128 | >128 | >128 |
| *Veillonella* spp. (10) | Finegold, 2004 | 16-128 | 32 | 128 |
| Other gram negative rods[a] (51) | Finegold, 2004 | 0.06 - >1024 | 1024 | >1024 |
| **GRAM NEGATIVE AEROBIC/FACULTATIVE** | | | | |
| *Enterobacter cloacae* (6) & *E. aerogenes* (6) | Optimer | >64 - >64 | >64 | NC |
| *Escherichia coli* (9) | Optimer | >64 - >64 | >64 | NC |
| *Klebsiella* oxytoca (6) & *Klebsiella* spp. (1) | Optimer | >64 - >64 | >64 | NC |
| *Proteus mirabilis* (5) | Optimer | >64 - >64 | >64 | NC |
| *Pseudomonas aeruginosa* (16) | Optimer | >64 - >64 | >64 | NC |
| **GRAM POSITIVE ANAEROBES** | | | | |
| *Peptostreptococcus tetradius* (16) | Credito, 2004 | 0.25-2 | 1 | 1 |
| *Peptostreptococcus asaccharolyticus* (15) | Credito, 2004 | 0.25-1 | 0.5 | 1 |
| *Peptostreptococcus anaerobius* (15) | Credito, 2004 | ≤0.016-0.03 | ≤0.016 | ≤0.016 |

| Organism (N) | Reference | MIC Range | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|
| *Finegoldia magna* (15) | Credito, 2004 | 0.25-2 | 1 | 1 |
| *Micromonas micros* (14) | Credito, 2004 | ≤0.016-0.06 | 0.03 | 0.06 |
| *Peptostreptococcus prevotii* (3) | Credito, 2004 | 0.25-1 | NC | NC |
| *Propionibacterium acnes* (20) | Credito, 2004 | 0.5-4 | 4 | 4 |
| *Eggerthella lenta* (10) | Credito, 2004 | ≤0.016-0.06 | ≤0.016 | 0.03 |
| Anaerobic gram (+) nonsporeforming rods[b] (63) | Finegold, 2004 | 0.06 - >1024 | 1 | 32 |
| Misc. gram (+) nonsporeforming rods[c] (20) | Credito, 2004 | ≤0.016-16 | 0.125 | 16 |
| Anaerobic gram (+) cocci[d] (49) | Finegold, 2004 | 0.06-1024 | 0.5 | 2 |
| **NON-DIFFICILE CLOSTRIDIA** | | | | |
| *Clostridium bifermentans* (9) | Finegold, 2004 | 0.06-06 | NC | NC |
| *Clostridium bolteae* (7) | Finegold, 2004 | 1-64 | NC | NC |
| *Clostridium clostridioforme* (4) | Finegold, 2004 | 4-128 | NC | NC |
| *Clostridium glycolicum* (9) | Finegold, 2004 | 0.06-1 | NC | NC |
| *Clostridium innocuum* (9) | Finegold, 2004 | 32-128 | NC | NC |
| *Clostridium paraputrificum* (8) | Finegold, 2004 | 0.06-8 | NC | NC |
| *Clostridium perfringens* (14) | Finegold, 2004 | 0.06-0.06 | 0.062 | 0.062 |
| *Clostridium perfringens* (35) | Credito, 2004 | ≤0.016-0.06 | ≤0.016 | 0.03 |
| *Clostridium ramosum* (10) | Finegold, 2004 | 256-512 | 512 | 512 |
| *Clostridium sordellii* (5) | Finegold, 2004 | 0.06-0.06 | NC | NC |
| Other non-difficile Clostridia (9) | Finegold, 2004 | 0.06-1024 | NC | NC |
| Non-difficile *Clostridium* species (19) | Credito, 2004 | ≤0.016-0.06 | ≤0.016 | 0.03 |
| **GRAM POSITIVE AEROBIC/FACULTATIVE** | | | | |
| *Streptococcus*, formerly *S. milleri* group (14) | Finegold, 2004 | 16-64 | 32 | 32 |
| *Streptococcus* spp. (9) | Finegold, 2004 | 16-128 | NC | NC |
| *Enterococcus* spp. (21) | Finegold, 2004 | 2-16 | 8 | 8 |
| *Staphylococcus aureus* (9) & S. *epidermidis* (10) | Finegold, 2004 | 0.25-2 | 0.5 | 2 |

[a]By genus: *Bilophila* (10) *Fusobacterium* (12) *Porphyromonas* (11) *Prevotella* (8) *Sutterella* (10)
[b]By genus: *Actinomyces* (8) *Atopobium* (3) *Bifidobacterium* (9) *Collinsella* (7) *Eggerthella* (5) *Eubacterium* (10) *Lactobacillus* (10) *Propionibacterium* (11)
[c]By genus: *Actinomyces* (4) *Bifidobacterium* (8) *Lactobacillus* (8)
[d]By genus: *Anaerococcus* (13) *Finegoldia* (7) *Peptoniphilus* (6) *Peptostreptococcus* (13) *Ruminococcus* (10)

Similar to the parent compound, the main metabolite, OP-1118, has a narrow spectrum of activity comparable to that of fidaxomicin, although with lower activity, with an $MIC_{90}$ against *C. difficile* of 8 µg/mL [Citron Report, 2010]. Given the high fecal concentrations of the metabolite and its activity versus *C. difficile*, it can be concluded that the metabolite is likely to play a role in the microbiologic activity of fidaxomicin.

## 5.3 Resistance

### 5.3.1 Spontaneous Resistance

The rate of spontaneous resistance is an important measure of the speed at which organisms can be expected to develop resistance. The frequency of spontaneous resistance (FSR) development of fidaxomicin was compared to that of vancomycin and metronidazole, and compared to that of vancomycin and rifaximin. The FSR values of fidaxomicin and vancomycin at 8× MIC concentration in laboratory (ATCC 9689 and 700057) and clinical strains of *C. difficile* ranged from $<1.41 \times 10^{-9}$ to $<4.13 \times 10^{-9}$. All 4 isolates, however, produced resistance to rifaximin at 8× MIC, with FSR values for rifaximin ranging from $5.56 \times 10^{-9}$ to $1.73 \times 10^{-7}$.

Serial passage was also used to examine the development of resistance. *C. difficile* ATCC 43255 was serially passaged at 0.0625 µg/mL, one half the initial MIC, on agar (Figure 3). Through 12 passages, the MIC remained within 1 to 2 dilutions of the original MIC. By passage 13, the MIC was beginning to increase, eventually reaching a plateau at 2 µg/mL after 14 passages. The MIC did not increase through 4 further passages.

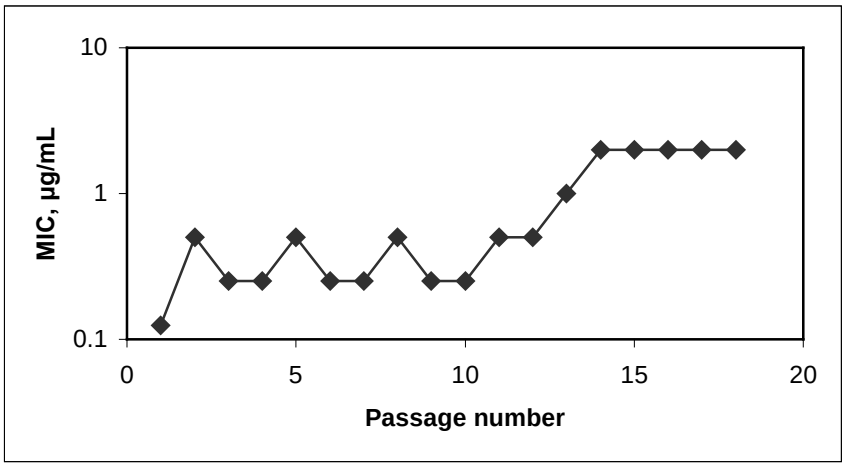



**Figure 3. Fidaxomicin MIC Versus Passage Number for *C. difficile* ATCC 43255 Passaged on 0.0625 µg/mL Fidaxomicin Through 18 Passages**

### 5.3.2 Mechanism of Resistance

To delineate potential fidaxomicin binding sites and investigate target modification as a possible mechanism mediating resistance of *C. difficile* toward fidaxomicin, the genes comprising the RNA polymerase core enzyme (*rpoA, rpoB,* and *rpoC*) of fidaxomicin-resistant *C. difficile* clones were sequenced and analyzed for mutations. Ten fidaxomicin-resistant clones were generated by either nitrosoguanidine treatment or by spontaneous means after plating wild type strains at 4× MIC drug concentration. DNA isolated from resistant clones and wild-type parental strains (ATCC 700057 and ATCC 9689) was amplified in segments by polymerase chain reaction (PCR) and sequenced. Sequencing focused primarily on the β and β' subunits, as these have been identified by others as sites for lipiarmycin resistance [Gualtieri, 2006; Kurabachew, 2008]. Sequencing of fidaxomicin-resistant clones revealed mutations of four residues in *rpoB* (Gln1074Lys, Ile1132Arg, Val1143Phe, and Leu1144Phe) and two residues of *rpoC* (Asp237Tyr and Glu1134Lys). Isolation and activity testing of the Asp237Tyr mutant revealed that it has a 4.4-fold increased $IC_{50}$ toward fidaxomicin as compared to the wild type enzyme. Of these mutations, three (Gln1074Lys, Val1143Phe, and Asp237Tyr) have been previously identified at homologous positions in organisms resistant to lipiarmycin, a related macrocyclic compound [Ebright, 2006; Gaultieri, 2006; Kurabachew, 2008].

### 5.3.3 Cross-resistance

Cross-resistance studies using laboratory strains with reduced susceptibility to fidaxomicin or with organisms resistant to other antibiotics, including a macrolide-resistant *C. difficile* (ATCC 43597), showed lack of cross-resistance to the antibiotics tested, including

macrolides, β-lactams, fluoroquinolones, rifampin, vancomycin or metronidazole. Lack of cross-resistance with other classes of antimicrobial agents indicates a unique mode of action that is different from known RNA polymerase inhibitors.

### 5.3.4 Synergy

The interaction of fidaxomicin and its metabolite (OP-1118) with eight other antimicrobials (ampicillin, azithromycin, ciprofloxacin, clindamycin, metronidazole, rifampin, rifaximin, telithromycin and vancomycin) was studied *in vitro* against *C. difficile* ATCC 43255, using the checkerboard technique.

Neither fidaxomicin nor its main metabolite OP-1118 demonstrated antagonistic interactions with the other classes of antibiotics, but both were strongly synergistic with the rifamycin class of compounds, which are also known RNA polymerase inhibitors. Both compounds also demonstrated synergy with ampicillin and metronidazole but not ciprofloxacin or vancomycin. In contrast to the metabolite, fidaxomicin also demonstrated synergy with clindamycin, however, due to inherent variability of the checkerboard technique, the synergistic interaction of both fidaxomicin and OP-1118 with azithromycin and telithromycin could not be verified. Similarly, the interaction of the OP-1118 with clindamycin could not be conclusively determined by this method.

### 5.3.5 Killing Kinetics

The bactericidal activity of fidaxomicin and its major metabolite OP-1118 was compared to that of vancomycin against four *C. difficile* strains that included two clinical REA group BI isolates (an epidemic hypervirulent *C. difficile* strain) and two ATCC strains, 43255, and 9689 (the latter was not tested against OP-1118), as well as a laboratory-generated strain with an elevated MIC against fidaxomicin. A representative kinetic curve for fidaxomicin is shown in Figure 4.

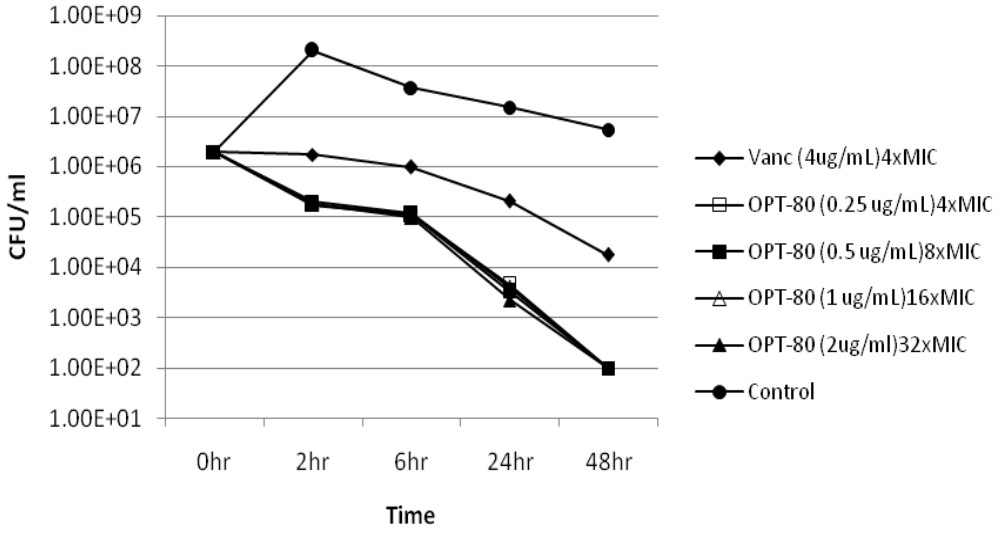



**Figure 4. Killing Kinetics of Fidaxomicin versus *C. difficile* ATCC 43255 at Various Multiples Over the MIC**

Both fidaxomicin and OP-1118 at 4× MIC demonstrated bactericidal activity towards all strains, with a ≥3 $\log_{10}$ drop in colony forming units (CFU) in 48 hours, for all isolates, with the exception of OP-1118 versus one of the clinical isolates, which required a higher multiple over the MIC to accomplish 3 $\log_{10}$ killing in 48 hours. These curves also demonstrate the lack of concentration dependence to the killing: killing was time-dependent, not concentration-dependent, above the MIC.

### 5.3.6 Post-Antibiotic Effect

The post-antibiotic effect (PAE) of fidaxomicin was measured versus a laboratory strain (ATCC 43255) and a clinical isolate (LC3) strain of *C. difficile*. The PAE was estimated at approximately 10 hours for ATCC strains 43255 and 9689, and 5.5 hours for the clinical isolate, following treatment at 4× MIC. Recovery kinetics data are shown for ATCC 9689 in Figure 5

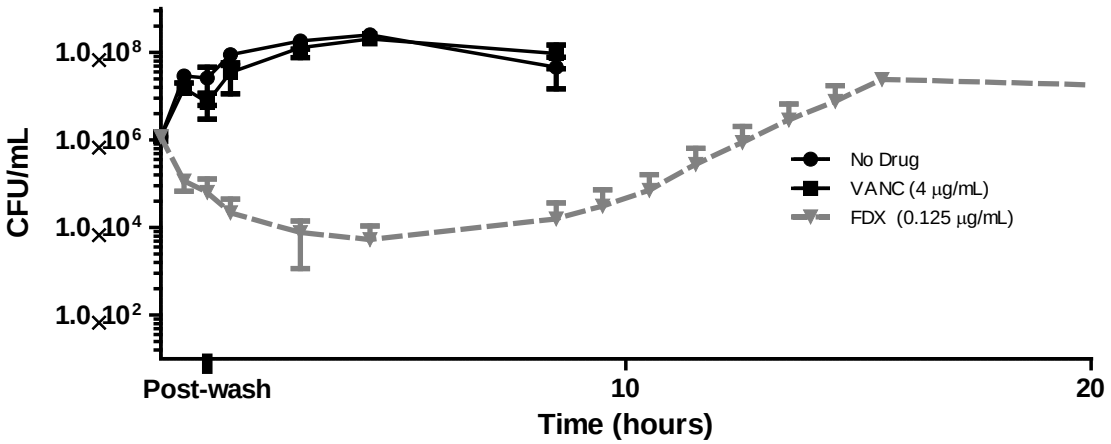



**Figure 5. Recovery Kinetics of *C. difficile* ATCC 9689 Following Treatment with Vancomycin (4 µg/mL) and Fidaxomicin (0.125 µg/mL)**

The major metabolite OP-1118 also had a PAE, although this was shorter than that of the parent compound. The PAE of OP-1118 versus the two *C. difficile* strains was approximately 3 hours at 4× MIC.

These findings indicate that the anticlostridial activity of fidaxomicin persists after its removal, and this feature may be beneficial in *C. difficile* infection, a disease in which rapid intestinal transit due to diarrhea may hasten fecal excretion of drug.

### 5.3.7 Breakpoints

Since fidaxomicin is not absorbed in the GI tract, it can be considered to act locally, and as such, clinical breakpoints are not applicable.

Further, levels of active drug and metabolite in the GI tract have been shown to be many fold higher (~5000 times) than the MIC of *C. difficile*. Due to the fact that *C. difficile* represents a

wild type population only and is not characterized by the existence of other resistant populations, it is not possible to define meaningful clinical breakpoints.

Quality control parameters, however, have been established so that laboratories that perform susceptibility testing can monitor the relationship of the *in vitro* MIC test result to the clinical efficacy of fidaxomicin.

# 6 REVIEW OF FIDAXOMICIN EFFICACY

## 6.1 Overview of Clinical Development Program

All the clinical studies included in the drug development program were conducted according to Good Clinical Practice (GCP). The efficacy of fidaxomicin was evaluated in one Phase 2A dose-finding study (OPT-80 Phase 2A) and two Phase 3 pivotal studies (101.1.C.003 and 101.1.C.004). Both of the Phase 3 efficacy studies were conducted as randomized, double-blind, active comparator studies, fulfilling the requirements of a robust study design. Subjects included in these trials presented at baseline with different degrees of disease severity, with or without a prior occurrence of CDI, and are therefore representative of the general CDI population. Vancomycin was selected as the comparator in both studies since it is recommended as the best treatment for the full range of severity that is likely to be encountered in a randomized clinical trial (i.e., from non-severe to severe cases) [Bauer, 2009b]. In addition, vancomycin is the only FDA approved treatment for CDI. A summary of these efficacy studies is provided in Table 13.

**Table 13. Summary of Fidaxomicin Efficacy Studies**

| Study ID | Title | Treatment duration; dose per day | | Number of randomized subjects |
|---|---|---|---|---|
| | | Fidaxomicin | Comparator | |
| OPT-80 Phase 2A | An Open-Label, Dose Ranging, Randomized Clinical Evaluation of OPT-80 in Patients with *Clostridium difficile*-Associated Diarrhea | 10 days<br>50 mg q12h,<br>100 mg q12h,<br>200 mg q12h | None | 49 |
| 101.1.C.003 Phase 3 | A Multi-National, Multi-Center, Double-Blind, Randomized, Parallel Group Study To Compare The Safety And Efficacy Of 200 mg PAR-101 Taken Q12h With 125mg Vancomycin Taken Q6h For Ten Days In Subjects With *Clostridium difficile*-Associated Diarrhea | 10 days:<br>400 mg<br>(200 mg q12h)<br>N=306 | Vancomycin<br>500 mg<br>(125 mg q6h)<br>N=323 | 629 |
| 101.1.C.004 Phase 3 | A Multi-National, Multi-Center, Double-Blind, Randomized, Parallel Group Study To Compare The Safety And Efficacy Of 200 mg PAR-101 Taken Q12h With 125mg Vancomycin Taken Q6h For Ten Days In Subjects With *Clostridium difficile*-Associated Diarrhea | 10 days:<br>400 mg<br>(200 mg q12h)<br>N=271 | Vancomycin<br>500 mg<br>(125 mg q6h)<br>N=264 | 535 |

PAR-101 = OPT-80 = fidaxomicin

## 6.2 Phase 2 Study

The efficacy of fidaxomicin is supported by the results of the Phase 2A dose-finding study. This study was an open-label, dose-ranging, randomized, safety and clinical evaluation in which fidaxomicin tablets were administered to subjects with CDI at doses of 100 mg/day

(50 mg q12h), 200 mg/day (100 mg q12h), and 400 mg/day (200 mg q12h) for 10 days. Males and females were recruited in this study, aged 18 years or older, and they could either be hospitalized or treated in an outpatient setting. All subjects were required to have a confirmed diagnosis of CDI, with diarrhea (defined as a change in bowel habits, with either 3 or more unformed bowel movements [UBMs] in 24 hours or more than 6 UBMs in 36 hours) and the presence of either toxin A or B of *C. difficile* in the stool.

The primary endpoint was relief of symptoms (defined as resolution to ≤3 UBMs per day without other associated signs/symptoms such as fever, abdominal pain, and elevated white blood cells [WBC]). In addition, at the EOT visit the investigator determined if the subject had been cured or failed based on his clinical judgment. The time to resolution of diarrhea (TTROD) was also assessed. Those who did not fail at the end of therapy remained in the trial and were followed for an additional six weeks during which time they were assessed for recurrence of CDI.

Of the 49 subjects who entered the study, 48 received study drug (16 subjects per dose group). Overall 41 subjects completed the study as scheduled (12 in the 100 mg/day group, 13 in the 200 mg/day group and 16 in the 400 mg/day group). The most common reason for early withdrawal was treatment failure (Table 14).

**Table 14. Withdrawals from Study in OPT-80 Phase 2A (Safety Population)**

| | **Fidaxomicin 100 mg/day** (N=16) n (%) | **Fidaxomicin 200 mg/day** (N=16) n (%) | **Fidaxomicin 400 mg/day** (N=16) n (%) |
|---|---|---|---|
| Total who terminated early | 4 (25.0) | 3 (18.8) | - |
| Reason for early termination | | | |
| Withdrawal of consent | 1 (6.3) | - | - |
| Non-compliance | 1 (6.3) | - | - |
| Treatment failure | 2 (12.5) | 2 (12.5) | - |
| Other[a] | 1 (6.3) | 1 (6.3) | - |

NOTE: A subject can have multiple reasons for study termination
[a]Other includes inability to tolerate oral medication, and other antibiotic therapy

In the 400 mg/day treatment group, a large majority of subjects experienced total relief of symptoms (86.7% subjects) compared to those who did not experience relief (13.3% subjects). In the 200 mg/day treatment group, more subjects had total relief (50.0% subjects) than did not experience relief (37.5% subjects). Fewer subjects in the 100 mg/day treatment group had relief of symptoms of CDI than those who did not have their symptoms relieved (37.5% subjects vs. 56.3% subjects, respectively) (Table 15).

The proportion of subjects cured following fidaxomicin treatment was high in all groups and increased numerically with increasing dose (Table 15). One subject, considered a clinical cure, was removed from the mITT population in the 400 mg group as the subject did not have ≥3 UBMs/day at entry. In the 400 mg group a 100% cure rate was observed.

**Table 15. Relief of Symptoms of CDI and Clinical Cure Rates in Study OPT-80 Phase 2A (mITT Population)**

| | Fidaxomicin 100 mg/day N=16 | | Fidaxomicin 200 mg/day N=16 | | Fidaxomicin 400 mg/day N=15[a] | |
|---|---|---|---|---|---|---|
| | n | % | n | % | N | % |
| Relief of symptoms | | | | | | |
| Relief | 6 | (37.5) | 8 | (50.0) | 13 | (86.7) |
| No Relief | 9 | (56.3) | 6 | (37.5) | 2 | (13.3) |
| Unknown | 1 | (6.3) | 2 | (12.5) | 0 | (0.0) |
| 95% confidence interval (CI) surrounding the difference in No Relief: | | | | | | |
| Fidaxomicin 100-Fidaxomicin 200 | | | 18.8 (-18.3, 55.8) | | | |
| Fidaxomicin 100-Fidaxomicin 400 | | | 42.9 (9.8, 76.0) | | | |
| Fidaxomicin 200-Fidaxomicin 400 | | | 24.2 (-8.5, 56.8) | | | |
| Clinical cure | 12 | (75.0) | 13 | (81.3) | 15 | (100.0) |

NOTE: Relief of symptoms of CDI was defined as ≤3 UBMs per day without other associated signs and symptoms such as fever, abdominal pain and elevated WBC by Day 10 of the study. Subjects with any of these symptoms remaining by Day 10 were considered No Relief. Clinical cure was imputed to failure for subjects who discontinued the study during treatment.

[a]One subject, who was considered a cure by the investigator, was not included in the mITT population as they did meet the baseline criteria for ≥3 UBMs in 24 hours

Of the 27 subjects meeting the defined criteria of relief of all symptoms by Day 10 for cure, only two subjects (one subject in the 100 mg/day treatment group and one subject in the 400 mg/day treatment group) experienced clinical recurrence. In the subjects cured at the end of Day 10 but with signs and symptoms of CDI, no recurrences were seen. The median TTROD also suggested that higher doses of fidaxomicin were more efficacious, with the median TTROD decreasing with increasing dose (duration of 5.5 days in the 100 mg/day group, 3.5 days in the 200 mg/day group and 3.0 days in the 400 mg/day group).

In conclusion, based on the different clinical endpoints assessed in this trial, fidaxomicin was seen to provide relief of symptoms of CDI, with rate of relief and cure rates increasing and TTROD decreasing with increasing dose. The dose ranging identified 400 mg/day (200 mg q12h) as the most appropriate dose for treatment of CDI in adults, and this was subsequently used in the Phase 3 studies.

## 6.3 Phase 3 Studies

### 6.3.1 Study Design

The Phase 3 studies were of a similar design, with the primary difference being that the first study was conducted only in the US and Canada whereas the second study also included approximately 40% of subjects from European countries. Both Phase 3 trials were conducted as double-blind studies. 125 mg vancomycin (Vancocin® HCl Capsules), 200 mg fidaxomicin, and matching placebo capsules were all over-encapsulated to appear identical, and were packaged in blister cards. All subjects were administered study drug 4 times a day, either as 4 doses of vancomycin or 2 doses of fidaxomicin plus 2 placebo doses (depending on the treatment the subject was randomized to), to ensure study blinding was maintained. The dose of fidaxomicin of 200 mg q12h was selected based on the results of the Phase 2A study. The dose of vancomycin of 125 mg q6h is the current recommended dose

[Missaghi, 2008; Kelly, 2010], which has also been endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) treatment guidelines [Bauer, 2009b] and the Clinical Practice Guidelines issued by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) [Cohen, 2010].

In both studies, after informed consent was obtained, the investigative site called the Interactive Voice Response System (IVRS) or logged into the Interactive Web Response System (IWRS) and a randomization number and medication kit number were given for each subject based on a computer-generated randomization schedule. The randomization was stratified by number of prior episodes of CDI within the prior 3 months (0 versus 1) and site. The treatment group allocated remained blinded to all study site staff until all subjects had completed study and the database was locked.

All subjects were interviewed daily by study staff on Days 1 to 12 for CDI status. Subjects were interviewed weekly thereafter (Day 17 ±1, Day 24 ±1 and Day 31 ±1) until the post-study visit for recurrence of CDI symptoms, unless they were a study failure or recurred, at which time they were considered to have completed the study.

In both studies, the primary endpoint was the clinical cure rate, based on the following definitions:

- 3 or fewer unformed stools for 2 consecutive days and maintained through the end of therapy, and
- The investigators clinical judgment that the subject no longer needed specific anti-Clostridium antibacterial treatment after completion of the course of study medication.

Conversely, subjects who required further *C. difficile* infection therapy within two days of completion of study medication were considered a failure.

This endpoint was chosen as the primary endpoint because it has been used in all recent clinical trials performed in CDI subjects and is the most clinically meaningful endpoint from a subject care perspective (bearing in mind that no biological or microbiological marker has been shown to correlate with clinical outcomes [Teasley, 1983; Zimmerman, 1997]).
A sensitivity analysis of the primary endpoint was based on achieving 3 or fewer UBMs for 2 consecutive days that was maintained to EOT, removing the investigators clinical judgment on need for further therapy from the analysis. Subjects who did not meet this definition were considered failures in this sensitivity analysis.

A prespecified secondary endpoint in both studies was recurrence rate. Recurrence was defined as:

- The re-establishment of diarrhea to an extent (based on frequency of passed unformed stools) that was greater than that noted on the last day of study medication,
- Demonstration of either toxin A or B or both of *C. difficile,*

- Investigator's opinion that retreatment with CDI anti-infective therapy was needed.

Subjects who developed diarrhea associated with a negative *C. difficile* stool toxin test were not considered a recurrence (note that the endpoint of recurrence can only be evaluated in the subgroup of subjects who achieve clinical cure).

The global cure rate was an exploratory endpoint in study 101.1.C.003 and a secondary endpoint in study 101.1.C.004. Global cure was a composite endpoint encompassing cure and absence of recurrence, and was defined as the number of subjects in each treatment group who were evaluated as cured at EOT and did not have recurrence at any time up to the post-study visit. This endpoint was considered important because it evaluates the CDI process in terms of the whole disease resolution rather than resolution of the initial CDI episode. In a recent Cochrane review, this endpoint was called 'symptomatic cure' and was considered important for evaluating a new therapy for CDI [Nelson, 2007].

In addition, an exploratory endpoint of TTROD was also included in both studies, which was defined as the time (in hours) from the first dose of study medication to the earliest resolution of diarrhea. The day of resolution of diarrhea was defined as the first of two consecutive days of ≤3 unformed stools (watery or loose) within a 24-hour period and was sustained for the duration of treatment up to study Day 10.

### 6.3.2 Statistical Analysis

Two analysis populations were defined in the study protocols. The modified intent-to-treat (mITT) population was defined as the group of randomized subjects with:

- CDI confirmed by >3 UBMs in the 24 hours prior to randomization and a positive toxin assay

  AND

- Who received at least one dose of study medication

The per protocol (PP) population was defined as the group of subjects who met all the following criteria:

- Included in the mITT population
- Met all study inclusion criteria and met no study exclusion criteria
- Had received at least 3 complete days of treatment for failure <u>or</u> 8 complete days of treatment for cure
- Had an EOT clinical evaluation
- Did not have a significant protocol violation

Although not a prespecified analysis population in either of the Phase 3 study, the intent-to-treat (ITT) population was defined as all randomized subjects.

In both studies, the primary analysis assessing non-inferiority of the clinical cure rate for fidaxomicin relative to vancomycin was carried out in the PP and mITT populations. The protocol stated that non-inferiority had to be demonstrated in both populations in order to justify the conclusion that fidaxomicin was non-inferior to vancomycin. A non-inferiority design was used to demonstrate the efficacy of fidaxomicin compared to vancomycin, and was consistent with the FDA's draft Guidance for Industry on "Non-Inferiority Clinical Trials" from March 2010. The point estimate of the difference and the 2-sided 95% confidence interval (CI) for the difference between treatment groups were computed. If the lower limit of the CI was greater than -10%, the clinical non-inferiority of fidaxomicin was demonstrated. CIs for the difference of cure rates were calculated using the method recommended by Agresti and Caffo [Agresti, 2000].

The -10% non-inferiority margin is justified based on data from a review article by Weiss [Weiss, 2009]. The clinical success rates based on the results of tolevamer (a surrogate for placebo) and vancomycin in two well controlled Phase 3 trials showed point estimates of the risk difference of 34.7% (95% CI 25.81, 43.64) and 38.6% (95% CI 29.55, 47.73) (Table 16). Preserving 50% of the treatment difference provides a non-inferiority margin of 12.9% and 14.8%, respectively. Based on this information, a non-inferiority limit of -10% is justified.

**Table 16. Non-Inferiority Margin Based on Data from Weiss, 2009**

| Study | Cure Rates n/N (%) | | |
|---|---|---|---|
| | Tolevamer | Vancomycin | Risk Difference (%) [95% CI] |
| **Study 301** | 124/266 (46.6) | 109/134 (81.3) | 34.7 [25.81, 43.64] |
| **Study 302** | 113/268 (42.2) | 101/125 (80.8) | 38.6 [29.55, 47.73] |

The pre-specified statistical analyses in the two fidaxomicin Phase 3 studies were similar (Table 17). The main difference between the two studies was the different approaches used for the analysis of the secondary and exploratory endpoints.

The secondary endpoint of recurrence rate and the endpoint of global cure (exploratory in study 101.1.C.003, secondary in study 101.1.C.004) were also analyzed in both the mITT and PP populations. In study 101.1.C.004, the secondary endpoints of recurrence and global cure were analyzed according to a prespecified hierarchical testing procedure in order to control the overall alpha level [Westfall, 2001]. If the primary analysis of clinical cure rate demonstrated noninferiority of fidaxomicin to vancomyin in both the mITT and PP populations, then a superiority analysis comparing the recurrence rates of fidaxomicin and vancomycin was completed. If these analyses demonstrated superiority of fidaxomicin in both the mITT and PP populations, then the global cure rates would be compared, again using a superiority analysis in both the mITT and PP populations.

**Table 17. Summary of Pre-specified Statistical Analyses Used in Studies 101.1.C.003 and 101.1.C.004**

| | Study 101.1.C.003 | Study 101.1.C.004 |
|---|---|---|
| Primary Endpoint | Clinical Cure (PP and mITT)<br>• 1-sided 97.5% CI of fidaxomicin minus vancomycin cure rate<br>• Non-inferiority is demonstrated if lower limit of the CI is >-10%<br>• Superiority of fidaxomicin is demonstrated if lower limit of the CI is >0 | Clinical Cure (PP and mITT)<br>• 2-sided 95% CI of fidaxomicin minus vancomycin cure rate<br>• Non-inferiority is demonstrated if lower limit of the CI is greater than -10%<br>• Superiority of fidaxomicin is demonstrated if lower limit of the CI is >0 |
| Supplemental Analysis to Primary Endpoint | Sensitivity Analysis of Cure<br>• 2-sided 95% CI of fidaxomicin minus vancomycin cure rate<br>• Non-inferiority demonstrated if lower limit of the is greater than -10%<br>• Superiority of fidaxomicin is demonstrated if lower limit of the CI is >0 | Sensitivity Analysis of Cure<br>• 2-sided 95% CI of fidaxomicin minus vancomycin cure rate<br>• Non-inferiority demonstrated if lower limit of the CI is greater than -10%<br>• Superiority of fidaxomicin is demonstrated if lower limit of the CI is >0 |
| Secondary Endpoints | Recurrence (mITT and PP)<br>• 2-sided 95% CI for the difference of two proportions using Agresti and Caffo (2000) method. | 1. Recurrence (mITT and PP)<br>2. Global Cure (mITT and PP)<br>• Gate-keeping strategy:<br>a) If non-inferiority of fidaxomicin to vancomycin is demonstrated, superiority comparison of treatments for recurrence rates is made (2-sided alpha=0.05)<br>b) If treatment comparison for recurrence rates is statistically significant in favor of OPT-80 (both mITT and PP), the superiority comparison of treatments for global cure rate will be made (two-sided alpha=0.05). |
| Exploratory Analysis | Global Cure (mITT and PP)<br>• 2-sided 95% CI on the difference between treatment<br><br>Time-to-Resolution of Diarrhea:<br>• Kaplan-Meier, Cox proportional hazards model<br>• Quartile estimates (25th, 50th, and 75th) and their two-sided 95% confidence intervals for both treatment groups. | Time-to-Resolution of Diarrhea (mITT and PP)<br>• Cox proportional hazards model<br>• Quartile estimates (25th, 50th, and 75th) and their 95% CIs, Wilcoxon test<br>• Kaplan-Meier Median estimates and their 95% CIs |

A pooled analysis of the two fidaxomicin Phase 3 studies was also carried out to provide useful information regarding the robustness of the efficacy data across two very similarly designed Phase 3 studies. The pooled analysis was designed as an adjunct to the individual study analyses.

### 6.3.3 Key Inclusion / Exclusion Criteria

Inclusion Criteria

1. Male or female inpatients or outpatients, who were 16 years of age or older (or 18 years or older in German sites in study 101.1.C.004) and who had CDI as defined by:
   - Diarrhea: defined as a change in bowel habits, with >3 UBMs (or >200 mL unformed stool for subjects having rectal collection devices) in the 24 hours before randomization, and
   - Presence of either toxin A or B of *C. difficile* in the stool within 48 hours of randomization (study 101.1.C.004 clarified this further, stating "Presence of either toxin A or B of *C. difficile* in the stool within 48 hours of randomization for metronidazole failures, or within 96 hours of randomization for subjects with ≤24 hours pretreatment with CDI therapy").
2. Female subjects of childbearing potential were required to have been using an adequate and reliable method of contraception (e.g., barrier with additional spermicide foam or jelly, intrauterine device, hormonal contraception); females who were postmenopausal must have been postmenopausal ≥1 year. Subjects (both male and female) must have agreed to avoid conception during treatment and for 4 weeks following the end of study treatment. Note that the definition of adequate contraception was different for German sites in study 101.1.C.004, where it was defined as a highly effective method of contraception with a failure rate of <1% per year when used correctly and consistently, including implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, or a vasectomised partner.
3. All subjects were required to sign an Informed Consent Form.
4. Opiates were permitted as needed as long as subjects taking them were on stable doses at the time of randomization and expected to maintain these doses during the treatment period.
5. Individuals who failed at least a full 3-day course of metronidazole but continued to meet the definition of diarrhea without any significant clinical improvement and remained toxin positive could be enrolled in the study.

Exclusion Criteria

1. Life threatening or fulminant CDI (WBC count >30 × $10^9$/L; temperature >40°C; or evidence of hypotension [systolic blood pressure less than 90 mmHg], and septic shock, peritoneal signs, or significant dehydration).
2. Toxic megacolon.
3. Previous exposure to fidaxomicin.
4. Females who were pregnant or breastfeeding.

5. Likelihood of death within 72 hours from any cause.
6. Concurrent use of: oral vancomycin, metronidazole, oral bacitracin, fusidic acid, rifaximin, nitazoxanide, or related drugs. If the Investigator felt the clinical imperative to begin treatment before knowing the laboratory result for stool toxin, up to 4 doses but no more than 24 hours of treatment with metronidazole and/or vancomycin were allowed. While such pretreated subjects could be enrolled (i.e., no more than 24 hours of previous therapy), it was preferred that subjects be enrolled who had not received prior CDI treatment on this admission. The Investigators were encouraged to identify eligible subjects, whenever possible before other therapy was given and to "sensitize" their institution to this study so that subjects could be entered without prior therapy whenever possible.
7. The anticipated need to continue other anti-bacterials for a period exceeding 7 days from study start.
8. Subjects who in the opinion of the investigator required other drugs to control diarrhea (e.g., loperamide) or that could affect peristalsis.
9. Unable or unwilling to comply with the study protocol, including ingesting capsules, having blood drawn, and providing stool samples as scheduled.
10. Participation in other clinical research studies utilizing an investigational agent within 1 month before screening or within 5 half-lives of the investigational agent, whichever was longer.
11. History of ulcerative colitis or Crohn's disease.
12. Multiple occurrences (defined as more than 1 prior occurrence) of CDI within the past 3 months; subjects presenting with the first recurrence within 3 months could be enrolled.
13. Subjects the Investigator felt were inappropriate for the trial, e.g., subjects with known hypersensitivity to vancomycin.

### 6.3.4 Demography and Baseline Characteristics

The demographic profile of enrolled subjects was similar in the two Phase 3 studies, with a median age of subjects of 63 years in study 101.1.C.003 and 66 years in study 101.1.C.004. Most subjects were White (89.5%) and female (58.2%) (Table 18). The only differences of note were a slightly higher percentage of females enrolled into study 101.1.C.004, and the median age of subjects in study 101.1.C.004 was approximately 3 years greater than in study 101.1.C.003. Many subjects enrolled in the Phase 3 program were acutely ill with concomitant acute and chronic medical conditions in addition to CDI, including other recent infections and malignancies and treatments such as chemotherapy and bone marrow transplantation.

**Table 18. Demographic Characteristics in the Phase 3 Studies (mITT Population)**

| | Study 101.1.C.003 | | | Study 101.1.C.004 | | |
|---|---|---|---|---|---|---|
| | Fidaxomicin (N=289) | Vancomycin (N=307) | All subjects (N=596) | Fidaxomicin (N=253) | Vancomycin (N=256) | All subjects (N=509) |
| Sex, n (%) | | | | | | |
| Female | 164 (56.7) | 169 (55.0) | 333 (55.9) | 149 (58.9) | 161 (62.9) | 310 (60.9) |
| Male | 125 (43.3) | 138 (45.0) | 263 (44.1) | 104 (41.1) | 95 (37.1) | 199 (39.1) |
| Race, n (%) | | | | | | |
| White | 254 (87.9) | 265 (86.3) | 519 (87.1) | 233 (92.1) | 237 (92.6) | 470 (92.3) |
| Black | 30 (10.4) | 33 (10.7) | 63 (10.6) | 17 (6.7) | 17 (6.6) | 34 (6.7) |
| Asian | 4 (1.4) | 7 (2.3) | 11 (1.8) | 2 (0.8) | 1 (0.4) | 3 (0.6) |
| Other[a] | 1 (0.3) | 2 (0.7) | 3 (0.5) | 1 (0.4) | 1 (0.4) | 2 (0.4) |
| Ethnicity, n (%) | | | | | | |
| Hispanic | 12 (4.2) | 5 (1.6) | 17 (2.9) | 18 (7.1) | 20 (7.8) | 38 (7.5) |
| Age (yrs) | | | | | | |
| N | 289 | 307 | 596 | 253 | 256 | 509 |
| Mean±SD | 60.3±16.9 | 62.9±16.9 | 61.6±16.9 | 64.1±18.0 | 62.7±18.3 | 63.4±18.1 |
| Median | 61.0 | 64.0 | 63.0 | 67.0 | 65.0 | 66.0 |
| Range | 18, 94 | 19, 94 | 18, 94 | 18, 94 | 19, 93 | 18, 94 |
| Weight (kg) | | | | | | |
| N | 289 | 306 | 595 | 252 | 256 | 508 |
| Mean±SD | 78.0±24.1 | 76.1±21.4 | 77.0±22.8 | 71.4±20.6 | 70.9±19.8 | 71.2±20.2 |
| Median | 74.0 | 73.1 | 74.0 | 68.0 | 67.3 | 68.0 |
| Range | 36.4, 230.6 | 36.0, 242.3 | 36.0, 242.3 | 32.0, 231.6 | 32.8, 181.4 | 32.0, 231.6 |
| Height (cm) | | | | | | |
| N | 289 | 306 | 595 | 252 | 255 | 507 |
| Mean±SD | 167.2±11.1 | 166.9±12.1 | 167±11.6 | 167.0±9.7 | 165.8±10.9 | 166.4±10.3 |
| Median | 167.0 | 167.6 | 167.6 | 166.0 | 165.0 | 165.1 |
| Range | 124.0, 193.0 | 129.5, 198.0 | 124.0,198.0 | 146.0, 195.6 | 114.0, 208.0 | 114.0, 208.0 |
| BMI ($kg/m^2$)[b] | | | | | | |
| N | 289 | 306 | 595 | 252 | 255 | 507 |
| Mean±SD | 27.9±8.1 | 27.4±7.4 | 27.6±7.8 | 25.5±6.3 | 25.7±6.3 | 25.6±6.3 |
| Median | 26.3 | 26.1 | 26.2 | 24.2 | 24.8 | 24.5 |
| Range | 15.9, 79.6 | 15.4, 83.6 | 15.4, 83.6 | 12.5, 63.8 | 12.8, 51.9 | 12.5, 63.8 |

BMI = body mass index, SD = standard deviation
[a]Other includes: American Indian and Alaska native
[b]Calculated body mass index is defined as (weight in kg)/(height in meters)$^2$

With regard to baseline CDI characteristics, more subjects in the 101.1.C.004 study were inpatients (68.2%) compared to subjects in study 101.1.C.003 (59.4%), and subjects in study 101.1.C.004 had slightly fewer bowel movements on average per day at baseline (median of 6 compared to 7) (Table 19). In addition, a larger proportion of subjects in the 101.1.C.004 study had previously used antibiotics for CDI within the previous 24 hours, as allowed by the protocol, (87.4% overall), compared to only 44.8% in study 101.1.C.003. The reason for these differences could be related to the different treatment practices in US and Europe, since approximately 40% of the subjects enrolled in study 101.1.C.004 were from European sites.

**Table 19. Summary of Baseline Characteristics in the Phase 3 Studies (mITT Population)**

| | Study 101.1.C.003 | | | Study 101.1.C.004 | | |
|---|---|---|---|---|---|---|
| | Fidaxomicin (N=289) | Vancomycin (N=307) | All subjects (N=596) | Fidaxomicin (N=253) | Vancomycin (N=256) | All subjects (N=509) |
| Subject status, n (%) | | | | | | |
| Inpatient | 168 (58.1) | 186 (60.6) | 354 (59.4) | 175 (69.2) | 172 (67.2) | 347 (68.2) |
| Outpatient | 121 (41.9) | 121 (39.4) | 242 (40.6) | 78 (30.8) | 84 (32.8) | 162 (31.8) |
| Stratum, n (%) | | | | | | |
| No Prior Episode | 241 (83.4) | 253 (82.4) | 494 (82.9) | 213 (84.2) | 220 (85.9) | 433 (85.1) |
| Single Prior Episode | 48 (16.6) | 54 (17.6) | 102 (17.1) | 40 (15.8) | 36 (14.1) | 76 (14.9) |
| Daily Bowel Movements | | | | | | |
| N | 289 | 307 | 596 | 252 | 256 | 508 |
| Mean ±SD | 8.1±4.2 | 8.3±5.3 | 8.2±4.8 | 7.5±4.4 | 7.5±4.3 | 7.5±4.3 |
| Median | 7.0 | 6.0 | 7.0 | 6.0 | 6.0 | 6.0 |
| Min, Max | 4, 32 | 4, 50 | 4, 50 | 4, 30 | 3.3, 30 | 3.3, 30 |
| Baseline disease severity[a], n (%) | | | | | | |
| Mild | 65 (22.5) | 79 (25.7) | 144 (24.2) | 83 (32.8) | 97 (37.9) | 180 (35.4) |
| Moderate | 111 (38.4) | 106 (34.5) | 217 (36.4) | 81 (32.0) | 70 (27.3) | 151 (29.7) |
| Severe | 113 (39.1) | 122 (39.7) | 235 (39.4) | 89 (35.2) | 89 (34.8) | 178 (35.0) |
| *C. difficile* Toxin, n (%) | | | | | | |
| Positive | 289 (100) | 307 (100) | 596 (100) | 253 (100) | 256 (100) | 509 (100) |
| Negative | - | - | - | - | - | - |
| CDI Indication, n (%) | | | | | | |
| Diarrhea Alone | 50 (17.3) | 67 (21.8) | 117 (19.6) | 64 (25.3) | 65 (25.4) | 129 (25.3) |
| Diarrhea and Other Symptoms | 239 (82.7) | 240 (78.2) | 479 (80.4) | 189 (74.7) | 191 (74.6) | 380 (74.7) |
| Prior Use of CDI Antibiotics, n (%) | | | | | | |
| Prior Use | 129 (44.6) | 138 (45.0) | 267 (44.8) | 226 (89.3) | 219 (85.5) | 445 (87.4) |
| No Prior Use | 160 (55.4) | 169 (55.0) | 329 (55.2) | 27 (10.7) | 37 (14.5) | 64 (12.6) |
| Metronidazole Failure, n (%) | | | | | | |
| Yes | 13 (4.5) | 17 (5.5) | 30 (5.0) | 12 (4.7) | 9 (3.5) | 21 (4.1) |
| No | 276 (95.5) | 290 (94.5) | 566 (95.0) | 241 (95.3) | 247 (96.5) | 488 (95.9) |

[a] Baseline disease severity categories are defined as: Mild CDI = 4-5 UBM/day or WBC ≤12,000/mm³; Moderate CDI = 6-9 UBM/day or WBC 12,001-15,000 mm³; Severe CDI ≥10 UBM/day or WBC ≥15,001/mm³

### 6.3.5 Subject Disposition

In study 101.1.C.003, 629 subjects were enrolled and randomized, 306 to fidaxomicin and 323 to vancomycin (Figure 6). A total of 596 subjects were included in the mITT population for cure (289 on fidaxomicin and 307 on vancomycin) and 548 subjects were included in the PP population for cure (268 on fidaxomicin and 280 on vancomycin). A total of 518 subjects were included in the mITT population for recurrences (255 on fidaxomicin and 263 on vancomycin) and 432 subjects were included in the PP population for recurrences (213 on fidaxomicin and 219 on vancomycin).

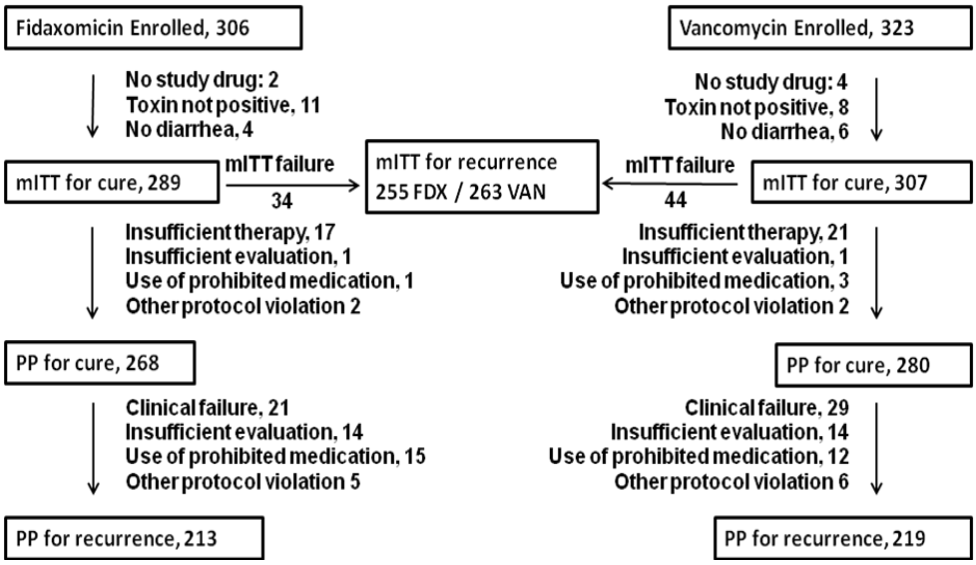



**Figure 6. Subject Disposition in Study 101.1.C.003 by Treatment Randomized**

In study 101.1.C.004, 535 subjects were enrolled and randomized, 271 to fidaxomicin and 264 to vancomycin (Figure 7). A total of 509 subjects were included in the mITT population for cure (253 on fidaxomicin and 256 on vancomycin) and 451 subjects were included in the PP population for cure (217 on fidaxomicin and 234 on vancomycin). A total of 444 subjects were included in the mITT population for recurrences (222 in each treatment group) and 362 subjects were included in the PP population for recurrences (181 in each treatment group).

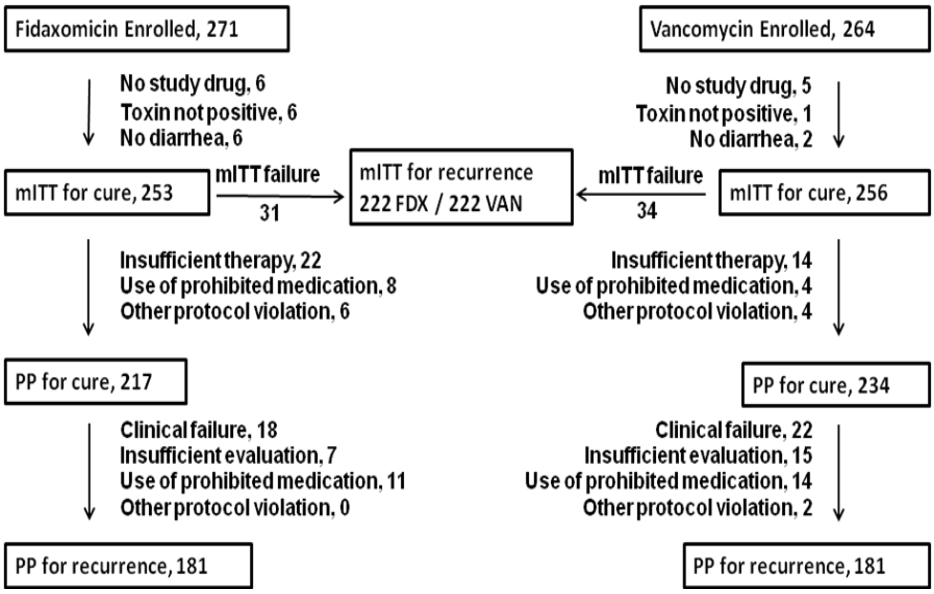



**Figure 7. Subject Disposition in Study 101.1.C.004 by Treatment Randomized**

### 6.3.6 Study Drug Compliance

In both studies compliance was high. In study 101.1.C.003, 91.5% of the prescribed doses were taken in the fidaxomicin group and 90.7% were taken in the vancomycin group and in study 101.1.C.004, 91.3% of the prescribed doses were taken in the fidaxomicin group and 91.9% were taken in the vancomycin group (see Section 7.1).

### 6.3.7 Primary Efficacy Endpoint – Clinical Cure Rates

In both Phase 3 studies, the clinical cure rates in both the PP and mITT populations were similar (Table 20), with a difference between treatment groups of 2.5 (95% CIs -2.4, 7.3) in the PP population in study 101.1.C.003 in favor of fidaxomicin, and a difference of 1.1 (95% CIs -4.2, 6.4) in study 101.1.C.004. Similar results were seen in the mITT analyses. The 95% CI lower limit in all cases was well above the non-inferiority margin of -10%, demonstrating the non-inferiority of fidaxomicin relative to vancomycin. Similar results were seen in sensitivity analyses using an endpoint based strictly on the objective measure of resolution of diarrhea (i.e., ≤3 UBMs during treatment that was sustained to the EOT visit), with a difference of -1.7 (95% CIs -7.7, 4.2) being seen in the PP population in study 101.1.C.003 and a difference of 2.0 (95% CIs -4.6, 8.5) being seen in the study 101.1.C.004 (Table 21). The vancomycin cure rates (86.1% and 84.2%) are similar to those seen in previous studies of CDI [Wenisch, 1996; de Lalla, 1992; Wullt, 2004].

**Table 20. Summary of Clinical Cure Rates at End of Therapy in the Phase 3 Studies**

| | **Study 101.1.C.003** | | | **Study 101.1.C.004** | | | **Pooled 003 and 004** | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] |
| PP population | 247/268 (92.2) | 251/280 (89.6) | 2.5 (-2.4,7.3) | 199/217 (91.7) | 212/234 (90.6) | 1.1 (-4.2,6.4) | 446/485 (92.0) | 463/514 (90.1) | 1.9 (-1.7,5.4) |
| 95% CI around PE[b] | (88.2,94.9) | (85.5,92.7) | | (87.2,94.7) | (86.1,93.7) | | (89.2,94.1) | (87.2,92.4) | |
| mITT population | 255/289 (88.2) | 263/307 (85.7) | 2.6 (-2.9, 8.0) | 222/253 (87.7) | 222/256 (86.7) | 1.0 (-4.8, 6.8) | 477/542 (88.0) | 485/563 (86.1) | 1.9 (-2.1,5.8) |
| 95% CI around PE[b] | (84.0,91.5) | (81.3,89.2) | | (83.1,91.2) | (82.0,90.4) | | (85.0,90.5) | (83.0,88.8) | |
| ITT population | 265/306 (86.6) | 269/323 (83.3) | 3.3 (-2.3, 8.9) | 232/271 (85.6) | 224/264 (84.8) | 0.8 (-5.3, 6.8) | 497/577 (86.1) | 493/587 (84.0) | 2.1 (-2.0, 6.2) |
| 95% CI around PE[b] | (82.3,90.0) | (78.8,87.0) | | (80.9,89.3) | (80.0,88.7) | | (83.1,88.7) | (80.8,86.7) | |

[a]2-sided 95% CI using method recommended by Agresti and Caffo, 2000
[b]PE = point estimate

**Table 21. Summary of Clinical Cure Rates at End of Therapy in the Phase 3 Studies – Sensitivity Analysis of Clinical Cure Rates**

| | Study 101.1.C.003 | | | Study 101.1.C.004 | | | Pooled 003 and 004 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] |
| PP population | 226/268 (84.3) | 241/280 (86.1) | -1.7 (-7.7,4.2) | 187/217 (86.2) | 197/234 (84.2) | 2.0 (-4.6,8.5) | 413/485 (85.2) | 438/514 (85.2) | -0.1 (-4.5,4.3) |
| 95% CI around PE[b] | (79.4,88.2) | (81.5,89.7) | | (80.9,90.2) | (78.9,88.3) | | (81.7,88.0) | (81.9,88.0) | |
| mITT population | 228/289 (78.9) | 247/307 (80.5) | -1.6 (-8.0, 4.9) | 201/253 (79.4) | 203/256 (79.3) | 0.1 (-6.9, 7.2) | 429/542 (79.2) | 450/563 (79.9) | -0.8 (-5.5,4.0) |
| 95% CI around PE[b] | (73.8,83.2) | (75.6,84.5) | | (74.0,84.0) | (73.9,83.8) | | (75.5,82.4) | (76.4,83.0) | |
| ITT population | 237/306 (77.5) | 254/323 (78.6) | -1.2 (-7.6, 5.3) | 211/271 (77.9) | 205/264 (77.7) | 0.2 (-6.8, 7.2) | 448/577 (77.6) | 459/587 (78.2) | -0.6 (-5.3, 4.2) |
| 95% CI around PE[b] | (72.4,81.8) | (73.8,82.8) | | (72.5,82.4) | 72.2,82.3) | | (74.1,80.9) | (74.7,81.3) | |

[a]2-sided 95% CI using method recommended by Agresti and Caffo, 2000
[b]PE = point estimate

### 6.3.8 Secondary and Exploratory Efficacy Endpoints

Apart from the initial assessment of cure rates (as assessed by the primary efficacy parameter), it is also important to consider whether the cure is maintained over time, i.e., whether recurrence occurs. In addition to the recurrence rate, the composite endpoint of global cure was assessed, defined as achieving a cure response at EOT and not having a recurrence at any time up to the post-study visit. A summary of the results of these secondary endpoints is provided in Table 22 for the mITT, PP and ITT populations.

The results showed that the recurrence rate was lower in the fidaxomicin group compared to the vancomycin group, with the difference being statistically significant. The p-values were all below $p \leq 0.008$, indicating a robust superiority of fidaxomicin over vancomycin in the risk of recurrence. Similarly, the global cure rate in subjects treated with fidaxomicin was statistically and clinically superior to subjects treated with vancomycin ($p \leq 0.007$).

**Table 22. Summary of Secondary and Exploratory Endpoints at End of Therapy**

| | Study 101.1.C.003 | | | Study 101.1.C.004 | | | Pooled 003 and 004 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] |
| **Recurrence rates** | | | | | | | | | |
| mITT population | 40/255 (15.7) | 66/263 (25.1) | -9.4 (-16.2,-2.5) p=0.008 | 28/222 (12.6) | 60/222 (27.0) | -14.4 (-21.6,-7.0) p<0.001 | 68/477 (14.3) | 126/485 (26.0) | -11.7 (-16.7,-6.7) p<0.001 |
| PP population | 28/213 (13.1) | 53/219 (24.2) | -11.1 (-18.2,-3.7) p=0.003 | 23/181 (12.7) | 46/181 (25.4) | -12.7 (-20.6,-4.6) p=0.002 | 51/394 (12.9) | 99/400 (24.8) | -11.8 (-17.1,-6.4) p<0.001 |
| ITT population | 41/265 (15.5) | 69/269 (25.7) | -10.2 (-17.0,-3.4) p=0.004 | 28/232 (12.1) | 61/224 (27.2) | -15.2 (-22.4,-8.0) p<0.001 | 69/497 (13.9) | 130/493 (26.4) | -12.5 (-17.4,-7.5) p<0.001 |
| **Global cure rates** | | | | | | | | | |
| mITT population | 215/289 (74.4) | 197/307 (64.2) | 10.2 (2.8,17.5) p=0.007 | 194/253 (76.7) | 162/256 (63.3) | 13.4 (5.4, 21.1) p=0.001 | 409/542 (75.5) | 359/563 (63.8) | 11.7 (6.3,17.0) p<0.001 |
| PP population | 208/268 (77.6) | 188/280 (67.1) | 10.5 (3.0,17.8) p=0.006 | 173/217 (79.7) | 153/234 (65.4) | 14.3 (6.1, 22.3) p<0.001 | 381/485 (78.6) | 341/514 (66.3) | 12.2 (6.7, 17.6) p<0.001 |
| ITT population | 224/306 (73.2) | 200/323 (61.9) | 11.3 (4.0,18.5) p=0.003 | 204/271 (75.3) | 163/264 (61.7) | 13.5 (5.8, 21.3) p<0.001 | 428/577 (74.2) | 363/587 (61.8) | 12.3 (7.0,17.6) p<0.001 |

[a]2-sided 95% CI using method recommended by Agresti and Caffo, 2000
[b]p-value using Pearson's chi-square test

Analysis of time to recurrence showed that subjects treated with fidaxomicin experienced recurrence of CDI later than subjects treated with vancomycin (Figure 8 and Figure 9), with the results being statistically significant using both the log-rank test and the Wilcoxon-Gehan test in both the mITT and PP populations. It is possible that this reflects a difference between relapse of the original infection and re-infection from a new environmental source. It can be postulated that early reduction in recurrence represents prevention of relapse from germination of the resident *C. difficile* spores, and within this time frame fidaxomicin is clearly more effective than vancomycin. However, CDI recurrence after 14 days is more likely to represent a new infection from environmental sources, where rates of recurrence were similar for both treatment groups. This theory is supported by the work of Barbut [Barbut, 2000], who differentiated relapse from re-infection based on extensive microbiologic evaluation of isolates before and after therapy. He concluded that the median time for relapse from the original infection was 7 days, while for re-infection it was 20 days. Preservation of existing gut microflora with fidaxomicin might suppress spore germination and overgrowth to prevent re-infection, while vancomycin, which disrupts the flora, could facilitate germination of spores.

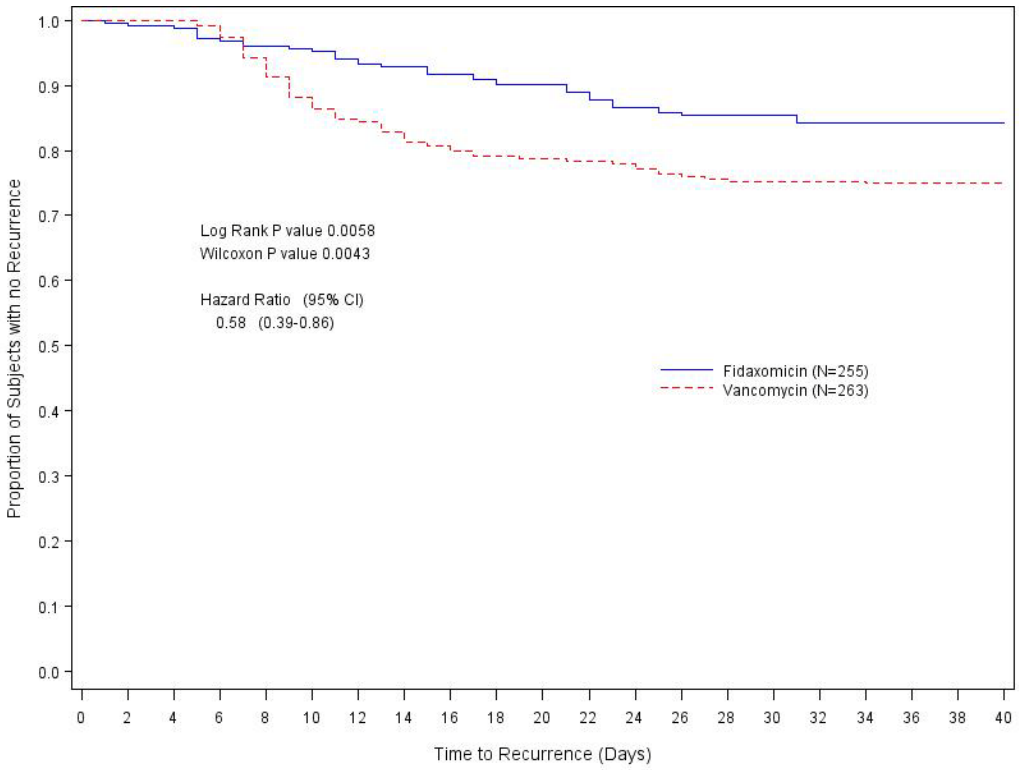



**Figure 8. Time to Recurrence in Phase 3 Study 101.1.C.003 (mITT population)**

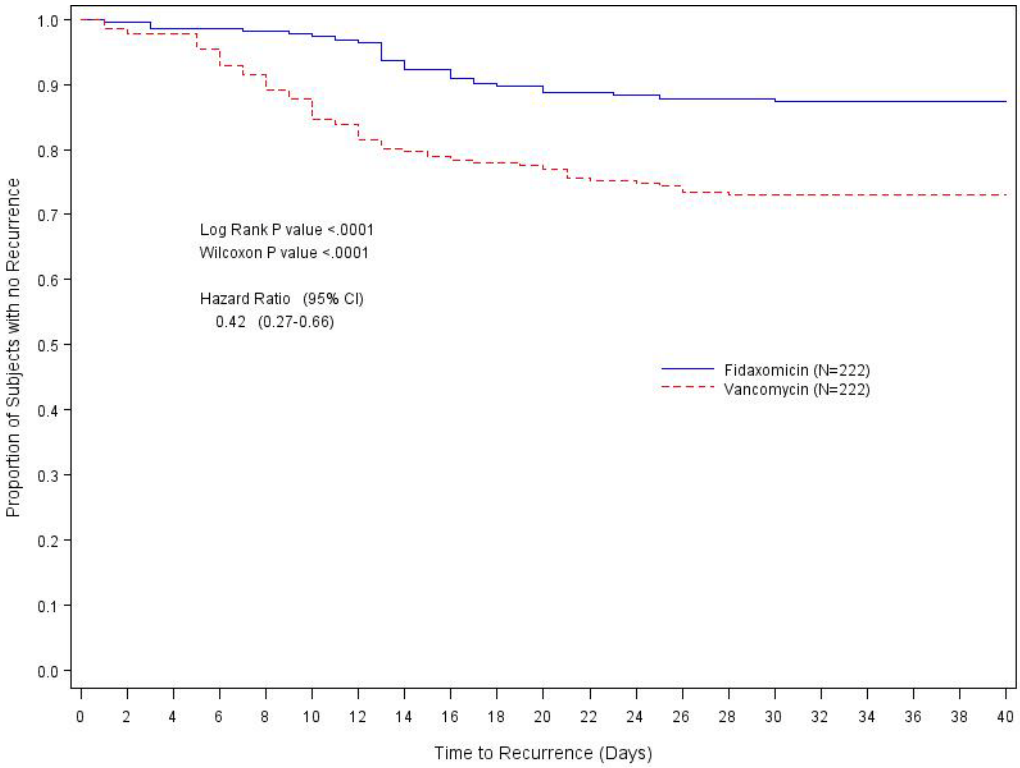



**Figure 9. Time to Recurrence in Phase 3 Study 101.1.C.004 (mITT population)**

For the exploratory endpoint of TTROD, median time to resolution of diarrhea in study 101.1.C.003 was 9 hours earlier in the fidaxomicin group compared with the vancomycin group for the mITT population (73 hours versus 82 hours), however, in study 101.1.C.004, the median TTROD was only 2 hours earlier in the fidaxomicin group compared with the vancomycin group (78 hours versus 80 hours) (Table 23). These differences were not statistically significant. Similar results were seen in the PP population.

**Table 23. Time to Resolution of Diarrhea (Hours) in the Phase 3 Studies (mITT Population)**

| | Study 101.1.C.003 | | Study 101.1.C.004 | | Pooled 003 and 004 | |
|---|---|---|---|---|---|---|
| | Fidaxomicin | Vancomycin | Fidaxomicin | Vancomycin | Fidaxomicin | Vancomycin |
| Resolved, n/N (%) | 188/289 (75.5) | 209/307 (77.7) | 176/253 (77.2) | 174/256 (76.7) | 364/542 (76.3) | 383/563 (77.2) |
| Median (95% CI)[a] | 73.0 (58.0, 84.0) | 82.0 (76.0, 104.0) | 78.0 (60.0, 98.0) | 80.0 (62.0, 97.0) | 75.0 (64.0, 83.0) | 81.0 (75.0, 97.0) |
| p-value: | | | | | | |
| Log-rank | 0.922 | | 0.843 | | 0.809 | |
| Wilcoxon-Gehan | 0.417 | | 0.982 | | 0.527 | |

[a]Kaplan- Meier estimates

### 6.3.9 Subgroup Analyses

Efficacy subgroup analyses for clinical cure, recurrence, and global cure were summarized by the following subgroups:

- Sex
- Race
- Country
- Prior occurrence (no prior episode, single prior episode)
- CDI-prescribed antibiotic within 24 hours prior to study treatment (yes, no)
- Metronidazole failure prior to the study (yes, no)
- Baseline disease severity based on European Society of Clinical Microbiology and Infectious Disease (ESCMID) criteria [Bauer, 2009b] (severe, non-severe)
- Subject status (inpatient, outpatient)
- Initial strain of CDI (BI, non-BI)
- Age group (<65, ≥65)
- Use of concomitant systemic antibacterials (specifically WHO Drug category 'Antiinfectives for Systemic Use' following removal of antiviral and antifungal agents; antibodies and vaccines; and topical or ophthalmic preparations)

### 6.3.9.1 Subgroup Analysis for Clinical Cure Rate

The cure rates for fidaxomicin and vancomycin were similar for all the subgroups evaluated, with no clinically relevant differences being seen, although for some of the subgroups non-inferiority could no longer be concluded due to the small sample sizes. Some differences in clinical cure rates were seen between the subgroups (Table 24), but these were related to the disease characteristics (e.g., subjects in both treatment groups with severe disease had a lower cure rate than those with non-severe disease). A decrease in cure rate was seen in both treatment groups with increasing age, but this difference was not considered clinically relevant since elderly people generally respond less well to treatment for a variety of reasons (e.g., reduced immune response, concomitant illnesses, etc.).

As noted previously, the initial therapeutic approach to a diagnosed CDI case is to stop the causative antibiotic, however, this is not always feasible since continuation of the antibiotic might be necessary to treat the coexistent infection. It is therefore important to evaluate the efficacy of the study drugs in the presence of concomitant antibacterials. In this subgroup analysis it was seen that subjects who received concomitant antibacterials and were randomized to the fidaxomicin group had a higher cure rate than those who were randomized to vancomycin (difference in favor of fidaxomicin of 8.6 [95% CIs -5.1, 21.1] in study 101.1.C.003 and 14.4 [95% CIs -2.2, 30.0] in study 101.1.C.004), demonstrating an important benefit of fidaxomicin treatment in this subgroup of patients.

**Table 24. Summary of Clinical Cure Rates at End of Therapy by Subgroups in the Phase 3 Studies (PP Population)**

| | Study 101.1.C.003 | | | Study 101.1.C.004 | | | Pooled 003 and 004 | | |
|---|---|---|---|---|---|---|---|---|---|
| Subgroup | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] |
| PP for all subjects | 247/268 (92.2) | 251/280 (89.6) | 2.5 (-2.4,7.3) | 199/217 (91.7) | 212/234 (90.6) | 1.1 (-4.2,6.4) | 446/485 (92.0) | 463/514 (90.1) | 1.9 (-1.7,5.4) |
| **Sex** | | | | | | | | | |
| Male | 103/116 (88.8) | 112/125 (89.6) | -0.8 (-8.8, 7.1) | 80/86 (93.0) | 79/88 (89.8) | 3.3 (-5.4,11.7) | 183/202 (90.6) | 191/213 (89.7) | 0.9 (-4.9, 6.7) |
| Female | 144/152 (94.7) | 139/155 (89.7) | 5.1 (-1.1, 11.1) | 119/131 (90.8) | 133/146 (91.1) | -0.3 (-7.2, 6.6) | 263/283 (92.9) | 272/301 (90.4) | 2.6 (-2.0, 7.1) |
| **Race** | | | | | | | | | |
| White | 216/234 (92.3) | 219/246 (89.0) | 3.3 (-2.0, 8.5) | 185/203 (91.1) | 194/215 (90.2) | 0.9 (-4.8, 6.5) | 401/437 (91.8) | 413/461 (89.6) | 2.2 (-1.7, 6.0) |
| Black | 26/29 (89.7) | 25/27 (92.6) | -2.9 (-18.5,13.4) | 11/11 (100.0) | 16/17 (94.1) | 5.9 (-16.5,22.2) | 37/40 (92.5) | 41/44 (93.2) | -0.7 (-12.7,11.1) |
| Asian | 4/4 (100.0) | 6/6 (100.0) | 0.0 (-39.2,30.9) | 2/2 (100.0) | 1/1 (100.0) | 0.0 (-51.5,68.1) | 6/6 (100.0) | 7/7 (100.0) | 0.0 (-30.5,27.7) |
| American Indian/Alaska Native | 1/1 (100.0) | 1/1 (100.0) | 0.0 (-65.3,65.3) | 1/1 (100.0) | 1/1 (100.0) | 0.0 (-65.3,65.3) | 2/2 (100.0) | 2/2 (100.0) | 0.0 (-53.7,53.7) |
| **Country** | | | | | | | | | |
| Canada | 111/117 (94.9) | 109/114 (95.6) | -0.7 (-6.5, 5.1) | 67/70 (95.7) | 74/78 (94.9) | 0.8 (-6.7, 8.1) | 178/187 (95.2) | 183/192 (95.3) | -0.1 (-4.6, 4.3) |
| USA | 136/151 (90.1) | 142/166 (85.5) | 4.5 (-2.8,11.6) | 54/62 (87.1) | 59/68 (86.8) | 0.3 (-11.5,12.0) | 190/213 (89.2) | 201/234 (85.9) | 3.3 (-2.9,9.4) |
| Belgium | NA | NA | NA | 17/18 (94.4) | 15/16 (93.8) | 0.7 (-18.0,20.2) | 17/18 (94.4) | 15/16 (93.8) | 0.7 (-18.0,20.2) |
| Germany | NA | NA | NA | 12/14 (85.7) | 14/17 (82.4) | 3.4 (-23.5,28.1) | 12/14 (85.7) | 14/17 (82.4) | 3.4 (-23.5,28.1) |
| Spain | NA | NA | NA | 5/5 (100.0) | 3/3 (100.0) | 0.0 (-34.4,45.9) | 5/5 (100.0) | 3/3 (100.0) | 0.0 (-34.4,45.9) |

| Subgroup | Study 101.1.C.003 | | | Study 101.1.C.004 | | | Pooled 003 and 004 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] |
| France | NA | NA | NA | 8/9 (88.9) | 6/7 (85.7) | 3.2 (-29.7,37.8) | 8/9 (88.9) | 6/7 (85.7) | 3.2 (-29.7,37.8) |
| UK | NA | NA | NA | 20/23 (87.0) | 22/25 (88.0) | -1.0 (-20.5,18.1) | 20/23 (87.0) | 22/25 (88.0) | -1.0 (-20.5,18.1) |
| Italy | NA | NA | NA | 13/13 (100.0) | 12/13 (92.3) | 7.7 (-14.0,27.3) | 13/13 (100.0) | 12/13 (92.3) | 7.7 (-14.0,27.3) |
| Sweden | NA | NA | NA | 3/3 (100.0) | 7/7 (100.0) | 0.0 (-46.4,28.6) | 3/3 (100.0) | 7/7 (100.0) | 0.0 (-46.4,28.6) |
| **Stratum** | | | | | | | | | |
| No Prior Episode | 206/225 (91.6) | 206/232 (88.8) | 2.8 (-2.8, 8.2) | 166/181 (91.7) | 181/199 (91.0) | 0.8 (-5.0, 6.4) | 372/406 (91.6) | 387/431 (89.8) | 1.8 (-2.1, 5.8) |
| Single Prior Episode | 41/43 (95.3) | 45/48 (93.8) | 1.6 (-9.0, 11.7) | 33/36 (91.7) | 31/35 (88.6) | 3.1 (-11.5 17.5) | 74/79 (93.7) | 76/83 (91.6) | 2.1 (-6.4,10.4) |
| **CDI Antibiotic 24 Hours Prior to Study** | | | | | | | | | |
| Yes | 86/101 (85.1) | 91/108 (84.3) | 0.9 (-9.0, 10.6) | 73/83 (88.0) | 74/87 (85.1) | 2.9 (-7.6, 13.1) | 159/184 (86.4) | 165/195 (84.6) | 1.8 (-5.3, 8.9) |
| No | 160/166 (96.4) | 160/172 (93.0) | 3.4 (-1.6, 8.2) | 126/134 (94.0) | 138/147 (93.9) | 0.2 (-5.7, 5.9) | 286/300 (95.3) | 298/319 (93.4) | 1.9 (-1.8,5.6) |
| **Metronidazole Failure Prior to Study** | | | | | | | | | |
| Yes | 13/13 (100.0) | 14/16 (87.5) | 12.5 (-10.7,30.7) | 12/12 (100.0) | 6/7 (85.7) | 14.3 (-13.8,44.0) | 25/25 (100.0) | 20/23 (87.0) | 13.0 (-3.4,28.0) |
| No | 234/255 (91.8) | 237/264 (89.8) | 2.0 (-3.1, 7.0) | 187/205 (91.2) | 206/227 (90.7) | 0.5 (-5.0, 5.9) | 421/460 (91.5) | 443/491 (90.2) | 1.3 (-2.4,5.0) |
| **Baseline Disease Severity** | | | | | | | | | |
| Severe | 54/63 (85.7) | 58/72 (80.6) | 5.2 (-7.7, 17.5) | 45/53 (84.9) | 42/53 (79.2) | 5.7 (-9.1,20.0) | 99/116 (85.3) | 100/125 (80.0) | 5.3 (-4.3,14.7) |
| Non-severe | 193/205 (94.1) | 193/208 (92.8) | 1.4 (-3.5,6.2) | 154/164 (93.9) | 170/181 (93.9) | -0.0 (-5.3, 5.1) | 347/369 (94.0) | 363/389 (93.3) | 0.7 (-2.8, 4.2) |
| **Subject Status** | | | | | | | | | |
| Inpatient | 130/148 (87.8) | 134/160 (83.8) | 4.1 (-3.8,11.8) | 129/144 (89.6) | 135/154 (87.7) | 1.9 (-5.4, 9.1) | 259/292 (88.7) | 269/314 (85.7) | 3.0 (-2.3, 8.3) |
| Outpatient | 117/120 (97.5) | 117/120 (97.5) | -0.0 (-4.5, 4.5) | 70/73 (95.9) | 77/80 (96.3) | -0.4 (-7.3, 6.4) | 187/193 (96.9) | 194/200 (97.0) | -0.1 (-3.7, 3.5) |
| **Initial Strain of CDI** | | | | | | | | | |
| BI | 57/66 (86.4) | 60/71 (84.5) | 1.9 (-10.1,13.6) | 49/55 (89.1) | 48/55 (87.3) | 1.8 (-10.5,14.1) | 106/121 (87.6) | 108/126 (85.7) | 1.9 (-6.7,10.4) |
| Non-BI | 116/120 (96.7) | 118/125 (94.4) | 2.3 (-3.3,7.7) | 110/117 (94.0) | 101/110 (91.8) | 2.2 (-4.7,9.1) | 226/237 (95.4) | 219/235 (93.2) | 2.2 (-2.1, 6.4) |
| **Age Group[b]** | | | | | | | | | |
| <65 | 147/154 (95.5) | 130/143 (90.9) | 4.5 (-1.4, 10.4) | 96/104 (92.3) | 110/119 (92.4) | -0.1 (-7.4, 7.0) | 243/258 (94.2) | 240/262 (91.6) | 2.6 (-1.9, 7.0) |
| ≥65 | 100/114 (87.7) | 121/137 (88.3) | -0.6 (-8.9,7.4) | 103/113 (91.2) | 102/115 (88.7) | 2.5 (-5.5, 10.3) | 203/227 (89.4) | 223/252 (88.5) | 0.9 (-4.8, 6.5) |
| **Concomitant Antibacterials[b]** | | | | | | | | | |
| Yes | 43/48 (89.6) | 51/63 (81.0) | 8.6 (-5.1, 21.1) | 39/43 (90.7) | 29/38 (76.3) | 14.4 (-2.2, 30.0) | 82/91 (90.1) | 80/101 (79.2) | 10.9 (0.5, 20.7) |
| No | 204/220 (92.7) | 200/217 (92.2) | 0.6 (-4.5,5.6) | 160/174 (92.0) | 183/196 (93.4) | -1.4 (-6.9, 4.0) | 364/394 (92.4) | 383/413 (92.7) | -0.4 (-4.0, 3.3) |

[a]2-sided 95% CI using method recommended by Agresti and Caffo, 2000, NA = not applicable
[b]Added as post-hoc analyses

### 6.3.9.2 Subgroup Analysis for Recurrence

For the majority of subgroups, the recurrence rate was numerically lower for the fidaxomicin group than the associated vancomycin group. The exception was for subjects infected with BI strains in the 101.1.C.003 study, which showed a numerically higher recurrence rate for the fidaxomicin group. Conversely, in the 101.1.C.004 study, the recurrence rate was lower in the fidaxomicin group. For non-BI strains, fidaxomicin had a significantly lower recurrence rate in all populations studied. Higher recurrence rates were seen in both treatment groups

with increasing age, which is not unexpected given that the elderly are more prone to CDI compared to younger subjects. This is probably due to increased exposure to health care facilities, pre- existing co-morbidities, and weakened immune systems [Wistrom, 2001; Calfee, 2008]. In addition, subjects who presented with a prior episode of CDI showed higher recurrence rates, which again is not unexpected since subjects having a previous episode might be harboring *C. difficile* spores leading to relapsing infection. Finally, subjects who used CDI therapy within 24 hours of first dose of study treatment or who were given concomitant anti-infective therapy during the study had higher recurrence rates. This again is expected, since CDI is attributed to the frequent prescription of broad-spectrum antibiotics [Wilcox, 1996].

**Table 25. Summary of Recurrence Rates at End of Therapy by Subgroups in the Phase 3 Studies (mITT Population)**

| | Study 101.1.C.003 | | | Study 101.1.C.004 | | | Pooled 003 and 004 | | |
|---|---|---|---|---|---|---|---|---|---|
| Subgroup | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] |
| mITT for all subjects | 40/255 (15.7) | 66/263 (25.1) | -9.4 (-16.2,-2.5) p=0.008 | 28/222 (12.6) | 60/222 (27.0) | -14.4 (-21.6,-7.0) p<0.001 | 68/477 (14.3) | 126/485 (26.0) | -11.7 (-16.7,-6.7) p<0.001 |
| **Sex** | | | | | | | | | |
| Male | 17/107 (15.9) | 31/119 (26.1) | -10.2 (-20.4, 0.5) p=0.062 | 13/92 (14.1) | 24/80 (30.0) | -15.9 (-27.8,-3.4) p=0.012 | 30/199 (15.1) | 55/199 (27.6) | -12.6 (-20.4,-4.5) p=0.002 |
| Female | 23/148 (15.5) | 35/144 (24.3) | -8.8 (-17.8, 0.4) p=0.061 | 15/130 (11.5) | 36/142 (25.4) | -13.8 (-22.6,-4.6) p=0.004 | 38/278 (13.7) | 71/286 (24.8) | -11.2 (-17.5,-4.6) p<0.001 |
| **Race** | | | | | | | | | |
| White | 34/223 (15.2) | 63/229 (27.5) | -12.3 (-19.6,-4.7) p=0.002 | 26/203 (12.8) | 56/204 (27.5) | -14.6 (-22.1,-6.9) p<0.001 | 60/426 (14.1) | 119/433 (27.5) | -13.4 (-18.7,-8.0) p<0.001 |
| Black | 5/27 (18.5) | 3/27 (11.1) | 7.4 (-12.1,25.9) p=0.444 | 2/16 (12.5) | 4/16 (25.0) | -12.5 (-37.3,15.1) p=0.365 | 7/43 (16.3) | 7/43 (16.3) | 0.0 (-15.6,15.6) p=1.000 |
| Asian | 0/4 (0.0) | 0/6 (0.0) | 0.0 (-30.9,39.2) | 0/2 (0.0) | 0/1 (0.0) | 0.0 (-68.1,51.5) | 0/6 (0.0) | 0/7 (0.0) | 0.0 (-27.7,30.5) |
| American Indian/Alaska Native | 1/1 (100.0) | 0/1 (0.0) | 100.0 (-32.2,98.7) p=0.157 | 0/1 (0.0) | 0/1 (0.0) | 0.0 (-65.3,65.3) | 1/2 (50.0) | 0/2 (0.0) | 50.0 (-33.0,83.0) p=0.248 |
| **Country** | | | | | | | | | |
| Canada | 14/113 (12.4) | 29/112 (25.9) | -13.5 (-23.4,-3.2) p=0.010 | 12/70 (17.1) | 24/75 (32.0) | -14.9 (-28.0,-0.8) p=0.039 | 26/183 (14.2) | 53/187 (28.3) | -14.1 (-22.2,-5.8) p<0.001 |
| USA | 26/142 (18.3) | 37/151 (24.5) | -6.2 (-15.4, 3.2) p=0.197 | 8/63 (12.7) | 17/65 (26.2) | -13.5 (-26.5, 0.4) p=0.055 | 34/205 (16.6) | 54/216 (25.0) | -8.4 (-16.0,-0.6) p=0.034 |
| Belgium | NA | NA | NA | 2/21 (9.5) | 5/16 (31.3) | -21.7 (-45.4,4.8) p=0.095 | 2/21 (9.5) | 5/16 (31.3) | -21.7 (-45.4, 4.8) p=0.095 |
| Germany | NA | NA | NA | 0/14 (0.0) | 1/14 (7.1) | -7.1 (-25.7,13.2) p=0.309 | 0/14 (0.0) | 1/14 (7.1) | -7.1 (-25.7,13.2) p=0.309 |
| Spain | NA | NA | NA | 3/5 (60.0) | 2/4 (50.0) | 10.0 (-43.3,57.6) p=0.764 | 3/5 (60.0) | 2/4 (50.0) | 10.0 (-43.3,57.6) p=0.764 |
| France | NA | NA | NA | 1/10 (10.0) | 1/7 (14.3) | -4.3 (-38.3,27.2) p=0.787 | 1/10 (10.0) | 1/7 (14.3) | -4.3 (-38.3,27.2) p=0.787 |
| UK | NA | NA | NA | 1/22 (4.5) | 7/22 (31.8) | -27.3 (-46.4,-3.6) p=0.019 | 1/22 (4.5) | 7/22 (31.8) | -27.3 (-46.4,-3.6) p=0.019 |

| Subgroup | Study 101.1.C.003 Fidaxomicin n/N (%) | Study 101.1.C.003 Vancomycin n/N (%) | Study 101.1.C.003 Difference 95% CI[a] p-value[b] | Study 101.1.C.004 Fidaxomicin n/N (%) | Study 101.1.C.004 Vancomycin n/N (%) | Study 101.1.C.004 Difference 95% CI[a] p-value[b] | Pooled 003 and 004 Fidaxomicin n/N (%) | Pooled 003 and 004 Vancomycin n/N (%) | Pooled 003 and 004 Difference 95% CI[a] p-value[b] |
|---|---|---|---|---|---|---|---|---|---|
| Italy | NA | NA | NA | 0/14 (0.0) | 1/12 (8.3) | -8.3 (-29.2,13.1) p=0.271 | 0/14 (0.0) | 1/12 (8.3) | -8.3 (-29.2,13.1) p=0.271 |
| Sweden | NA | NA | NA | 1/3 (33.3) | 2/7 (28.6) | 4.8 (-42.2,55.6) p=0.880 | 1/3 (33.3) | 2/7 (28.6) | 4.8 (-42.2,55.6) p=0.880 |
| **Stratum** | | | | | | | | | |
| No Prior Episode | 31/213 (14.6) | 51/215 (23.7) | -9.2 (-16.5,-1.7) p=0.016 | 21/185 (11.4) | 49/190 (25.8) | -14.4 (-22.0,-6.6) p<0.001 | 52/398 (13.1) | 100/405 (24.7) | -11.6 (-16.9,-6.2) p<0.001 |
| Single Prior Episode | 9/42 (21.4) | 15/48 (31.3) | -9.8 (-27.0, 8.4) p=0.293 | 7/37 (18.9) | 11/32 (34.4) | -15.5 (-35.0, 5.4) p=0.145 | 16/79 (20.3) | 26/80 (32.5) | -12.2 (-25.4,1.5) p=0.080 |
| **CDI Antibiotic 24 Hours Prior to Study** | | | | | | | | | |
| Yes | 16/89 (18.0) | 25/96 (26.0) | -8.1 (-19.6, 3.9) p=0.187 | 13/83 (15.7) | 25/80 (31.3) | -15.6 (-28.0,-2.5) p=0.019 | 29/172 (16.9) | 50/176 (28.4) | -11.5 (-20.1,-2.7) p=0.010 |
| No | 24/165 (14.5) | 41/167 (24.6) | -10.0 (-18.3,-1.4) p=0.022 | 15/139 (10.8) | 35/142 (24.6) | -13.9 (-22.4,-4.9) p=0.002 | 39/304 (12.8) | 76/309 (24.6) | -11.8 (-17.8,-5.6) p<0.001 |
| **Metronidazole Failure Prior to Study** | | | | | | | | | |
| Yes | 2/13 (15.4) | 2/15 (13.3) | 2.1 (-24.0,28.7) p=0.877 | 1/12 (8.3) | 1/8 (12.5) | -4.2 (-35.2,23.8) p=0.761 | 3/25 (12.0) | 3/23 (13.0) | -1.0 (-20.5,18.1) p=0.913 |
| No | 38/242 (15.7) | 64/248 (25.8) | -10.1 (-17.1,-2.9) p=0.006 | 27/210 (12.9) | 59/214 (27.6) | -14.7 (-22.1,-7.1) p<0.001 | 65/452 (14.4) | 123/462 (26.6) | -12.2 (-17.4,-7.0) p<0.001 |
| **Baseline Disease Severity** | | | | | | | | | |
| Severe | 11/56 (19.6) | 18/63 (28.6) | -8.9 (-23.6, 6.5) p=0.258 | 4/48 (8.3) | 14/43 (32.6) | -24.2 (-39.3,-7.4) p=0.004 | 15/104 (14.4) | 32/106 (30.2) | -15.8 (-26.5,-4.5) p=0.006 |
| Non-severe | 29/199 (14.6) | 48/200 (24.0) | -9.4 (-17.0,-1.7) p=0.017 | 24/174 (13.8) | 46/179 (25.7) | -11.9 (-19.9,-3.6) p=0.005 | 53/373 (14.2) | 94/379 (24.8) | -10.6 (-16.1,-4.9) p<0.001 |
| **Subject Status** | | | | | | | | | |
| Inpatient | 25/137 (18.2) | 39/145 (26.9) | -8.6 (-18.2, 1.1) p=0.083 | 19/151 (12.6) | 36/142 (25.4) | -12.8 (-21.5,-3.7) p=0.005 | 44/288 (15.3) | 75/287 (26.1) | -10.9 (-17.3,-4.2) p=0.001 |
| Outpatient | 15/118 (12.7) | 27/118 (22.9) | -10.2 (-19.7,-0.3) p=0.041 | 9/71 (12.7) | 24/80 (30.0) | -17.3 (-29.4,-4.2) p=0.010 | 24/189 (12.7) | 51/198 (25.8) | -13.1 (-20.6,-5.2) p=0.001 |
| **Initial Strain of CDI** | | | | | | | | | |
| BI | 16/60 (26.7) | 14/66 (21.2) | 5.5 (-9.4,20.1) p=0.473 | 12/54 (22.2) | 19/50 (38.0) | -15.8 (-32.3, 1.8) p=0.079 | 28/114 (24.6) | 33/116 (28.4) | -3.9 (-15.1,7.5) p=0.504 |
| Non-BI | 13/118 (11.0) | 33/120 (27.5) | -16.5 (-26.0,-6.4) p=0.001 | 11/120 (9.2) | 29/106 (27.4) | -18.2 (-27.9,-8.0) p<0.001 | 24/238 (10.1) | 62/226 (27.4) | -17.3 (-24.2,-10.0) p<0.001 |
| **Age Group[c]** | | | | | | | | | |
| <65 | 19/151 (12.6) | 27/133 (20.3) | -7.7 (-16.3,1.0) p=0.078 | 12/101 (11.9) | 30/114 (26.3) | -14.4 (-24.4,-3.9) p=0.008 | 31/252 (12.3) | 57/247 (23.1) | -10.8 (-17.3,-4.1) p=0.002 |
| ≥65 | 21/104 (20.2) | 39/130 (30.0) | -9.8 (-20.5, 1.4) p=0.088 | 16/121 (13.2) | 30/108 (27.8) | -14.6 (-24.7,-4.0) p=0.006 | 37/225 (16.4) | 69/238 (29.0) | -12.5 (-19.9,-4.9) p=0.001 |

| Subgroup | Study 101.1.C.003 | | | Study 101.1.C.004 | | | Pooled 003 and 004 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] |
| **Concomitant Antibacterials[c]** | | | | | | | | | |
| Yes | 13/60 (21.7) | 22/75 (29.3) | -7.7 (-21.8,7.2) p=0.313 | 13/74 (17.6) | 12/55 (21.8) | -4.3 (-18.2, 9.5) p=0.546 | 26/134 (19.4) | 34/130 (26.2) | -6.8 (-16.7, 3.4) p=0.191 |
| No | 27/195 (13.8) | 44/188 (23.4) | -9.6 (-17.2, -1.7) p=0.016 | 15/148 (10.1) | 48/167 (28.7) | -18.6 (-26.7,-9.9) p<0.001 | 42/343 (12.2) | 92/355 (25.9) | -13.7 (-19.3,-7.9) p<0.001 |

[a]2-sided 95% CI using method recommended by Agresti and Caffo, 2000
[b]p-value using Pearson's chi-square test
[c]Added as post-hoc analyses

### 6.3.9.3 Subgroup Analysis for Global Cure Rate

A number of subgroup variables showed an association with global cure rate in the mITT population in both studies (Table 26). These variables were stratum (lower global cure rate for subjects with a prior episode); use of CDI therapy within 24 hours of first dose of study treatment (users had a lower global cure rate); subject status (inpatients had a lower global cure rate than outpatients); disease severity at baseline (subjects with severe disease had a lower global cure rate than those with non-severe disease); BI strain versus non-BI strain (lower global cure rate for BI strain); and use of concomitant antibacterials (users had a lower global cure rate). In addition, a decrease in global cure rates were seen in both treatment groups with increasing age, related to the decrease in clinical cure rate and the increase in recurrence rates with increasing age, as noted previously. For the majority of the subgroup variables, the global cure rate for the fidaxomicin group was higher than that of the associated vancomycin group. For the variables where this difference was not seen, only a small number of subjects were included in the subgroups, so no meaningful conclusions can be drawn.

**Table 26. Summary of Global Cure Rates at End of Therapy by Subgroups in the Phase 3 Studies (mITT Population)**

| Subgroup | Study 101.1.C.003 | | | Study 101.1.C.004 | | | Pooled 003 and 004 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] |
| mITT for all subjects | 215/289 (74.4) | 197/307 (64.2) | 10.2 (2.8,17.5) p=0.007 | 194/253 (76.7) | 162/256 (63.3) | 13.4 (5.4, 21.1) p=0.001 | 409/542 (75.5) | 359/563 (63.8) | 11.7 (6.3,17.0) p<0.001 |
| **Sex** | | | | | | | | | |
| Male | 90/125 (72.0) | 88/138 (63.8) | 8.2 (-3.1, 19.2) p=0.154 | 79/104 (76.0) | 56/95 (58.9) | 17.0 (4.0, 29.4) p=0.010 | 169/229 (73.8) | 144/233 (61.8) | 12.0 (3.5, 20.3) p=0.006 |
| Female | 125/164 (76.2) | 109/169 (64.5) | 11.7 (1.9, 21.2) p=0.019 | 115/149 (77.2) | 106/161 (65.8) | 11.3 (1.3, 21.1) p=0.027 | 240/313 (76.7) | 215/330 (65.2) | 11.5 (4.5, 18.4) p=0.001 |

| Subgroup | Study 101.1.C.003 Fidaxomicin n/N (%) | Study 101.1.C.003 Vancomycin n/N (%) | Study 101.1.C.003 Difference 95% CI[a] p-value[b] | Study 101.1.C.004 Fidaxomicin n/N (%) | Study 101.1.C.004 Vancomycin n/N (%) | Study 101.1.C.004 Difference 95% CI[a] p-value[b] | Pooled 003 and 004 Fidaxomicin n/N (%) | Pooled 003 and 004 Vancomycin n/N (%) | Pooled 003 and 004 Difference 95% CI[a] p-value[b] |
|---|---|---|---|---|---|---|---|---|---|
| **Race** | | | | | | | | | |
| White | 189/254 (74.4) | 166/265 (62.6) | 11.8 (3.8, 19.6) p=0.004 | 177/233 (76.0) | 148/237 (62.4) | 13.5 (5.2, 21.6) p=0.002 | 366/487 (75.2) | 314/502 (62.5) | 12.6 (6.8, 18.3) p<0.001 |
| Black | 22/30 (73.3) | 24/33 (72.7) | 0.6 (-20.8,21.7) p=0.957 | 14/17 (82.4) | 12/17 (70.6) | 11.8 (-16.6,37.6) p=0.419 | 36/47 (76.6) | 36/50 (72.0) | 4.6 (-12.7,21.4) p=0.605 |
| Asian | 4/4 (100.0) | 6/7 (85.7) | 14.3 (-32.2,43.3) p=0.428 | 2/2 (100.0) | 1/1 (100.0) | 0.0 (-51.5,68.1) | 6/6 (100.0) | 7/8 (87.5) | 12.5 (-24.5,39.5) p=0.369 |
| American Indian/Alaska Native | 0/1 (0.0) | 1/2 (50.0) | -50.0 (-80.3,47.0) p=0.387 | 1/1 (100.0) | 1/1 (100.0) | 0.0 (-65.3,65.3) | 1/2 (50.0) | 2/3 (66.7) | -16.7 (-68.8,48.8) p=0.709 |
| **Country** | | | | | | | | | |
| Canada | 99/124 (79.8) | 83/121 (68.6) | 11.2 (0.3, 21.9) p=0.044 | 58/79 (73.4) | 51/82 (62.2) | 11.2 (-3.2, 25.1) p=0.128 | 157/203 (77.3) | 134/203 (66.0) | 11.3 (2.6, 19.9) p=0.011 |
| USA | 116/165 (70.3) | 114/186 (61.3) | 9.0 (-0.9, 18.7) p=0.076 | 55/74 (74.3) | 48/76 (63.2) | 11.2 (-3.6, 25.4) p=0.141 | 171/239 (71.5) | 162/262 (61.8) | 9.7 (1.5, 17.8) p=0.021 |
| Belgium | NA | NA | NA | 19/22 (86.4) | 11/20 (55.0) | 31.4 (3.7, 53.8) p=0.025 | 19/22 (86.4) | 11/20 (55.0) | 31.4 (3.7, 53.8) p=0.025 |
| Germany | NA | NA | NA | 14/18 (77.8) | 13/19 (68.4) | 9.4 (-18.7,35.4) p=0.522 | 14/18 (77.8) | 13/19 (68.4) | 9.4 (-18.7,35.4) p=0.522 |
| Spain | NA | NA | NA | 2/5 (40.0) | 2/4 (50.0) | -10.0 (-57.6,43.3) p=0.764 | 2/5 (40.0) | 2/4 (50.0) | -10.0 (-57.6,43.3) p=0.764 |
| France | NA | NA | NA | 9/11 (81.8) | 6/8 (75.0) | 6.8 (-28.0,41.9) p=0.719 | 9/11 (81.8) | 6/8 (75.0) | 6.8 (-28.0,41.9) p=0.719 |
| UK | NA | NA | NA | 21/26 (80.8) | 15/27 (55.6) | 25.2 (0.2,46.6) p=0.049 | 21/26 (80.8) | 15/27 (55.6) | 25.2 (0.2,46.6) p=0.049 |
| Italy | NA | NA | NA | 14/14 (100.0) | 11/13 (84.6) | 15.4 (-9.0,36.5) p=0.127 | 14/14 (100.0) | 11/13 (84.6) | 15.4 (-9.0,36.5) p=0.127 |
| Sweden | NA | NA | NA | 2/4 (50.0) | 5/7 (71.4) | -21.4 (-63.8,30.5) p=0.477 | 2/4 (50.0) | 5/7 (71.4) | -21.4 (-63.8,30.5) p=0.477 |
| **Stratum** | | | | | | | | | |
| No Prior Episode | 182/241 (75.5) | 164/253 (64.8) | 10.7 (2.6, 18.6) p=0.010 | 164/213 (77.0) | 141/220 (64.1) | 12.9 (4.3, 21.2) p=0.003 | 346/454 (76.2) | 305/473 (64.5) | 11.7 (5.9, 17.5) p<0.001 |
| Single Prior Episode | 33/48 (68.8) | 33/54 (61.1) | 7.6 (-10.7,25.3) p=0.420 | 30/40 (75.0) | 21/36 (58.3) | 16.7 (-4.4, 36.2) p=0.123 | 63/88 (71.6) | 54/90 (60.0) | 11.6 (-2.3, 25.0) p=0.103 |
| **CDI Antibiotic 24 Hours Prior to Study** | | | | | | | | | |
| Yes | 73/112 (65.2) | 71/122 (58.2) | 7.0 (-5.4, 19.1) p=0.273 | 70/98 (71.4) | 55/97 (56.7) | 14.7 (1.3, 27.6) p=0.032 | 143/210 (68.1) | 126/219 (57.5) | 10.6 (1.4, 19.5) p=0.024 |
| No | 141/176 (80.1) | 126/185 (68.1) | 12.0 (3.0, 20.8) p=0.009 | 124/155 (80.0) | 107/159 (67.3) | 12.7 (3.0, 22.1) p=0.011 | 265/331 (80.1) | 233/344 (67.7) | 12.3 (5.7, 18.8) p<0.001 |
| **Metronidazole Failure Prior to Study** | | | | | | | | | |
| Yes | 11/13 (84.6) | 13/17 (76.5) | 8.1 (-21.2,33.8) p=0.581 | 11/12 (91.7) | 7/9 (77.8) | 13.9 (-17.8,43.8) p=0.368 | 22/25 (88.0) | 20/26 (76.9) | 11.1 (-10.3,30.7) p=0.300 |
| No | 204/276 (73.9) | 184/290 (63.4) | 10.5 (2.8, 17.9) p=0.007 | 183/241 (75.9) | 155/247 (62.8) | 13.2 (5.0,21.1) p=0.002 | 387/517 (74.9) | 339/537 (63.1) | 11.7 (6.2, 17.2) p<0.001 |

| Subgroup | Study 101.1.C.003 | | | Study 101.1.C.004 | | | Pooled 003 and 004 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] | Fidaxo-micin n/N (%) | Vanco-mycin n/N (%) | Difference 95% CI[a] p-value[b] |
| **Baseline Disease Severity** | | | | | | | | | |
| Severe | 45/74 (60.8) | 45/81 (55.6) | 5.3 (-10.1,20.3) p=0.508 | 44/63 (69.8) | 29/61 (47.5) | 22.3 (5.1, 38.2) p=0.012 | 89/137 (65.0) | 74/142 (52.1) | 12.9 (1.3, 24.0) p=0.030 |
| Non-severe | 170/215 (79.1) | 152/226 (67.3) | 11.8 (3.5, 19.8) p=0.005 | 150/190 (78.9) | 133/195 (68.2) | 10.7 (1.9, 19.3) p=0.017 | 320/405 (79.0) | 285/421 (67.7) | 11.3 (5.3, 17.2) p<0.001 |
| **Subject Status** | | | | | | | | | |
| Inpatient | 112/168 (66.7) | 106/186 (57.0) | 9.7 (-0.4, 19.6) p=0.062 | 132/175 (75.4) | 106/172 (61.6) | 13.8 (4.0, 23.3) p=0.006 | 244/343 (71.1) | 212/358 (59.2) | 11.9 (4.9, 18.8) p<0.001 |
| Outpatient | 103/121 (85.1) | 91/121 (75.2) | 9.9 (-0.2, 19.7) p=0.053 | 62/78 (79.5) | 56/84 (66.7) | 12.8 (-0.9, 25.8) p=0.067 | 165/199 (82.9) | 147/205 (71.7) | 11.2 (3.0, 19.2) p=0.007 |
| **Initial Strain of CDI** | | | | | | | | | |
| BI | 44/76 (57.9) | 52/82 (63.4) | -5.5 (-20.4, 9.6) p=0.478 | 42/65 (64.6) | 31/60 (51.7) | 12.9 (-4.2, 29.4) p=0.142 | 86/141 (61.0) | 83/142 (58.5) | 2.5 (-8.8, 13.8) p=0.663 |
| Non-BI | 105/126 (83.3) | 87/131 (66.4) | 16.9 (6.3, 27.0) p=0.002 | 109/131 (83.2) | 77/121 (63.6) | 19.6 (8.7, 29.9) p<0.001 | 214/257 (83.3) | 164/252 (65.1) | 18.2 (10.6, 25.5) p<0.001 |
| **Age Group[c]** | | | | | | | | | |
| <65 | 132/166 (79.5) | 106/156 (67.9) | 11.6 (1.9,20.9) p=0.018 | 89/111 (80.2) | 84/125 (67.2) | 13.0 (1.7,23.7) p=0.025 | 221/277 (79.8) | 190/281 (67.6) | 12.2 (4.9,19.3) p=0.001 |
| ≥65 | 83/123 (67.5) | 91/151 (60.3) | 7.2 (-4.2, 18.3) p=0.217 | 105/142 (73.9) | 78/131 (59.5) | 14.4 (3.2, 25.2) p=0.011 | 188/265 (70.9) | 169/282 (59.9) | 11.0 (3.1, 18.8) p=0.007 |
| **Concomitant Antibacterials[c]** | | | | | | | | | |
| Yes | 47/73 (64.4) | 53/98 (54.1) | 10.3 (-4.5,24.5) p=0.176 | 61/83 (73.5) | 43/69 (62.3 | 11.2 (-3.7,25.6) p=0.140 | 108/156 (69.2) | 96/167 (57.5) | 11.7 (1.2, 21.9) p=0.029 |
| No | 168/216 (77.8) | 144/209 (68.9) | 8.9 (0.5, 17.1) p=0.038 | 133/170 (78.2) | 119/187 (63.6) | 14.6 (5.2, 23.6) p=0.003 | 301/386 (78.0) | 263/396 (66.4) | 11.6 (5.3, 17.7) p<0.001 |

[a]2-sided 95% CI using method recommended by Agresti and Caffo, 2000
[b]p-value using Pearson's chi-square test
[c]Added as post-hoc analyses

## 6.4 Correlation Between Susceptibility and Clinical Outcome

When clinical outcomes were analyzed by baseline strain susceptibility, there was no correlation identified, with susceptibilities being the same whether the subject was a cure or failure, or a recurrence or non-recurrence (Table 27). An analysis of cure rates at each MIC value also did not indicate a correlation between clinical outcome and MIC.

**Table 27. Baseline Strain Susceptibilities Versus Outcome for Pooled Phase 3 Studies (mITT Population)**

| Treatment Group | Outcome | | N | Geometric Mean | Range (min-max) | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|---|---|---|
| Fidaxomicin | Cure | Fidaxomicin | 352 | 0.10 | 0.007-1.0 | 0.125 | 0.25 |
| | | Vancomycin | 352 | 0.96 | 0.25-4.0 | 1.0 | 2.0 |
| | | Metronidazole | 352 | 0.46 | 0.05-4.0 | 0.5 | 1.0 |
| | | Rifaximin | 352 | 0.03 | 0.003-257.0 | 0.015 | 0.125 |
| | Failure | Fidaxomicin | 46 | 0.13 | 0.015-0.5 | 0.125 | 0.25 |
| | | Vancomycin | 46 | 1.20 | 0.5-4.0 | 1.0 | 4.0 |
| | | Metronidazole | 46 | 0.72 | 0.125-2.0 | 1.0 | 2.0 |
| | | Rifaximin | 46 | 0.04 | 0.003-257.0 | 0.015 | 2.0 |
| Vancomycin | Cure | Fidaxomicin | 342 | 0.10 | 0.003-0.5 | 0.125 | 0.25 |
| | | Vancomycin | 342 | 0.95 | 0.25-8.0 | 1.0 | 2.0 |
| | | Metronidazole | 342 | 0.47 | 0.02-4.0 | 0.5 | 1.0 |
| | | Rifaximin | 342 | 0.02 | 0.003-257.0 | 0.015 | 0.125 |
| | Failure | Fidaxomicin | 52 | 0.13 | 0.007-0.5 | 0.125 | 0.25 |
| | | Vancomycin | 52 | 1.04 | 0.5-4.0 | 1.0 | 2.0 |
| | | Metronidazole | 52 | 0.69 | 0.05-2.0 | 1.0 | 2.0 |
| | | Rifaximin | 52 | 0.03 | 0.003-257.0 | 0.015 | 0.06 |
| Overall | Cure | Fidaxomicin | 694 | 0.10 | 0.003-1.0 | 0.125 | 0.25 |
| | | Vancomycin | 694 | 0.95 | 0.25-8.0 | 1.0 | 2.0 |
| | | Metronidazole | 694 | 0.46 | 0.02-4.0 | 0.5 | 1.0 |
| | | Rifaximin | 694 | 0.03 | 0.003-257.0 | 0.015 | 0.125 |
| | Failure | Fidaxomicin | 98 | 0.13 | 0.007-0.5 | 0.125 | 0.25 |
| | | Vancomycin | 98 | 1.11 | 0.5-4.0 | 1.0 | 4.0 |
| | | Metronidazole | 98 | 0.70 | 0.05-2.0 | 1.0 | 2.0 |
| | | Rifaximin | 98 | 0.03 | 0.003-257.0 | 0.015 | 2.0 |

In the 101.1.C.003 study, within the BI subgroup (an epidemic hypervirulent *C. difficile* strain), the fidaxomicin arm had generally similar outcomes to the vancomycin arm (for all endpoints and analysis populations). However, in the 101.1.C.004 study, the fidaxomicin arm trended toward a lower recurrence rate and higher global cure rate than the vancomycin arm in subjects harboring a BI strain. In both studies, among subjects harboring a non-BI strain, the recurrence rate was lower and the global cure rate higher in the fidaxomicin arm compared to the vancomycin arm (Table 28).

**Table 28. Outcomes by Strain Type in Studies 101.1.C.003 and 101.1.C.004**

| Outcome | Study | Strain type | Fidaxomicin n/N (%) | Vancomycin n/N (%) |
|---|---|---|---|---|
| **Clinical cure (PP population)** | | | | |
| | 101.1.C.003 | BI | 57/66 (86.4) | 60/71 (84.5) |
| | 101.1.C.003 | Non-BI | 116/120 (96.7) | 118/125 (94.4) |
| | 101.1.C.004 | BI | 49/55 (89.1) | 48/55 (87.3) |
| | 101.1.C.004 | Non-BI | 110/117 (94.0) | 101/110 (91.8) |
| **Recurrence (mITT population)** | | | | |
| | 101.1.C.003 | BI | 16/60 (26.7) | 14/66 (21.2) |
| | 101.1.C.003 | Non-BI | 13/118 (11.0) | 33/120 (27.5) |
| | 101.1.C.004 | BI | 12/54 (22.2) | 19/50 (38.0) |
| | 101.1.C.004 | Non-BI | 11/120 (9.2) | 29/106 (27.4) |
| **Global cure (mITT population)** | | | | |
| | 101.1.C.003 | BI | 44/76 (57.9) | 52/82 (63.4) |
| | 101.1.C.003 | Non-BI | 105/126 (83.3) | 87/131 (66.4) |
| | 101.1.C.004 | BI | 42/65 (64.6) | 31/60 (51.7) |
| | 101.1.C.004 | Non-BI | 109/131 (83.2) | 77/121 (63.6) |

Efforts were made to isolate strains at failure or recurrence from all subjects who failed or recurred, in order to examine strains for changes in susceptibility. In the fidaxomicin-treated subjects with baseline isolates in whom a strain was isolated at failure or recurrence, in nearly all cases the final strain had the same MIC as the baseline strain (or was within a dilution of the baseline strain). The exception was one subject (classified as a clinical cure) in the fidaxomicin arm of study 101.1.C.004 whose isolates at baseline and EOT were of the same susceptibility, but whose strain at recurrence had increased from 0.06 µg/mL to 16 µg/mL (6 days after the last treatment dose). While the typing method could not discriminate the strains from each collection (all were non-specified REA type), the possibility remains that the strain developed reduced sensitivity to fidaxomicin during the study. However, since the strain had not developed reduced sensitivity at the end of therapy, it is not clear why it would do so once the selective pressure had been removed. An alternate explanation is that there was re-infection with a strain having an innately lower sensitivity to fidaxomicin, although an MIC of >2 µg/mL has not been seen previously within the wild type population. It is noteworthy that the isolate from the recurrence visit had a single mutation (Val1143Gly) in the β' subunit of RNA polymerase that was not present in isolates from baseline and EOT. Mutation of valine at residue 1143 was also identified in a laboratory-derived *C. difficile* mutant displaying decreased susceptibility to fidaxomicin.

Few subjects experiencing a clinical failure in either trial had both a baseline isolate and an EOT fecal PK sample. Although in study 101.1.C.003 there were lower mean fecal concentration:MIC ratios in the clinical failures, the same was not true in study 101.1.C.004, and in both cases, the standard deviation was very wide, with a large degree of overlap between the values in clinical cures and clinical failures. Thus fecal concentration/MIC does not appear to be a predictive pharmacodynamic metric.

## 6.5 Efficacy Conclusions

The efficacy of fidaxomicin for the treatment of CDI and for reducing the risk of recurrences at a dosage of 200 mg q12h for 10 days is demonstrated in two robust, well-controlled, Phase 3, randomized studies, with participating sites from US, Canada and Europe. Both studies were double-blinded, with all subjects and site staff remaining blinded to the treatment allocations until the database was locked.

Both studies were conducted using vancomycin as the comparator, since vancomycin is widely viewed to be the most effective drug for all levels of severity such as encountered in these clinical trials and seen in the population as a whole. In addition, vancomycin is the only drug approved by the FDA for treating CDI. Clinical cure rates at the EOT visit demonstrated the non-inferiority of fidaxomicin compared with vancomycin, with the robustness of the results supported by analysis between treatments with a modified cure definition based on objective criteria. Recurrence rates were lower in subjects treated with fidaxomicin, and subjects treated with fidaxomicin recurred later compared to subjects treated with vancomycin, with these differences being statistically significant as well as clinically relevant.

The advantage of fidaxomicin treatment over vancomycin treatment in higher global cure rates and lower recurrence rates was also generally consistent between treatments within study population subgroups and baseline characteristics, supporting the claim that fidaxomicin is indicated for the treatment of CDI and for the reducing the risk of recurrence after treatment for initial CDI.

# 7 REVIEW OF FIDAXOMICIN SAFETY

In all studies, the safety population was defined as all subjects who received at least one dose of treatment with the study drug fidaxomicin, placebo, or with the comparator vancomycin and who had at least one post-dose safety assessment. Safety variables assessed in all studies consisted of the following: occurrence of TEAEs, occurrence of treatment-emergent serious adverse events (treatment-emergent SAEs), changes in vital signs, changes in electrocardiogram (ECG), changes in laboratory evaluations, and changes in physical examination findings. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10. The primary data presented are the pooled TEAE data from the Phase 3 studies 101.1.C.003 and 101.1.C.004. Safety data from healthy subjects and from the Phase 2 study in subjects with CDI did not indicate any safety concerns so data from those subjects are only discussed briefly.

During clinical development, a total of 1321 subjects were treated in studies including 728 subjects who received fidaxomicin. A total of 126 subjects were treated in the healthy volunteer studies, of which 116 received fidaxomicin and 10 received placebo. In the studies enrolling subjects with CDI (i.e., Phase 2A and 3 studies), a total of 1195 subjects were treated, with 612 receiving fidaxomicin and 583 receiving vancomycin. In the pooled Phase 3 studies, 564 subjects were treated with fidaxomicin and 583 subjects were treated with vancomycin. Of the 1147 subjects that were included in the safety population for the pooled Phase 3 studies analysis, 567 (49.4%) were aged ≥65 years (272 treated with fidaxomicin and 295 treated with vancomycin). The numbers of subjects enrolled is considered sufficient to adequately demonstrate the efficacy and safety of fidaxomicin, and the inclusion of a large number of elderly is appropriate given the fact that the elderly are disproportionately affected by CDI [Wistrom, 2001; Calfee, 2008].

The safety data demonstrates that fidaxomicin was similar to vancomycin in the incidence and type of TEAEs, treatment-emergent SAEs, laboratory test abnormalities, and changes in vital signs and ECGs.

## 7.1 Study Drug Exposure

The duration of study drug exposure was defined as the time interval (in calendar days) beginning with the date of the first dose of study drug and ending with the date of the last dose of study drug.

Drug exposure was described using a frequency table with the number and percentage of subjects exposed to study drug during specified time intervals:

- <3 days
- 3 to 9 days
- 10 to 11 days
- ≥12 days

In the Phase 3 studies, fidaxomicin was to be administered twice daily (q12 hrs) for 10 days. Subjects enrolled in the morning would likely receive two doses each day for 10 days. Subjects enrolled later in the day may have only received one dose on Day 1, two doses on Days 2-10 and the last dose of study drug on Study Day 11; thus, their duration of dosing would be 11 calendar days, as defined by the definition of exposure in the Statistical Analysis Plan for the Integrated Summary of Safety. Subjects taking greater than 11 days of treatment includes subjects that missed doses (and made them up later), or subjects that took the spare day of dosing that was supplied in case of lost tablets. The most tablets that could have been taken by any subject was 11 days of treatment.

**Table 29. Summary of Exposure to Study Drug: Phase 1, 2, and 3 Studies (Safety Population)**

| | Placebo | Fidaxomicin | | | | | Vancomycin |
|---|---|---|---|---|---|---|---|
| | (N=10) n (%) | 100-200mg (N=54) n (%) | 300mg (N=12) n (%) | 400mg (N=608) n (%) | 450mg (N=11) n (%) | Any Dose (N=674) n (%) | 500mg (N=583) n (%) |
| Duration of Exposure (days) | | | | | | | |
| N | 10 | 54 | 12 | 608 | 11 | 674 | 583 |
| Mean | 6.0 | 6.8 | 5.5 | 9.8 | 5.9 | 9.6 | 10.2 |
| S.D. | 4.22 | 4.52 | 4.70 | 2.75 | 4.70 | 3.02 | 2.37 |
| Median | 6.0 | 10.0 | 5.5 | 11.0 | 10.0 | 11.0 | 11.0 |
| Min, Max | 2, 10 | 1, 11 | 1, 10 | 1, 14 | 1, 10 | 1, 14 | 1, 22 |
| <3 Days | 5 (50.0) | 19 (35.2) | 6 (50.0) | 44 (7.2) | 5 (45.5) | 63 (9.3) | 18 (3.1) |
| 3-9 Days | - | 4 (7.4) | - | 59 (9.7) | - | 63 (9.3) | 53 (9.1) |
| 10-11 Days | 5 (50.0) | 31 (57.4) | 6 (50.0) | 479 (78.8) | 6 (54.5) | 522 (77.4) | 469 (80.4) |
| ≥12 Days | - | - | - | 26 (4.3) | - | 26 (3.9) | 43 (7.4) |

NOTE: Does not include 52 subjects from Phase 1 DDI-studies

## 7.2 Treatment-Emergent Adverse Event Profile

A summary of the TEAEs for subjects in studies 101.1.C.003 and 101.1.C.004 (pooled data) is presented in Table 30. The safety profile for fidaxomicin was generally similar to that for the control (vancomycin). There were no clinically relevant differences between the fidaxomicin and vancomycin groups with respect to either the overall incidence of TEAEs, the relationship or severity of TEAEs, TEAEs leading to discontinuation of study drug, TEAEs leading to dose modification or use of concomitant medication, treatment-emergent SAEs, or TEAEs resulting in death.

**Table 30. Incidence of TEAEs in Pooled Phase 3 Studies (Safety Population)**

| **Subjects with ≥1 TEAE** | **Fidaxomicin 400mg (N=564) n (%)** | **Vancomycin 500mg (N=583) n (%)** |
|---|---|---|
| All TEAEs | 385 (68.3) | 382 (65.5) |
| TEAEs by Severity | | |
| Mild | 160 (28.4) | 171 (29.3) |
| Moderate | 117 (20.7) | 113 (19.4) |
| Severe | 108 (19.1) | 98 (16.8) |
| TEAEs by Relationship to Study Drug | | |
| Related | 60 (10.6) | 65 (11.1) |
| Not Related | 325 (57.6) | 317 (54.4) |
| TEAEs Leading to Discontinuation of Study Drug | 33 (5.9) | 40 (6.9) |
| TEAEs Leading to Dose Modification or Use of Concomitant Medication | 2 (0.4) | 8 (1.4) |
| Treatment-emergent Serious Adverse Events | 145 (25.7) | 135 (23.2) |
| TEAEs Resulting in Death | 36 (6.4) | 38 (6.5) |

### 7.2.1 Common Treatment-Emergent Adverse Events

Table 31 lists the TEAEs reported by ≥2% of subjects in either treatment group from the pooled Phase 3 studies. The overall incidence of TEAEs was similar between the two treatment groups, with 68.3% subjects receiving fidaxomicin reporting at least 1 TEAE compared with 65.5% receiving vancomycin. The most frequent preferred terms (PTs) in the pooled analysis were nausea, vomiting, hypokalemia, headache, abdominal pain, and diarrhea, all of which were reported by ≥5% of subjects in the fidaxomicin group. The TEAEs reported more frequently in subjects treated with fidaxomicin than vancomycin in the pooled analysis (i.e., ≥2% difference between the treatment groups) were headache (6.6% versus 4.6%), abdominal pain (5.9% versus 3.9%), and constipation (4.4% versus 2.1%). It should be noted that abdominal pain, nausea and hypokalemia are symptoms of the underlying CDI and so cannot be necessarily attributed to a drug effect. Also given that one of the main symptoms of CDI is diarrhea, TEAEs of constipation are not necessarily a negative effect since it is a sign of recovery from CDI.

**Table 31. TEAEs Occurring in ≥2% of Subjects in Either Treatment Group (Pooled Phase 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Fidaxomicin (N=564) n (%) | Vancomycin (N=583) n (%) |
|---|---|---|
| Any TEAE | 385 (68.3) | 382 (65.5) |
| Blood and Lympathic System Disorders | 37 (6.6) | 25 (4.3) |
| Anemia | 14 (2.5) | 12 (2.1) |
| Gastrointestinal Disorders | 177 (31.4) | 170 (29.2) |
| Nausea | 62 (11.0) | 66 (11.3) |
| Vomiting | 41 (7.3) | 37 (6.3) |
| Abdominal pain | 33 (5.9) | 23 (3.9) |
| Diarrhea | 28 (5.0) | 39 (6.7) |
| Constipation | 25 (4.4) | 12 (2.1) |
| Abdominal pain upper | 9 (1.6) | 12 (2.1) |
| General Disorders and Administration Site Conditions | 90 (16.0) | 113 (19.4) |
| Pyrexia | 24 (4.3) | 31 (5.3) |
| Edema peripheral | 20 (3.5) | 27 (4.6) |
| Fatigue | 17 (3.0) | 20 (3.4) |
| Chills | 3 (0.5) | 14 (2.4) |
| Infections and Infestations | 129 (22.9) | 121 (20.8) |
| Urinary tract infection | 20 (3.5) | 24 (4.1) |
| Pneumonia | 13 (2.3) | 18 (3.1) |
| Metabolism and Nutrition Disorders | 104 (18.4) | 87 (14.9) |
| Hypokalemia | 41 (7.3) | 38 (6.5) |
| Hyperkalemia | 16 (2.8) | 10 (1.7) |
| Hypomagnesemia | 8 (1.4) | 12 (2.1) |
| Musculoskeletal and Connective Tissue Disorders | 44 (7.8) | 40 (6.9) |
| Back pain | 8 (1.4) | 13 (2.2) |
| Nervous System Disorders | 71 (12.6) | 64 (11.0) |
| Headache | 37 (6.6) | 27 (4.6) |
| Dizziness | 16 (2.8) | 12 (2.1) |
| Psychiatric Disorders | 41 (7.3) | 44 (7.5) |
| Insomnia | 13 (2.3) | 14 (2.4) |
| Respiratory, Thoracic and Mediastinal Disorders | 63 (11.2) | 76 (13.0) |
| Dyspnea | 14 (2.5) | 13 (2.2) |
| Skin and Subcutaneous Tissue Disorders | 54 (9.6) | 56 (9.6) |
| Pruritus | 10 (1.8) | 14 (2.4) |
| Vascular Disorders | 36 (6.4) | 31 (5.3) |
| Hypotension | 11 (2.0) | 12 (2.1) |

The distributions of time to occurrence of the first TEAE in each treatment group are shown in Figure 10 and show comparable curves for both treatment groups (hazard ratio = 1.04 [95% CI: 0.91, 1.20]).

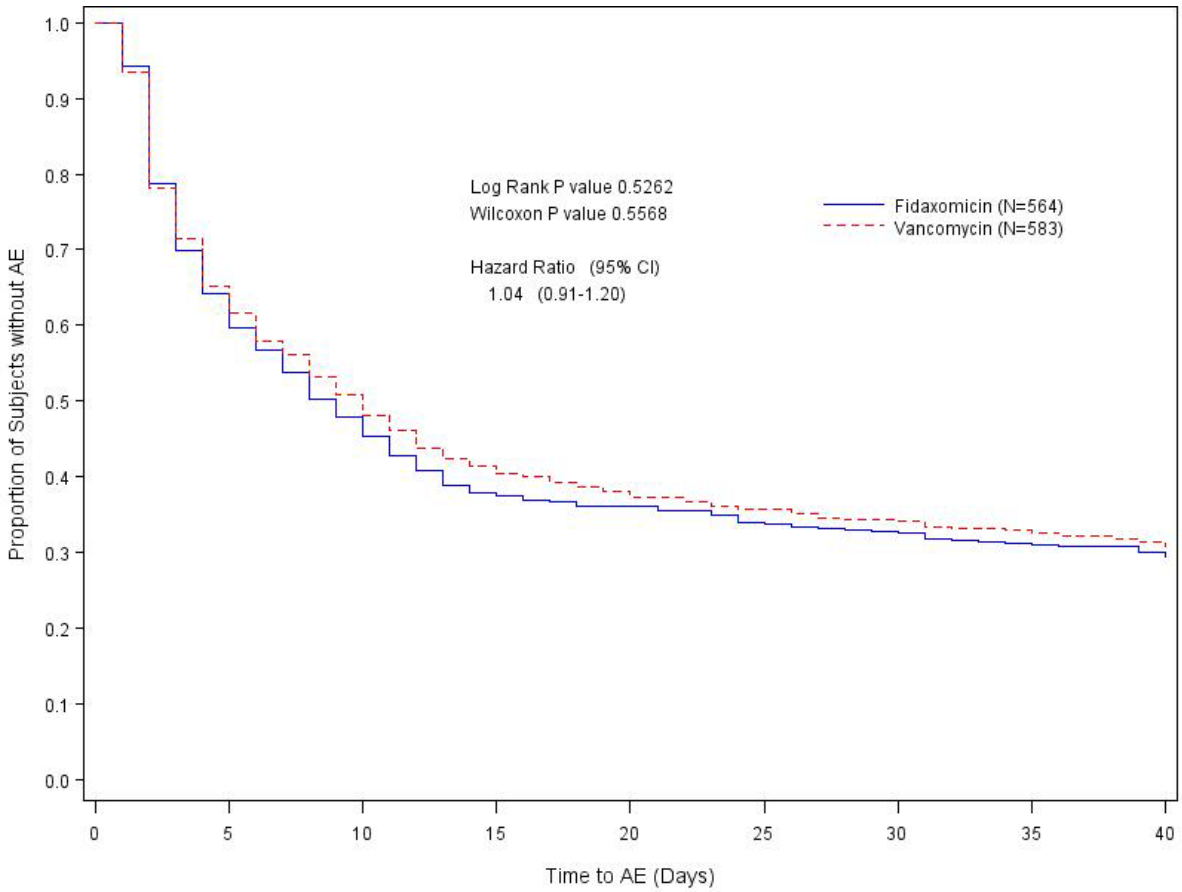



**Figure 10. Kaplan-Meier Survival Curves for Time to First TEAE (Safety population)**

### 7.2.2 Treatment-Related Treatment-Emergent Adverse Events

For the Phase 3 studies, the relationship of TEAEs to study drug was mapped to two categories, "related" and "not related". Events categorized as "related" are those assessed by the Investigator as possibly, probably, or definitely related to study drug. Events categorized as "not related" are those assessed by the Investigator as not related or unlikely related to study drug. In the pooled Phase 3 studies, the majority of TEAEs in each treatment group were assessed by investigators as unrelated to the study drug, with only 10.6% and 11.1% of subjects in the fidaxomicin and vancomycin groups, respectively, reporting related TEAEs. Table 32 summarizes the incidence of drug-related TEAEs that occurred in ≥1% of subjects in the fidaxomicin group, based on the pooled data from studies 101.1.C.003 and 101.1.C.004. Only nausea, vomiting, and constipation were reported as drug-related in ≥1% subjects in the fidaxomicin group.

**Table 32. Treatment-Related TEAEs Occurring in ≥1% Subjects in the Fidaxomicin Group (Pooled Phase 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Fidaxomicin (N=564) n (%) | Vancomycin (N=583) n (%) |
|---|---|---|
| Any treatment-related TEAEs | 60 (10.6) | 65 (11.1) |
| Gastrointestinal disorders | 33 (5.9) | 33 (5.7) |
| Nausea | 15 (2.7) | 20 (3.4) |
| Vomiting | 7 (1.2) | 8 (1.4) |
| Constipation | 7 (1.2) | 3 (0.5) |
| Investigations | 8 (1.4) | 6 (1.0) |
| Nervous system disorders | 9 (1.6) | 9 (1.5) |

## 7.3 Discontinuations Due to TEAEs

In the Phase 3 studies, the incidence of TEAEs for which drug was stopped permanently or the subject discontinued from the study was low (<10% across treatment groups) (Table 33). The overall incidence of TEAEs leading to study drug discontinuation was lower in the fidaxomicin group (5.9%) than in the vancomycin group (6.9%). In the fidaxomicin group, all TEAEs that led to discontinuation occurred in ≤1% of subjects. The system organ classes (SOCs) with the highest incidence of TEAEs leading to study drug discontinuation were GI disorders (2.3% and 1.4% in the fidaxomicin and vancomycin arms, respectively) and infections and infestations (1.2% and 1.5%). Vomiting was the primary TEAE leading to discontinuation of dosing; this occurred at an incidence of 0.5% in both the fidaxomicin and vancomycin patients in the Phase 3 studies.

**Table 33. TEAEs Reported by ≥2 Subject in Either Treatment Group in Phase 3 Studies for which Drug was Stopped Permanently or the Subject Discontinued From the Study (Safety Population)**

| System Organ Class<br>Preferred Term | Fidaxomicin (N=564) n (%) | Vancomycin (N=583) n (%) |
|---|---|---|
| Subjects with any TEAE leading to discontinuation | 33 (5.9) | 40 (6.9) |
| Gastrointestinal disorders | 13 (2.3) | 8 (1.4) |
| Vomiting | 3 (0.5) | 3 (0.5) |
| Megacolon | 2 (0.4) | - |
| Colitis | 2 (0.4) | - |
| Abdominal pain | 2 (0.4) | - |
| Nausea | - | 2 (0.3) |
| Infections and infestations | 7 (1.2) | 9 (1.5) |
| Pneumonia | 2 (0.4) | 2 (0.3) |
| Clostridium difficile colitis | 2 (0.4) | - |
| Sepsis | 1 (0.2) | 2 (0.3) |
| Escherichia sepsis | - | 2 (0.3) |
| Injury, poisoning and procedural complications | 1 (0.2) | 4 (0.7) |
| Wound dehiscence | - | 2 (0.3) |
| Metabolism and nutrition disorders | 1 (0.2) | 4 (0.7) |
| Dehydration | 1 (0.2) | 2 (0.3) |

| System Organ Class<br>Preferred Term | Fidaxomicin<br>(N=564)<br>n (%) | Vancomycin<br>(N=583)<br>n (%) |
|---|---|---|
| Psychiatric disorders | 1 (0.2) | 4 (0.7) |
| Confusional state | - | 2 (0.3) |
| Mental status changes | - | 2 (0.3) |
| Respiratory, thoracic and mediastinal disorders | - | 6 (1.0) |
| Respiratory failure | - | 4 (0.7) |

NOTE: SOC values are representative of all SAEs for that particular SOC

The incidence of TEAEs leading to dose modification or use of a concomitant medication was 0.4% in the fidaxomicin group and 1.4% in the vancomycin group. The SOC with the highest incidence of TEAEs leading to dose modification or concomitant medication was GI disorders reported in 2 subjects each in the fidaxomicin group (0.4%) and vancomycin group (0.3%).

## 7.4 Serious Adverse Events and Deaths

### 7.4.1 Treatment-Emergent Serious Adverse Events

In study OPT-80 Phase 2A, 5 fidaxomicin-treated subjects had treatment-emergent SAEs, all of which were considered to be unrelated to study drug. In the pooled treatment-emergentSAE data from studies 101.1.C.003 and 101.1.C.004, most of the treatment-emergent SAEs occurred in <1% of subjects, with the incidence of treatment-emergent SAEs being similar for the fidaxomicin (25.7%) and vancomycin (23.2%) groups.

Table 34 and this section summarizes the treatment-emergent SAEs that occurred in all of the Phase 1 to 3 studies except for the 3 Phase 1 drug-drug interaction studies, which included an additional 52 subjects who received fidaxomicin, none of whom experienced a treatment-emergent SAE. The incidence of treatment-emergent SAEs was similar for the fidaxomicin 400 mg (23.8%), fidaxomicin any dose (22.3%), and vancomycin 500 mg (23.2%) groups. The incidence of treatment-emergent SAEs in the fidaxomicin 100-200 mg group was 9.3%. No treatment-emergent SAEs were reported in the placebo, fidaxomicin 300 mg, and fidaxomicin 450 mg groups.

For subjects in the fidaxomicin 400 mg, fidaxomicin any dose, and vancomycin 500 mg groups, respectively, the highest incidence of treatment-emergent SAEs occurred in the following SOCs: infections and infestations (7.4%, 6.8%, and 8.6%); metabolism and nutrition disorders (4.4%, 4.0%, and 4.8%); GI disorders (4.3%, 4.0%, and 4.1%); investigations (3.9%, 3.6%, and 1.9%); and respiratory, thoracic, and mediastinal disorders (3.0%, 2.7%, and 4.1%). For subjects in the fidaxomicin 100-200 mg group, only 1 subject reported a treatment-emergent SAE in each of the following SOCs: cardiac disorders, gastrointestinal disorders, general disorders and administration site conditions; infections and infestations; renal and urinary disorders; and vascular disorders.

The treatment-emergent SAEs (preferred term) reported at the highest incidences in the fidaxomicin 400 mg group were *C. difficile* colitis and pneumonia in 8 (1.3%) subjects; sepsis in 7 (1.2%) subjects; hyponatraemia in 6 (1.0%) subjects; and congestive cardiac

failure, blood uric acid increased, hyperkalaemia, hypophosphataemia, and respiratory failure in 5 (0.8%) subjects. The treatment-emergent SAEs (preferred term) reported at the highest incidences in the fidaxomicin any dose group were *C. difficile* colitis and pneumonia in 8 (1.2%) subjects; sepsis in 7 (1.0%) subjects; cardiac failure congestive, hyponatraemia in 6 (0.9%) subjects; and gastrointestinal haemorrhage, blood uric acid increased, hyperkalaemia, hypophosphataemia, and respiratory failure in 5 (0.7%) subjects.
The treatment-emergent SAEs reported at the highest incidences in the vancomycin 500 mg group were pneumonia in 10 (1.7%) subjects; *C. difficile* colitis in 9 (1.5%) subjects; hyperglycaemia, hypokalaemia, and respiratory failure in 6 (1.0%) subjects; and sepsis in 5 (0.9%) subjects.

There was 1 report of pregnancy during the fidaxomicin clinical program. Subject 009021 in study 101.1.C.003 was a 19-year old female with precursor B-cell acute lymphocytic leukemia and who was receiving vincristine and methotrexate when she was diagnosed with *C. difficile* infection. Serum pregnancy tests 3 weeks prior to and at study entry were negative, however, the subject was confirmed pregnant on Day 25 of the study, with the detection of 5 live intrauterine fetuses (estimated approximately 4 weeks from conception). The subject discontinued chemotherapy at this time (approximately 1 month into the pregnancy). A treatment-emergent SAE was reported on Day 126 with the intrauterine death of 1 of the fetuses; a male fetus was spontaneously delivered 6 days later. Of the four remaining fetuses, 1 had no heartbeat. The subject was monitored for signs of infection, and though afebrile, had a WBC count that had increased to 15.7 from $13.6 \times 10^9$/L. A urine culture was positive for *E.coli* and Macrobid was initiated. Two days later, she was febrile and tachycardic with painful contractions and fundal tenderness. Macrobid was discontinued, and ampicillin and gentamicin were initiated. Subsequently, induction was started with removal of the cerclage. The remaining 4 fetuses were delivered approximately 3.5 months prematurely, 3 live, and 1 deceased. None survived. The deaths were not considered to be related to the study drug. One of the fetuses was found to have a cleft palate and extensive autolysis of organs. The remaining fetuses were found to be without any diagnostic abnormality. The TEAE of cleft palate was deemed not related to the study drug. Of note is that this subject had plasma drug concentrations that were lower than average, at 2.06 and 3.74 ng/mL for fidaxomicin and OP-1118, respectively, at 3.7 hours after dosing on Day 1; and below the limit of quantification for both fidaxomicin and OP-1118 (LLOQ 0.2 ng/mL) at the EOT 2 hours and 3.5 hours after dosing.

One subject received more than the planned dose of fidaxomicin (Subject 137011, study 101.1.C.003). This was recorded by the Investigator and coded on the database as 'overdose'. On Day 3 of study drug therapy, Doses 1, 2, 3, and 4 were given by the hospital nurse to the subject as a single dose (400 mg total, 2 active capsules and 2 matching placebo capsules at 19:00 hours). The subject did not experience any adverse signs or symptoms resulting from this. The subject was withdrawn from the study drug and was started on vancomycin 125 mg orally q6h. However, this is not regarded as an acute overdose, since subjects in a Phase 1 study received 450 mg fidaxomicin.

**Table 34. Summary of Treatment-Emergent SAEs: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin<br>100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| Number Of Subjects With ≥1 TE SAE | - | 5 (9.3) | - | 145 (23.8) | - | 150 (22.3) | 135 (23.2) |
| Blood And Lymphatic System Disorders | - | - | - | 13 (2.1) | - | 13 (1.9) | 8 (1.4) |
| Anaemia | - | - | - | 4 (0.7) | - | 4 (0.6) | 2 (0.3) |
| Febrile Neutropenia | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Granulocytopenia | - | - | - | - | - | - | 1 (0.2) |
| Leukocytosis | - | - | - | - | - | - | 1 (0.2) |
| Leukopenia | - | - | - | 4 (0.7) | - | 4 (0.6) | 1 (0.2) |
| Lymphadenopathy | - | - | - | - | - | - | 1 (0.2) |
| Lymphopenia | - | - | - | 3 (0.5) | - | 3 (0.4) | 2 (0.3) |
| Neutropenia | - | - | - | 4 (0.7) | - | 4 (0.6) | - |
| Thrombocytopenia | - | - | - | 3 (0.5) | - | 3 (0.4) | 2 (0.3) |
| Cardiac Disorders | - | 1 (1.9) | - | 12 (2.0) | - | 13 (1.9) | 14 (2.4) |
| Atrial Fibrillation | - | - | - | 4 (0.7) | - | 4 (0.6) | 1 (0.2) |
| Atrial Flutter | - | - | - | - | - | - | 1 (0.2) |
| Cardiac Arrest | - | - | - | - | - | - | 1 (0.2) |
| Cardiac Failure Congestive | - | 1 (1.9) | - | 5 (0.8) | - | 6 (0.9) | 3 (0.5) |
| Cardio-Respiratory Arrest | - | - | - | - | - | - | 2 (0.3) |
| Cardiogenic Shock | - | - | - | - | - | - | 2 (0.3) |
| Cor Pulmonale | - | - | - | - | - | - | 1 (0.2) |
| Myocardial Infarction | - | - | - | 4 (0.7) | - | 4 (0.6) | 2 (0.3) |
| Supraventricular Tachycardia | - | - | - | - | - | - | 1 (0.2) |
| Torsade De Pointes | - | - | - | - | - | - | 1 (0.2) |
| Ventricular Tachycardia | - | - | - | - | - | - | 1 (0.2) |
| Congenital, Familial And Genetic Disorders | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Cleft Palate | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Gastrointestinal Disorders | - | 1 (1.9) | - | 26 (4.3) | - | 27 (4.0) | 24 (4.1) |
| Abdominal Pain | - | - | - | 4 (0.7) | - | 4 (0.6) | 1 (0.2) |
| Abdominal Rebound Tenderness | - | - | - | - | - | - | 1 (0.2) |
| Anal Fissure | - | - | - | - | - | - | 1 (0.2) |

**Table 34. Summary of Treatment-Emergent SAEs: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin<br>100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| Ascites | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Colitis | - | - | - | 2 (0.3) | - | 2 (0.3) | - |
| Colitis Ischaemic | - | - | - | -- | - | - | 1 (0.2) |
| Crohn's Disease | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Diarrhoea | - | - | - | 3 (0.5) | - | 3 (0.4) | 3 (0.5) |
| Diarrhoea Haemorrhagic | - | - | - | 2 (0.3) | - | 2 (0.3) | - |
| Faecal Vomiting | - | - | - | -- | - | - | 1 (0.2) |
| Femoral Hernia | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Gastrointestinal Haemorrhage | - | 1 (1.9) | - | 4 (0.7) | - | 5 (0.7) | 1 (0.2) |
| Gastrointestinal Perforation | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Ileus | - | - | - | -- | - | - | 1 (0.2) |
| Ileus Paralytic | - | - | - | -- | - | - | 1 (0.2) |
| Inguinal Hernia, Obstructive | - | - | - | -- | - | - | 1 (0.2) |
| Intestinal Obstruction | - | - | - | 4 (0.7) | - | 4 (0.6) | 1 (0.2) |
| Large Intestine Perforation | - | - | - | -- | - | - | 2 (0.3) |
| Megacolon | - | - | - | 3 (0.5) | - | 3 (0.4) | - |
| Nausea | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Oesophageal Varices Haemorrhage | - | - | - | -- | - | - | 1 (0.2) |
| Peritonitis | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Small Intestinal Obstruction | - | - | - | 1 (0.2) | - | 1 (0.1) | 3 (0.5) |
| Upper Gastrointestinal Haemorrhage | - | - | - | -- | - | - | 1 (0.2) |
| Vomiting | - | - | - | 2 (0.3) | - | 2 (0.3) | 3 (0.5) |
| General Disorders And Administration Site Conditions | - | 1 (1.9) | - | 9 (1.5) | - | 10 (1.5) | 9 (1.5) |
| Chest Pain | - | 1 (1.9) | - | 2 (0.3) | - | 3 (0.4) | 1 (0.2) |
| Euthanasia | - | - | - | - | - | - | 1 (0.2) |
| Generalised Oedema | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Hypothermia | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Impaired Healing | - | - | - | 1 (0.2) | - | 1 (0.1) | - |

**Table 34. Summary of Treatment-Emergent SAEs: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin | | | | | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| | | 100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | |
| Malaise | - | -- | - | - | - | - | 1 (0.2) |
| Multi-Organ Failure | - | - | - | 1 (0.2) | - | 1 (0.1) | 3 (0.5) |
| Oedema Peripheral | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Pyrexia | - | - | - | 3 (0.5) | - | 3 (0.4) | 3 (0.5) |
| Hepatobiliary Disorders | - | - | - | 2 (0.3) | - | 2 (0.3) | 4 (0.7) |
| Cholecystitis Acute | - | - | - | - | - | - | 1 (0.2) |
| Cholelithiasis | - | - | - | - | - | - | 1 (0.2) |
| Cholestasis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Hepatic Cirrhosis | - | - | - | - | - | - | 1 (0.2) |
| Hyperbilirubinaemia | - | - | - | - | - | - | 1 (0.2) |
| Liver Disorder | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Immune System Disorders | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Anaphylactic Reaction | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Infections And Infestations | - | 1 (1.9) | - | 45 (7.4) | - | 46 (6.8) | 50 (8.6) |
| Abdominal Abscess | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Abdominal Sepsis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Aspergillosis | - | - | - | - | - | - | 1 (0.2) |
| Bacteraemia | - | - | - | 2 (0.3) | - | 2 (0.3) | 1 (0.2) |
| Beta Haemolytic Streptococcal Infection | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Bronchopulmonary Aspergillosis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Cellulitis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Clostridial Infection | - | - | - | 1 (0.2) | - | 1 (0.1) | 2 (0.3) |
| Clostridium Difficile Colitis | - | - | - | 8 (1.3) | - | 8 (1.2) | 9 (1.5) |
| Clostridium Difficile Sepsis | - | - | - | - | - | - | 1 (0.2) |
| Ear Infection | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Endocarditis | - | - | - | - | - | - | 1 (0.2) |
| Endocarditis Bacterial | - | - | - | - | - | - | 1 (0.2) |
| Enterocolitis Infectious | - | - | - | - | - | - | 1 (0.2) |
| Erysipelas | - | - | - | 1 (0.2) | - | 1 (0.1) | - |

**Table 34. Summary of Treatment-Emergent SAEs: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin | | | | | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| | | 100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | |
| Escherichia Bacteraemia | - | - | - | - | - | - | 1 (0.2) |
| Escherichia Sepsis | - | - | - | - | - | - | 3 (0.5) |
| Fungaemia | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Influenza | - | - | - | - | - | - | 1 (0.2) |
| Liver Abscess | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Localised Infection | - | - | - | - | - | - | 1 (0.2) |
| Meningitis | - | - | - | - | - | - | 1 (0.2) |
| Neutropenic Sepsis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Osteomyelitis | - | - | - | - | - | - | 1 (0.2) |
| Pneumonia | - | - | - | 8 (1.3) | - | 8 (1.2) | 10 (1.7) |
| Pneumonia Fungal | - | - | - | - | - | - | 1 (0.2) |
| Pneumonia Klebsiella | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Postoperative Wound Infection | - | - | - | - | - | - | 1 (0.2) |
| Pseudomonal Sepsis | - | - | - | - | - | - | 1 (0.2) |
| Pyelocystitis | - | - | - | - | - | - | 1 (0.2) |
| Pyelonephritis Acute | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Sepsis | - | - | - | 7 (1.2) | - | 7 (1.0) | 5 (0.9) |
| Sepsis Syndrome | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Septic Shock | - | - | - | 1 (0.2) | - | 1 (0.1) | 2 (0.3) |
| Shunt Infection | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Sinusitis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Staphylococcal Bacteraemia | - | - | - | 1 (0.2) | - | 1 (0.1) | 2 (0.3) |
| Staphylococcal Infection | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Staphylococcal Sepsis | - | 1 (1.9) | - | 1 (0.2) | - | 2 (0.3) | 3 (0.5) |
| Subacute Endocarditis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Subcutaneous Abscess | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Systemic Candida | - | - | - | - | - | - | 2 (0.3) |
| Urinary Tract Infection | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Urosepsis | - | - | - | 2 (0.3) | - | 2 (0.3) | 4 (0.7) |

**Table 34. Summary of Treatment-Emergent SAEs: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin<br>100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| Wound Infection Staphylococcal | - | - | - | - | - | - | 1 (0.2) |
| Injury, Poisoning And Procedural Complications | - | - | - | 7 (1.2) | - | 7 (1.0) | 7 (1.2) |
| Accidental Overdose | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Fall | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Femoral Neck Fracture | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Femur Fracture | - | - | - | - | - | - | 1 (0.2) |
| Gastrointestinal Anastomotic Leak | - | - | - | - | - | - | 1 (0.2) |
| Graft Haemorrhage | - | - | - | - | - | - | 1 (0.2) |
| Hip Fracture | - | - | - | 2 (0.3) | - | 2 (0.3) | 1 (0.2) |
| Injury | - | - | - | - | - | - | 1 (0.2) |
| Joint Dislocation | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Muscle Strain | - | - | - | - | - | - | 1 (0.2) |
| Vascular Graft Occlusion | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Wound Dehiscence | - | - | - | - | - | - | 2 (0.3) |
| Investigations | - | - | - | 24 (3.9) | - | 24 (3.6) | 11 (1.9) |
| Alanine Aminotransferase Increased | - | - | - | 2 (0.3) | - | 2 (0.3) | 2 (0.3) |
| Aspartate Aminotransferase Increased | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Blood Alkaline Phosphatase Increased | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Blood Bicarbonate Decreased | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Blood Calcium Decreased | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Blood Calcium Increased | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Blood Glucose Abnormal | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Blood Glucose Increased | - | - | - | - | - | - | 1 (0.2) |
| Blood Phosphorus Abnormal | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Blood Phosphorus Decreased | - | - | - | - | - | - | 1 (0.2) |
| Blood Potassium Decreased | - | - | - | - | - | - | 1 (0.2) |
| Blood Sodium Decreased | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Blood Urea Abnormal | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Blood Uric Acid Abnormal | - | - | - | 1 (0.2) | - | 1 (0.1) | - |

**Table 34. Summary of Treatment-Emergent SAEs: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin<br>100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| Blood Uric Acid Increased | - | - | - | 5 (0.8) | - | 5 (0.7) | 1 (0.2) |
| Electrocardiogram QT Prolonged | - | - | - | - | - | - | 1 (0.2) |
| Hepatic Enzyme Increased | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| International Normalised Ratio Increased | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Lipase Increased | - | - | - | - | - | - | 1 (0.2) |
| Liver Function Test Abnormal | - | - | - | 2 (0.3) | - | 2 (0.3) | 1 (0.2) |
| Lymphocyte Count Abnormal | - | - | - | - | - | - | 1 (0.2) |
| Lymphocyte Count Decreased | - | - | - | 4 (0.7) | - | 4 (0.6) | 1 (0.2) |
| Neutrophil Count Decreased | - | - | - | 2 (0.3) | - | 2 (0.3) | - |
| Platelet Count Decreased | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| White Blood Cell Count Decreased | - | - | - | 2 (0.3) | - | 2 (0.3) | - |
| Metabolism And Nutrition Disorders | - | - | - | 27 (4.4) | - | 27 (4.0) | 28 (4.8) |
| Dehydration | - | - | - | 2 (0.3) | - | 2 (0.3) | 4 (0.7) |
| Failure To Thrive | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Hyperglycaemia | - | - | - | 3 (0.5) | - | 3 (0.4) | 6 (1.0) |
| Hyperkalaemia | - | - | - | 5 (0.8) | - | 5 (0.7) | 2 (0.3) |
| Hyperuricaemia | - | - | - | 2 (0.3) | - | 2 (0.3) | 4 (0.7) |
| Hypocalcaemia | - | - | - | - | - | - | 1 (0.2) |
| Hypoglycaemia | - | - | - | 3 (0.5) | - | 3 (0.4) | - |
| Hypokalaemia | - | - | - | 2 (0.3) | - | 2 (0.3) | 6 (1.0) |
| Hyponatraemia | - | - | - | 6 (1.0) | - | 6 (0.9) | 3 (0.5) |
| Hypophosphataemia | - | - | - | 5 (0.8) | - | 5 (0.7) | - |
| Malnutrition | - | - | - | - | - | - | 2 (0.3) |
| Metabolic Acidosis | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Musculoskeletal And Connective Tissue Disorders | - | - | - | - | - | - | 1 (0.2) |
| Pain In Extremity | - | - | - | - | - | - | 1 (0.2) |
| Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) | - | - | - | 7 (1.2) | - | 7 (1.0) | 5 (0.9) |
| Acute Myeloid Leukaemia | - | - | - | 1 (0.2) | - | 1 (0.1) | - |

**Table 34. Summary of Treatment-Emergent SAEs: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin<br>100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| Adrenal Gland Cancer Metastatic | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Colon Cancer | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Endometrial Cancer | - | - | - | - | - | - | 1 (0.2) |
| Gallbladder Cancer | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Lung Cancer Metastatic | - | - | - | - | - | - | 1 (0.2) |
| Lung Neoplasm Malignant | - | - | - | - | - | - | 1 (0.2) |
| Lymphatic System Neoplasm | - | - | - | - | - | - | 1 (0.2) |
| Lymphoproliferative Disorder | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Metastasis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Renal Cell Carcinoma Stage Unspecified | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| T-Cell Lymphoma | - | - | - | - | - | - | 1 (0.2) |
| Nervous System Disorders | - | - | - | 3 (0.5) | - | 3 (0.4) | 3 (0.5) |
| Cerebral Infarction | - | - | - | - | - | - | 1 (0.2) |
| Cerebrovascular Accident | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Coma | - | - | - | - | - | - | 1 (0.2) |
| Convulsion | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Syncope | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Pregnancy, Puerperium And Perinatal Conditions | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Intra-Uterine Death | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Pregnancy | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Psychiatric Disorders | - | - | - | 2 (0.3) | - | 2 (0.3) | 5 (0.9) |
| Affective Disorder | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Alcoholism | - | - | - | - | - | - | 1 (0.2) |
| Confusional State | - | - | - | - | - | - | 1 (0.2) |
| Hallucination | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Mental Status Changes | - | - | - | - | - | - | 3 (0.5) |
| Renal And Urinary Disorders | - | 1 (1.9) | - | 11 (1.8) | - | 12 (1.8) | 7 (1.2) |
| Nephrolithiasis | - | 1 (1.9) | - | 1 (0.2) | - | 2 (0.3) | - |
| Renal Failure | - | - | - | 4 (0.7) | - | 4 (0.6) | 4 (0.7) |

**Table 34. Summary of Treatment-Emergent SAEs: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin<br>100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| Renal Failure Acute | - | - | - | 4 (0.7) | - | 4 (0.6) | 3 (0.5) |
| Renal Impairment | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Urinary Retention | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Reproductive System And Breast Disorders | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Prostatitis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Respiratory, Thoracic And Mediastinal Disorders | - | - | - | 18 (3.0) | - | 18 (2.7) | 24 (4.1) |
| Acute Pulmonary Oedema | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Acute Respiratory Failure | - | - | - | - | - | - | 2 (0.3) |
| Chronic Obstructive Pulmonary Disease | - | - | - | 2 (0.3) | - | 2 (0.3) | - |
| Dyspnoea | - | - | - | 1 (0.2) | - | 1 (0.1) | 3 (0.5) |
| Epistaxis | - | - | - | - | - | - | 1 (0.2) |
| Haemopneumothorax | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Hypoxia | - | - | - | 2 (0.3) | - | 2 (0.3) | 1 (0.2) |
| Pleural Effusion | - | - | - | 1 (0.2) | - | 1 (0.1) | 2 (0.3) |
| Pneumonia Aspiration | - | - | - | 1 (0.2) | - | 1 (0.1) | 3 (0.5) |
| Pulmonary Embolism | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Pulmonary Oedema | - | - | - | 2 (0.3) | - | 2 (0.3) | 4 (0.7) |
| Respiratory Arrest | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Respiratory Disorder | - | - | - | - | - | - | 1 (0.2) |
| Respiratory Distress | - | - | - | 3 (0.5) | - | 3 (0.4) | - |
| Respiratory Failure | - | - | - | 5 (0.8) | - | 5 (0.7) | 6 (1.0) |
| Tachypnoea | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Vascular Disorders | - | 1 (1.9) | - | 10 (1.6) | - | 11 (1.6) | 4 (0.7) |
| Arterial Occlusive Disease | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Cerebral Haemorrhage | - | 1 (1.9) | - | - | - | 1 (0.1) | - |
| Deep Vein Thrombosis | - | - | - | 2 (0.3) | - | 2 (0.3) | 2 (0.3) |
| Haemorrhage | - | - | - | - | - | - | 1 (0.2) |
| Hypertensive Crisis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Hypotension | - | - | - | 2 (0.3) | - | 2 (0.3) | 1 (0.2) |

**Table 34. Summary of Treatment-Emergent SAEs: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin | | | | | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| | | 100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | |
| Peripheral Arterial Occlusive Disease | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Peripheral Embolism | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Peripheral Ischaemia | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Vena Cava Thrombosis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |

NOTE: Does not include 52 subject from DDI-studies, none of whom experienced an SAE

### 7.4.2 Deaths

In study OPT-80 Phase 2A, one subject died during the study. This subject (receiving 200 mg fidaxomicin per day) had staphylococcal sepsis and a cerebral hemorrhage on Day 10, both of severe severity, leading to death on Day 16. These TEAEs were considered by the investigator to be unrelated to study drug. In the pooled 101.1.C.003 and 101.1.C.004 studies, a total of 36 deaths occurred among subjects treated with fidaxomicin and 38 deaths occurred among those treated with vancomycin.

The SOCs with the highest incidence of TEAEs resulting in death from the pooled data from all studies in the fidaxomicin 400 mg, fidaxomicin any dose, and vancomycin 500 mg groups, respectively, were infections and infestations (1.8%, 1.6%, and 1.9%); respiratory, thoracic, and mediastinal disorders (1.5%, 1.3%, and 0.5%); and neoplasms benign, malignant and unspecified (0.8%, 0.7%, and 0.5%) (Table 35). The TEAEs resulting in death reported at the highest incidences in the fidaxomicin 400 mg group were respiratory failure in 4 (0.7%) subjects; and pneumonia and sepsis in 3 (0.5%) subjects. The TEAEs resulting in death reported at the highest incidences in the fidaxomicin any dose group were respiratory failure in 4 (0.6%) subjects; and pneumonia and sepsis in 3 (0.4%) subjects. The TEAEs resulting in death reported at the highest incidences in the vancomycin 500 mg group were sepsis in 4 (0.7%) subjects; and multi-organ failure in 3 (0.5%) subjects.

None of the TEAEs resulting in death were assessed as related to study drug by the Investigator.

**Table 35. Summary of TEAEs Resulting in Death: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin | | | | | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| | | 100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | |
| Number Of Subjects With ≥1 TEAE Resulting In Death | - | 1 (1.9) | - | 36 (5.9) | - | 37 (5.5) | 38 (6.5) |
| Cardiac Disorders | - | - | - | 2 (0.3) | - | 2 (0.3) | 7 (1.2) |
| Cardiac Arrest | - | - | - | - | - | - | 1 (0.2) |
| Cardiac Failure Congestive | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Cardio-Respiratory Arrest | - | - | - | - | - | - | 2 (0.3) |
| Cardiogenic Shock | - | - | - | - | - | - | 2 (0.3) |
| Myocardial Infarction | - | - | - | 1 (0.2) | - | 1 (0.1) | 2 (0.3) |
| Gastrointestinal Disorders | - | - | - | 3 (0.5) | - | 3 (0.4) | 6 (1.0) |
| Ascites | - | - | - | - | - | - | 1 (0.2) |
| Gastrointestinal Haemorrhage | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Gastrointestinal Perforation | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Intestinal Obstruction | - | - | - | - | - | - | 1 (0.2) |
| Large Intestine Perforation | - | - | - | - | - | - | 1 (0.2) |
| Peritonitis | - | - | - | 1 (0.2) | - | 1 (0.1) | 1 (0.2) |
| Small Intestinal Obstruction | - | - | - | - | - | - | 2 (0.3) |
| General Disorders And Administration Site Conditions | - | - | - | 1 (0.2) | - | 1 (0.1) | 4 (0.7) |
| Euthanasia | - | - | - | - | - | - | 1 (0.2) |
| Multi-Organ Failure | - | - | - | 1 (0.2) | - | 1 (0.1) | 3 (0.5) |
| Infections And Infestations | - | - | - | 11 (1.8) | - | 11 (1.6) | 11 (1.9) |
| Bacteraemia | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Bronchopulmonary Aspergillosis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Escherichia Sepsis | - | - | - | - | - | - | 1 (0.2) |
| Neutropenic Sepsis | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Pneumonia | - | - | - | 3 (0.5) | - | 3 (0.4) | 2 (0.3) |
| Sepsis | - | - | - | 3 (0.5) | - | 3 (0.4) | 4 (0.7) |
| Sepsis Syndrome | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Septic Shock | - | - | - | 1 (0.2) | - | 1 (0.1) | 2 (0.3) |

**Table 35. Summary of TEAEs Resulting in Death: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin | | | | | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| | | 100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | |
| Urosepsis | - | - | - | - | - | - | 2 (0.3) |
| Injury, Poisoning And Procedural Complications | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Vascular Graft Occlusion | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Metabolism And Nutrition Disorders | - | - | - | - | - | - | 3 (0.5) |
| Dehydration | - | - | - | - | - | - | 1 (0.2) |
| Failure To Thrive | - | - | - | - | - | - | 1 (0.2) |
| Malnutrition | - | - | - | - | - | - | 1 (0.2) |
| Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) | - | - | - | 5 (0.8) | - | 5 (0.7) | 3 (0.5) |
| Acute Myeloid Leukaemia | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Adrenal Gland Cancer Metastatic | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Colon Cancer | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Endometrial Cancer | - | - | - | - | - | - | 1 (0.2) |
| Gallbladder Cancer | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Lung Cancer Metastatic | - | - | - | - | - | - | 1 (0.2) |
| Lung Neoplasm Malignant | - | - | - | - | - | - | 1 (0.2) |
| Renal Cell Carcinoma Stage Unspecified | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Nervous System Disorders | - | - | - | - | - | - | 1 (0.2) |
| Cerebral Infarction | - | - | - | - | - | - | 1 (0.2) |
| Renal And Urinary Disorders | - | - | - | 3 (0.5) | - | 3 (0.4) | - |
| Renal Failure | - | - | - | 2 (0.3) | - | 2 (0.3) | - |
| Renal Failure Acute | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Respiratory, Thoracic And Mediastinal Disorders | - | - | - | 9 (1.5) | - | 9 (1.3) | 3 (0.5) |
| Chronic Obstructive Pulmonary Disease | - | - | - | 2 (0.3) | - | 2 (0.3) | - |
| Pneumonia Aspiration | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Respiratory Arrest | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Respiratory Distress | - | - | - | 1 (0.2) | - | 1 (0.1) | - |
| Respiratory Failure | - | - | - | 4 (0.7) | - | 4 (0.6) | 2 (0.3) |
| Tachypnoea | - | - | - | - | - | - | 1 (0.2) |

**Table 35. Summary of TEAEs Resulting in Death: All Pooled Data (Phase 1, 2, 3 Studies: Safety Population)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=10)<br>n (%) | Fidaxomicin | | | | | Vancomycin<br>500mg<br>(N=583)<br>n (%) |
|---|---|---|---|---|---|---|---|
| | | 100-200mg<br>(N=54)<br>n (%) | 300mg<br>(N=12)<br>n (%) | 400mg<br>(N=608)<br>n (%) | 450mg<br>(N=11)<br>n (%) | Any Dose<br>(N=674)<br>n (%) | |
| Vascular Disorders | - | 1 (1.9) | - | 1 (0.2) | - | 2 (0.3) | - |
| Cerebral Haemorrhage | - | 1 (1.9) | - | - | - | 1 (0.1) | - |
| Peripheral Ischaemia | - | - | - | 1 (0.2) | - | 1 (0.1) | - |

NOTE: Does not include 52 subjects from DDI-studies, none of whom experienced a TEAE resulting in death

For the Phase 3 studies, Kaplan-Meier plots for survival are shown in Figure 11 and show comparable curves for both treatment groups (hazard ratio = 0.76 [95% CI: 0.47, 1.23]).

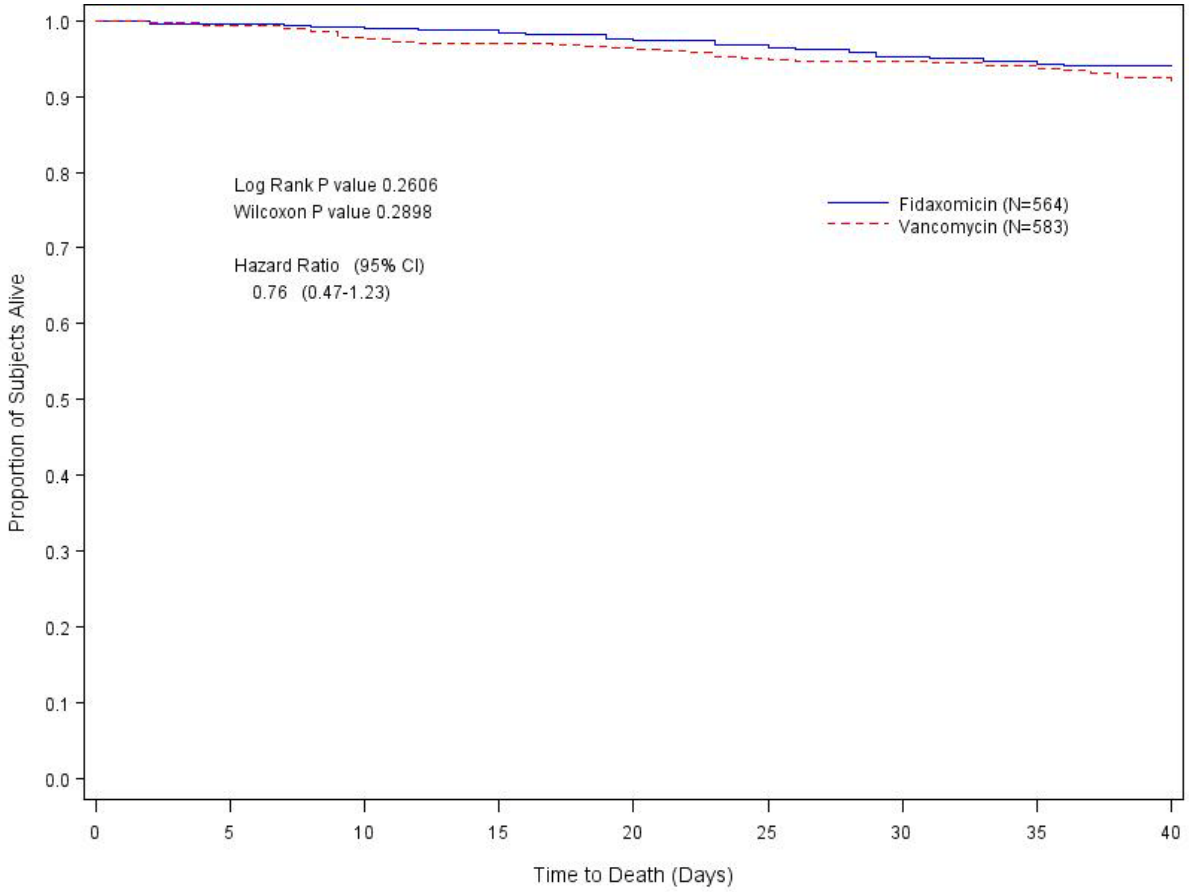



**Figure 11. Kaplan-Meier Survival Curves for Time to Death (Safety population)**

## 7.5 Treatment-Emergent Adverse Events of Special Interest

### 7.5.1 Gastrointestinal TEAEs

It is of interest to look at GI TEAEs since the majority of fidaxomicin remains in the intestinal lumen and exerts its activity there. The number of GI TEAEs and treatment-emergent SAEs was similar between the fidaxomicin group and the vancomycin group (Table 36). Slightly more GI TEAEs led to discontinuation from the study in the fidaxomicin group, mainly due to abdominal pain, colitis and megacolon each in 2 subjects, but these events could be CDI-related rather than drug-related.

**Table 36. Overview of GI Events from Phase 3 Studies**

| GI Disorders | Fidaxomicin 400mg (N=564) n (%) | Vancomycin 500mg (N=583) n (%) |
|---|---|---|
| Total TEAEs | 177 (31.4) | 170 (29.2) |
| TEAEs leading to discontinuation | 13 (2.3) | 8 (1.4) |
| Total treatment-emergent SAEs | 26 (4.6) | 24 (4.1) |

Deaths due to any GI TEAE were reported in 3 subjects in the fidaxomicin group and 6 subjects in the vancomycin group (Table 37).

**Table 37. Deaths Reported in the Phase 3 Studies from Any GI TEAE**

| System Organ Class<br>Preferred Term | Fidaxomicin 400mg<br>(N=564)<br>n (%) | Vancomycin 500mg<br>(N=583)<br>n (%) |
|---|---|---|
| Total number of deaths due to GI TEAE | 3 (0.5) | 6 (1.1) |
| Ascites | - | 1 (0.2) |
| GI hemorrhage | 1 (0.2) | - |
| GI perforation | 1 (0.2) | - |
| Intestinal obstruction | - | 1 (0.2) |
| Large intestine perforation | - | 1 (0.2) |
| Peritonitis | 1 (0.2) | 1 (0.2) |
| Small intestinal obstruction | - | 2 (0.3) |

### 7.5.2 Gastrointestinal Bleeding

Special care was taken to review all available information related to GI bleeding TEAEs in the Phase 3 studies. However, it should be noted that such an endeavor is confounded by several factors, such as:

- GI bleeding is an inherent component and complication of CDI itself
- Many of the subjects in the Phase 3 clinical studies had underlying medical conditions that would predispose them to GI bleeding during the 10-day dosing period or 30-day study follow-up period, such as:
  - A prior history of GI bleeding and/or recent bowel surgery
  - A co-morbid condition such as end-stage renal disease on dialysis, hepatic cirrhosis, neoplasms with recent marrow-suppressive chemotherapy and bone marrow transplantation and/or coagulopathies
  - Taking medications with anti-coagulant properties, such as aspirin, Plavix, heparin or coumadin.

In some cases, a GI bleeding TEAE was reported as a stand-alone TEAE with an easily recognizable MedDRA preferred term clearly reflecting GI bleeding (such as “gastrointestinal haemorrhage”), whereas in other cases GI bleeding was considered a manifestations of a larger syndrome reported as a diagnosis such as “GI perforation”. Therefore three strategies were implemented to identify all cases of GI bleeding:

First, the Phase 3 safety database was searched for all MedDRA preferred terms possibly reflecting GI bleeding (including terms such as GI hemorrhage, rectal hemorrhage, hemorrhagic diarrhea, hematemesis and hematochezia). In the first Phase 3 study (101.1.C.003), more such GI bleeding TEAEs were reported in the fidaxomicin group (11 [3.6%]) than in the vancomycin group (3 [0.9%]). In the second Phase 3 study (101.1.C.004), GI bleeding TEAEs occurred at a comparable rate in the two treatment groups

(9 [2.6%] versus 7 [1.9%]). In the pooled TEAE data from the Phase 3 studies, the TEAEs with MedDRA preferred terms related to GI bleeding are shown in Table 38.

**Table 38. GI Bleeding TEAEs (Preferred Terms, Phase 3 Studies)**

| Preferred Term | Fidaxomicin 400mg (N=564) n (%) | Vancomycin 500mg (N=583) n (%) |
|---|---|---|
| **Total** | **20 (3.5)** | **10 (1.7)** |
| Hematochezia | 7 (1.2) | 1 (0.2) |
| Diarrhoea haemorrhagic | 5 (0.9) | - |
| Gastrointestinal haemorrhage | 5 (0.9) | 1 (0.2) |
| Rectal haemorrhage | 2 (0.4) | 3 (0.5) |
| Haemorrhoidal haemorrhage | 1 (0.2) | 1 (0.2) |
| Haematemesis | - | 1 (0.2) |
| Oesophageal varices haemorrhage | - | 1 (0.2) |
| Upper gastrointestinal haemorrhage | - | 1 (0.2) |
| Occult blood positive | - | 1 (0.2) |

Next, the Sponsor reviewed all verbatim terms used by the site to report TEAEs to ensure that the preferred terms noted above captured all relevant TEAEs. This exercise uncovered one additional case (in a fidaxomicin-treated subject in study 101.1.C.003) with a verbatim term of “bleeding haemorrhoids” which had been coded to “haemorrhoids” rather than “haemorrhoidal haemorrhage”.

Finally, the Sponsor reviewed the narrative summaries for all treatment-emergent SAEs and deaths in both the fidaxomicin and vancomycin groups to identify subjects in which GI bleeding had been noted in the narrative but not reported as a stand-alone TEAE (because a more global diagnosis such as megacolon or GI perforation had been used as the reported treatment-emergent SAE term).

Table 39 summarizes all GI bleeding TEAEs identified by these three processes. This analysis suggests that the incidence of GI bleeding was comparable for fidaxomicin and vancomycin treated subjects.

### Table 39. All Identified GI Bleeding TEAEs (Phase 3 Studies)

| Preferred Term | Fidaxomicin 400mg (N=564) n (%) | Vancomycin 500mg (N=583) n (%) |
|---|---|---|
| **Total** | **23 (3.9)** | **18 (2.6)** |
| **Identified via MedDRA Preferred Term** | | |
| Hematochezia | 7 (1.2) | 1 (0.2) |
| Diarrhoea haemorrhagic | 5 (0.9) | - |
| Gastrointestinal haemorrhage | 5 (0.9) | 1 (0.2) |
| Rectal haemorrhage | 2 (0.4) | 3 (0.5) |
| Haemorrhoidal haemorrhage | 1 (0.2) | 1 (0.2) |
| Haematemesis | - | 1 (0.2) |
| Oesophageal varices haemorrhage | - | 1 (0.2) |
| Upper gastrointestinal haemorrhage | - | 1 (0.2) |
| Occult blood positive | - | 1 (0.2) |
| **Identified via Verbatim Term** | | |
| Haemorrhoids (bleeding) | 1 (0.2) | - |
| **Identified via treatment-emergent SAE narratives** | | |
| Ischemic colitis (with bloody stools) | - | 1 (0.2) |
| Large intestine perforation (with GI bleed) | - | 2 (0.4) |
| CDI recurrence (with bloody stools) | - | 1 (0.2) |
| Toxic megacolon (with bloody diarrhea) | 2 (0.4) | 1 (0.2) |
| Feculent vomiting (with melena) | - | 1 (0.2) |
| Urosepsis (with occult blood positive) | - | 1 (0.2) |
| Meningitis (with bloody stools) | - | 1 (0.2) |
| Septic shock (with rectal bleeding) | - | 1 (0.2) |

The timing of these events is also of interest (see Table 40). About half of the aforementioned GI bleeding TEAEs in both treatment groups occurred while the subject was expected to be exposed to study drug (Study Days 1-12). Most of these early TEAEs tended to be mild, self-limited GI bleeding (such as a single bloody bowel movement or intermittent bleeding from pre-existing rectal haemorrhoids) not requiring intervention. The few subjects with early TEAEs that were more serious in nature most likely reflected underlying pathology present at enrollment, since these subjects usually only received a few doses of study drug and it is unlikely that the study drug could have exerted a marked effect on the GI tract so quickly.

### Table 40. Timing of GI Bleeding TEAEs (Phase 3 Studies)

| System Organ Class Preferred Term | Fidaxomicin 400mg (N=564) n (%) | Vancomycin 500mg (N=583) n (%) |
|---|---|---|
| Total GI bleeding events | 23 | 18 |
| Time to GI bleeding TEAE (days) | | |
| Median | 14.0 | 17.5 |
| Range | 2, 46 | 2, 43 |
| TEAEs with onset beyond Study Day 13 | 12 | 11 |
| TEAEs with onset >5 days after last dose of study drug | 13 | 11 |

Most of the more serious GI bleeding TEAEs tended to occur weeks after study drug dosing and are more likely to reflect other intercurrent co-morbid conditions and interventions in these very sick patients rather than an effect of study drug. Brief summaries of each treatment-emergent SAE which included a GI bleeding component are provided in the Appendix. Each of these cases was associated with either recurrent CDI , a previous history of GI bleeding, and/or other co-morbid conditions and therapies which would predispose to GI bleeding. Thus, there does not appear to be an increased risk of significant GI bleeding (or other adverse GI effects) with fidaxomicin compared to vancomycin. Preclinical studies also did not indicate a risk of GI bleeding or other GI toxicity, even at much higher daily oral doses of approximately 1 g/kg in dogs given for 3 months.

Fidaxomicin did not exhibit any adverse effect on platelet counts and was not associated with an increase in bleeding TEAEs in other (non-GI) organ systems.

### 7.5.3 Potential Effects on ECG and QTc Interval

A specific QTc study was not carried out since the very low plasma levels seen after oral fidaxomicin dosing in healthy subjects makes the supra-therapeutic exposure necessary for such a study not feasible. However, ECG parameters and QTc intervals were measured in subjects participating in the Phase 3 studies.

The overall ECG interpretation was reported as “Normal” or “Abnormal” and the shifts reflect the change from baseline to the worst post-baseline finding. Shifts from normal to abnormal in ECG interpretation occurred at a lower incidence in the fidaxomicin group than in the vancomycin group (Table 41), thus, fidaxomicin does not appear to have an adverse effect on ECG parameters.

**Table 41. Shift in Overall Interpretation of ECG: Phase 3 Studies (Safety Population)**

| Shift from Baseline to Post-Baseline | Fidaxomicin 400mg [N=564] n (%) | Vancomycin 500mg [N=583] n (%) |
|---|---|---|
| Abnormal to Normal | 77 (15.8) | 36 (7.4) |
| Abnormal to Abnormal | 226 (46.5) | 241 (49.3) |
| Normal to Normal | 155 (31.9) | 165 (33.7) |
| Normal to Abnormal | 28 (5.8) | 47 (9.6) |

QTc prolongation was summarized categorically for different cut-off points to examine outliers in more detail (Table 42). Examination of the data revealed no clinically significant changes from baseline to EOT in the mean values for corrected QT interval by the method of Bazett or corrected QT interval by the method of Fridericia for either of the treatment groups. Specifically, no evidence of QTc prolongation by fidaxomicin was identified. In study 101.1.C.004, 1 case of Torsade de Pointes was experienced by Subject 048003 who was receiving vancomycin.

**Table 42. Summary of 12-Lead ECG QTc Interval Results in Phase 3 Studies (Safety Population)**

| QTc intervals | Bazett's | | Fridericia's | |
|---|---|---|---|---|
| | Fidaxomicin (N=501) n (%) | Vancomycin (N=503) n (%) | Fidaxomicin (N=501) n (%) | Vancomycin (N=503) n (%) |
| **Changes in QTc interval from baseline** | | | | |
| >30 msec | 42 (8.7) | 32 (6.6) | 37 (7.7) | 35 (7.2) |
| >60 msec | 6 (1.2) | 6 (1.2) | 6 (1.2) | 5 (1.0) |
| **QTc interval at end of the study** | | | | |
| >450 msec | 96 (19.2) | 109 (21.7) | 43 (8.6) | 54 (10.7) |
| >480 msec | 26 (5.2) | 34 (6.8) | 13 (2.6) | 16 (3.2) |
| >500 msec | 12 (2.4) | 14 (2.8) | 7 (1.4) | 11 (2.2) |

NOTE: Only subjects with both baseline and end of study ECG values are included in this evaluation.

An additional subgroup analysis of subjects with high plasma levels (fidaxomicin + OP-1118 ≥150 ng/mL) using pooled data from studies 101.1.C.003 and 101.1.C.004 showed no association between QTc prolongation and plasma levels of fidaxomicin or OP-1118.

Cardiac deaths were also evaluated to see if there was any difference between the two treatment groups (Table 43). Overall the number of cardiac deaths in subjects treated with fidaxomicin was lower than in the group treated with vancomycin.

**Table 43. Deaths Reported in the Phase 3 Studies from Cardiac TEAEs**

| System Organ Class<br>Preferred Term | Fidaxomicin 400mg (N=564) n (%) | Vancomycin 500mg (N=583) n (%) |
|---|---|---|
| **Total number of deaths due to cardiac TEAEs** | **2 (0.4)** | **7 (1.2)** |
| Cardiac arrest | - | 1 |
| Congestive heart failure | 1 | - |
| Cardio-pulmonary arrest | - | 2 |
| Cardiogenic shock | - | 2 |
| Myocardial infarction | 1 | 2 |

The evaluation of CDI therapy on cardiac function, and in particular QT interval, is complex because of the clinical condition of the subjects. Diarrheal states can be associated with fluid and electrolyte disturbances that can result in dysarhythmic states. Evaluation is made more difficult by concomitant therapies, many of which have cardiac effects. However, the results from the two Phase 3 studies provided no evidence of QTc prolongation induced by fidaxomicin. Overall, it is more likely that any changes in the QTc interval reflect either the typical variability that occur in such studies or the underlying effects of diarrhea or concurrent drugs, rather than an effect of either study drug on the cardiac conducting system. This confirms the results of nonclinical safety pharmacology studies, where hERG current inhibition showed that neither fidaxomicin nor OP-1118 at concentrations up to 10 µg/mL inhibited the hERG current compared with background levels. In a study of telemeterized conscious dogs receiving a high dose of fidaxomicin (top dose 9600 mg), no effect was observed on QT or QTc intervals and there were no pharmacologically relevant effects on

heart rate, blood pressure, body temperature, PR interval, RR interval, QRS complex and QTc interval.

### 7.5.4 Liver Function

Although fidaxomicin produces minimal systemic exposure following oral dosing in humans and animals, liver function was examined in detail as this is the initial organ of exposure for any absorbed drug. Preclinical studies indicated no effect on liver function, even at very high oral doses (9600 mg) delivered to dogs for 3 months.

In humans, the incidence of TEAEs involving liver function tests (LFTs): aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin, were similar between groups (Table 44).

**Table 44. TEAEs Related to Liver Function Tests**

| System Organ Class<br>Preferred Term | Fidaxomicin 400mg (N=564) n (%) | Vancomycin 500mg (N=583) n (%) |
|---|---|---|
| **Investigations related to LFTs, total subjects** | **17 (3.0)** | **14 (2.4)** |
| ALT increased | 9 (1.6) | 6 (1.0) |
| AST | - | 1 (0.2) |
| AST abnormal | 1 (0.2) | - |
| AST increased | 2 (0.4) | 3 (0.5) |
| Blood alkaline phosphatase increased | 3 (0.5) | 1 (0.2) |
| Hepatic enzyme increased | 3 (0.5) | 1 (0.2) |
| Liver function test abnormal | 3 (0.5) | 4 (0.7) |
| Transaminases increased | - | 1 (0.2) |

Likewise, summary statistics around the changes in LFT values between baseline and end of therapy were similar between treatment arms (Table 45).

**Table 45. Summary Statistics for Changes in Liver Function Parameters Between Baseline and End of Therapy**

| Parameter | Fidaxomicin 400mg (N=564) | Vancomycin 500mg (N=583) |
|---|---|---|
| ALT (U/L) | | |
| N | 482 | 478 |
| Mean | 6.1 | -0.3 |
| SD | 48.62 | 71.52 |
| Median | 2.0 | 2.0 |
| Min, Max | -515, 599 | -1476, 120 |
| Alkaline Phosphatase (U/L) | | |
| N | 502 | 506 |
| Mean | 3.0 | 2.7 |
| SD | 59.07 | 47.19 |
| Median | -1.0 | 1.0 |
| Min, Max | -494, 908 | -227, 607 |
| AST (U/L) | | |
| N | 473 | 459 |
| Mean | 3.0 | -4.5 |
| SD | 24.26 | 136.48 |
| Median | 2.0 | 2.0 |
| Min, Max | -254, 217 | -2882, 169 |
| Bilirubin (µmol/L) | | |
| N | 485 | 481 |
| Mean | -0.647 | -0.922 |
| SD | 5.1667 | 15.1875 |
| Median | 0.0 | 0.0 |
| Min, Max | -37.62, 25.65 | -235.98, 121.41 |
| Direct Bilirubin (µmol/L) | | |
| N | 443 | 433 |
| Mean | -0.327 | -0.467 |
| SD | 2.8842 | 7.5026 |
| Median | 0.0 | 0.0 |
| Min, Max | -34.20, 23.94 | -123.12, 82.08 |

A shift from normal to high values for ALT and AST were seen in approximately 10% of subjects, but there was also a shift from high to normal of approximately the same proportion (Table 46). These shifts were similar in the fidaxomicin and vancomycin groups. Approximately 5% of subjects in each group had a shift from normal to high alkaline phosphatase, with similar shifts from high to normal,. No subjects in either group met Hy's Law.

**Table 46. Shift from Baseline in Liver Function Parameters (Pooled Phase 3 Studies: Safety Population)**

| Parameter | Fidaxomicin 400mg | | | Vancomycin 500mg | | |
|---|---|---|---|---|---|---|
| | End-of-Therapy | | | End-of-Therapy | | |
| **Alanine Aminotransferase** | N=482 | | | N=478 | | |
| Day 1 | Low | Normal | High | Low | Normal | High |
| Low | 1 | 15 | - | 4 | 4 | - |
| Normal | 1 | 338 | 48 | 1 | 359 | 43 |
| High | - | 38 | 41 | - | 31 | 36 |
| **Aspartate Aminotransferase** | N=473 | | | N=459 | | |
| Day 1 | Low | Normal | High | Low | Normal | High |
| Low | 1 | 11 | - | - | 10 | 1 |
| Normal | 4 | 347 | 44 | 5 | 328 | 42 |
| High | - | 32 | 34 | - | 33 | 40 |
| **Alkaline Phosphatase** | N=502 | | | N=506 | | |
| Day 1 | Low | Normal | High | Low | Normal | High |
| Low | - | 3 | - | - | 1 | - |
| Normal | - | 395 | 24 | 2 | 392 | 20 |
| High | - | 26 | 54 | - | 25 | 66 |
| **Bilirubin** | N=483 | | | N=481 | | |
| Day 1 | Low | Normal | High | Low | Normal | High |
| Low | 12 | 25 | - | 20 | 26 | - |
| Normal | 29 | 390 | 6 | 21 | 394 | 6 |
| High | - | 9 | 12 | - | 3 | 11 |

For those subjects with LFT increases of at least one NCI grade, plasma concentrations of fidaxomicin were similar to mean concentrations for all subjects, thus there did not appear to be a correlation with exposure (Table 47).

**Table 47. Plasma Levels in Subjects with LFT AEs**

| | Plasma levels, 3-5 hours post-dose | Fidaxomicin, ng/mL | | OP-1118, ng/mL | |
|---|---|---|---|---|---|
| All subjects with an LFT AE (N = 17) | | Day 1 | EOT | Day 1 | EOT |
| | N >LLOQ | 7 | 8 | 8 | 8 |
| | N <LLOQ | - | - | - | - |
| | Mean | 32.8 | 29.1 | 79.2 | 104 |
| | SD | 27.7 | 29.4 | 69.5 | 79.3 |
| | Min, Max | 1.92, 69.6 | 7.82, 99.7 | 4.57, 167 | 11.4, 236 |
| All subjects (N = 564) | | | | | |
| | N >LLOQ | 312 | 100 | 316 | 103 |
| | N <LLOQ | 13 | 2 | 14 | 2 |
| | Mean | 22.8 | 28.5 | 44.5 | 85.6 |
| | SD | 26.7 | 33.4 | 50.4 | 131 |
| | Min, Max | 0.364, 197 | 0.305, 191 | 0.283, 363 | 1.09, 871 |

Thus it can be concluded that fidaxomicin appears to have no impact on liver function based on lack of findings in preclinical and clinical studies.

### 7.5.5 Leukopenia

Shifts in WBCs (preferred terms of febrile neutropenia, granulocytopenia, leukopenia, lymphopenia, neutropenia, pancytopenia, neutropenic sepsis, WBC disorder, lymphocyte count abnormal, lymphocyte count decreased, neutrophil count decreased, WBC decreased) were not uncommon in either treatment arm, however, they were more prevalent in the fidaxomicin arm (23 subjects in the fidaxomicin group versus 11 in the vancomycin group) (Table 48).

**Table 48. Incidence of TEAEs Related to Decreases in White Blood Cell Counts**

| System Organ Class<br>Preferred Term | Fidaxomicin 400mg (N=564) n (%) | Vancomycin 500mg (N=583) n (%) |
|---|---|---|
| **Total subjects TEAE related to decrease in WBC counts** | **23 (4.1)** | **11 (1.9)** |
| Blood And Lymphatic System Disorders | | |
| Febrile Neutropenia | 2 ( 0.4) | - |
| Granulocytopenia | - | 1 ( 0.2) |
| Leukopenia | 8 ( 1.4) | 4 ( 0.7) |
| Lymphopenia | 4 ( 0.7) | 2 ( 0.3) |
| Neutropenia | 5 ( 0.9) | - |
| Pancytopenia | 1 ( 0.2) | - |
| White Blood Cell Disorder | - | 1 ( 0.2) |
| Infections And Infestations | | |
| Neutropenic Sepsis | 1 ( 0.2) | - |
| Investigations | | |
| Lymphocyte Count Abnormal | - | 1 ( 0.2) |
| Lymphocyte Count Decreased | 5 ( 0.9) | 2 ( 0.3) |
| Neutrophil Count Decreased | 5 ( 0.9) | - |
| White Blood Cell Count Decreased | 2 ( 0.4) | 1 ( 0.2) |

Nearly all of these shifts occurred in subjects with underlying hematological malignancies, prior bone marrow transplantation, and/or ongoing chemotherapy. The fidaxomicin arm had a higher incidence of pre-existing active blood and lymphatic disorders at enrollment compared to vancomycin subjects (38.7% versus 32.6%). The fidaxomicin arm also had a markedly higher prevalence of subjects concomitantly receiving treatment in the medication class of antineoplastic or immunomodulatory agents (67 subjects [11.9%] in the fidaxomicin group versus 48 subjects [8.2%] in the vancomycin group). Thus, these TEAEs are explained by underlying comorbidities and the difference between the treatment groups is adequately explained by the underlying differences in the proportion of subjects receiving chemotherapeutic agents.

## 7.6 Laboratory Evaluations

In both Phase 3 studies a central laboratory was used for evaluations. No meaningful differences in hematology laboratory measurements were noted between the fidaxomicin and vancomycin groups with respect to change from baseline to EOT or abnormal shifts from baseline to EOT. The incidence of clinically significant (high and low) hematology measurements at any post-baseline time point also showed no meaningful differences between the fidaxomicin and vancomycin treatment groups. The hematology parameters with

the highest incidences of clinically significant low values for both fidaxomicin-treated and vancomycin-treated subjects, respectively, were hemoglobin (9.0% vs. 10.3%), hematocrit (8.4% vs. 8.0%), and erythrocytes (8.0% vs. 8.2%). The parameters with the highest incidences (≥2%) of clinically significant high values were leukocytes, neutrophils, and platelets.

Markedly abnormal low (i.e., worsened by two or more grades from the baseline toxicity grade) hematology values were infrequent but occurred at a higher incidence in the fidaxomicin group than the vancomycin group: lymphocytes (3.9% vs. 2.1%), leukocytes (1.6% vs. 0.8%), and neutrophils (1.4% vs. 0.2%). No markedly high results were reported for either treatment group. Subjects with reductions in WBC parameters (e.g., leukocytes, lymphocytes, neutrophils) generally had concomitant diseases which could affect WBC counts (e.g., malignancies, lupus, etc), had recently received chemotherapy or immunomodulatory agents, and/or had undergone recent bone marrow ablation with stem cell transplantation. More fidaxomicin subjects than vancomycin subjects received concomitant anti-neoplastic/immunomodulating agents (11.9% vs. 8.2%, respectively). Furthermore, no markedly increased incidence of treatment-emergent infections and infestations with fidaxomicin versus vancomycin was observed (22.9% vs. 20.8%, respectively). Thus, reductions in WBC counts were considered to be related to the underlying condition.

No meaningful differences in clinical chemistry laboratory measurements were noted between the fidaxomicin and vancomycin groups with respect to change from baseline to EOT, abnormal shifts from baseline to EOT, or the incidence of high and low clinical chemistry measurements flagged as clinically significant by the laboratory at any post-baseline time point. Markedly abnormal low and high clinical chemistry values occurred at a similar or slightly higher incidence in the fidaxomicin group than the vancomycin group. These treatment differences were not considered to be clinically meaningful. Thus, fidaxomicin does not appear to be associated with any clinically significant effect on clinical chemistry parameters.

The specific changes in liver function parameters are discussed in more detail in Section 7.5.4 and changes in WBC counts are evaluated in Section 7.5.5.

## 7.7 Vital Signs

There were no clinically significant changes in any vital signs parameters in either of the two Phase 3 studies, and there were no notable differences between the vancomycin and fidaxomicin groups. The individual changes seen were likely to be as a result of the underlying medical conditions of these subjects.

## 7.8 Safety Subgroups

Clinical safety results were evaluated for the following subgroups: age (<65 years and ≥65 years); gender (male and female); race (White and non-White); country (Belgium, Canada, France, Germany, Italy, Spain, Sweden, United Kingdom, and US); exposure to study drug (<3 days vs. ≥3 days); stratum (no prior CDI episode versus single prior CDI

episode); patient status (inpatient versus outpatient); baseline *C. difficile* strain type (BI strain versus non-BI strain); baseline number of UBMs (<median 6 versus ≥median 6); renal insufficiency based on eCCL: mild (51-79 mL/min), moderate (31-50 mL/min), and severe (≤30 mL/min); and CDI disease severity at baseline by ESCMID score (severe versus non-severe). These subgroups were analyzed for all TEAEs, incidence of markedly abnormal (low or high) laboratory values of hematology analytes and serum chemistry analytes, and change from baseline in vital sign measurements.

### 7.8.1 Age

No relevant treatment group differences were observed in the overall incidence of TEAEs within each age group. As might be expected, TEAEs, treatment-emergent SAEs and deaths were increased in elderly subjects in both treatment groups; however, fidaxomicin was not associated with a disproportionate increase (Table 49).

Fidaxomicin was not associated with an increase in treatment-emergent SAEs in the elderly compared to vancomycin. No clinically meaningful treatment group differences were observed in the overall incidence of treatment-emergent SAEs within each age group. The treatment-emergent SAEs in subjects <65 years of age occurring at the highest incidence in the fidaxomicin group were leukopenia, neutropenia, thrombocytopenia, diarrhea, and hyperkalemia (1.0% each). The treatment-emergent SAEs in subjects <65 years of age occurring at the highest incidence in the vancomycin group were diarrhea, vomiting, hyperglycemia, hyponatremia, and renal failure (1.0% each). The treatment-emergent SAEs in subjects ≥65 years of age occurring at the highest incidence (>2.0%) in the fidaxomicin group were pneumonia (2.6%) and *C. difficile* colitis (2.2%). In the vancomycin group, treatment-emergent SAEs of pneumonia and *C. difficile* colitis were similarly reported in 2.7% and 2.4% of subjects ≥65 years of age, respectively.

**Table 49. Incidence of TEAEs in Elderly Subjects**

| | Age <65 years | | Age ≥65 years | |
|---|---|---|---|---|
| | **Fidaxomicin 400mg (N=292) n (%)** | **Vancomycin 500mg (N=288) n (%)** | **Fidaxomicin 400mg (N=272) n (%)** | **Vancomycin 500mg (N=295) n (%)** |
| TEAEs | 188 (64.4) | 176 (61.1) | 197 (72.4) | 206 (69.8) |
| Treatment-emergent SAEs | 61 (20.9) | 50 (17.4) | 84 (30.9) | 85 (28.8) |
| Deaths | 7 (2.4) | 9 (3.1) | 29 (10.7) | 29 (9.8) |

A lower incidence of markedly abnormally low lymphocyte values was reported in fidaxomicin subjects who were <65 years (2.7%) compared to ≥65 years (5.3%). In addition, younger fidaxomicin-treated subjects appear to have a lower incidence of abnormally high glucose values (3.3%) compared to older subjects (9.4%). However, these changes are considered to reflect other ageing changes rather than any effects of fidaxomicin.

### 7.8.2 Gender

No relevant treatment group differences were observed in the overall incidence of TEAEs within gender groups. The overall incidence of TEAEs for fidaxomicin-treated and vancomycin-treated subjects, respectively, was similar in male subjects (70.2% and 66.1%) as well as female subjects (66.8% and 65.1%).

No clinically meaningful treatment group differences were observed in the overall incidence of treatment-emergent SAEs for either gender. A higher incidence of treatment-emergent SAEs was observed in male subjects (29.3% and 28.1%) compared with female subjects (23.0% and 19.6%) in the fidaxomicin and vancomycin groups, respectively. The treatment-emergent SAEs in male subjects occurring at the highest incidence in the fidaxomicin group were *C. difficile* colitis (2.9%), sepsis and blood uric acid increased (2.1% each), and pneumonia and renal failure (1.7% each). The treatment-emergent SAEs in female subjects receiving fidaxomicin occurring at the highest incidence were hypophosphatemia (1.6%), and leukopenia, pneumonia, and hyperkalemia (1.2% each).

Male subjects had a higher incidence of markedly abnormally low lymphocyte values than female subjects for both fidaxomicin and vancomycin subjects.

### 7.8.3 Race

No relevant treatment group or race differences were observed in the overall incidence of TEAEs. Treatment-emergent SAEs were reported at a higher overall incidence in non-White subjects (33.9% and 36.5%) than White subjects (24.8% and 21.5%) for both fidaxomicin and vancomycin subjects, respectively.

The treatment-emergent SAEs occurring at the highest incidence in White subjects in the fidaxomicin group were *C. difficile* colitis and pneumonia (1.6% each), sepsis (1.4%), and hyponatremia (1.2%), while in non-White subjects the treatment-emergent SAEs occurring at the highest incidence were anemia, hypoglycemia, and hypophosphatemia, each occurring in 2 subjects.

Non-White subjects appeared to have slightly higher incidence of markedly abnormally low hematology parameters than White subjects, particularly with respect to low leukocyte values. However, this apparent difference may be due to the small number of subjects in the non-White subgroup.

Race did not appear to have an influence on the incidence of markedly abnormal clinical chemistry values.

### 7.8.4 Country

No significant differences between treatment groups were noted in the incidence of TEAEs within countries (Belgium, Canada, France, Germany, Italy, Spain, Sweden, United Kingdom, and US). Insignificant treatment and country differences were observed in the overall incidence of treatment-emergent SAEs; however, these differences are not unexpected due to differences in sample size.

### 7.8.5 Exposure

The safety of fidaxomicin was examined by days of exposure of subjects to study drug (<3 days vs. ≥3 days). Only 16 fidaxomicin subjects and 18 vancomycin subjects had dosing for <3 days, compared to 548 and 565, respectively, who were exposed for more than 3 days. No relevant treatment or exposure differences were observed in the overall incidence of TEAEs. The overall incidence of TEAEs was similar for fidaxomicin-treated and vancomycin-treated subjects with either <3 days exposure (62.5% and 66.7%) or ≥3 days exposure (68.4% and 65.5%).

In subjects with less than 3 days exposure, the overall incidence of treatment-emergent SAEs was somewhat lower for subjects in the fidaxomicin group (37.5%) than the vancomycin group (50.0%). In subjects with greater than or equal to 3 days exposure, the overall incidence of treatment-emergent SAEs was similar for subjects in the fidaxomicin (25.4%) and vancomycin (22.3%) groups. For subjects in the fidaxomicin 400 mg group with less than 3 days exposure, no treatment-emergent SAEs occurred in more than 1 subject. For subjects with greater than or equal to 3 days exposure to fidaxomicin, the treatment-emergent SAEs occurring at the highest incidence were *C. difficile* colitis (1.5%), pneumonia and sepsis (1.3% each). Amongst vancomycin subjects with at least 3 days exposure, these same treatment-emergent SAEs were reported for 1.6%, 1.8%, and 0.7% of subjects, respectively.

Subjects with a longer duration of exposure (≥3 days) had a generally higher incidence of markedly abnormally low hematology values than subjects with a shorter duration of exposure (<3 days). Subjects with a longer duration of exposure to either fidaxomicin or vancomycin had a higher incidence of markedly abnormally high glucose values than subjects with a shorter duration of exposure.

### 7.8.6 Stratum

The safety of fidaxomicin was examined in subjects by stratum (no prior CDI episode vs. single prior CDI episode). No relevant treatment group or stratum differences were observed in the overall incidence of TEAEs or treatment-emergent SAEs. The treatment-emergent SAEs occurring at the highest incidence (>2.0%) in the fidaxomicin group for subjects with a single prior episode of CDI were leukopenia (2.2%), megacolon (2.2%), urosepsis (2.2%), and hypophosphatemia (2.2%). The treatment-emergent SAEs occurring at the highest incidence in fidaxomicin subjects with no prior episode of CDI were *C. difficile* colitis and pneumonia (1.7%) and sepsis (1.3%).

Stratum appeared to have no influence on the incidence of markedly abnormal hematology values. No clinically relevant treatment differences in markedly abnormal clinical chemistry measurements were reported. However, subjects with a single prior episode of CDI had a slightly higher incidence of markedly abnormally high glucose values than subjects with no prior episode of CDI for both the fidaxomicin and vancomycin groups.

### 7.8.7 Patient Status

The safety of fidaxomicin was examined in subjects by patient status (inpatient vs. outpatient). No relevant treatment group differences were observed in the overall incidence

of TEAEs or treatment-emergent SAEs by patient status. A higher overall incidence of TEAEs and treatment-emergent SAEs was observed for inpatients compared with outpatients. The treatment-emergent SAEs occurring at the highest incidence (≥2.0%) in the fidaxomicin group for inpatients were *C. difficile* colitis (2.2%), pneumonia (2.0%), and sepsis (2.0%). For outpatients receiving fidaxomicin, the treatment-emergent SAE occurring at the highest incidence was hypophosphatemia (1.5%).

Inpatient status appears to be associated with a higher incidence of markedly abnormally low lymphocyte values and markedly abnormally high glucose values than outpatient status for both fidaxomicin and vancomycin subjects.

### 7.8.8 Baseline *C. difficile* Strain Type

The safety of fidaxomicin was evaluated by the initial strain of CDI isolated from subjects enrolled in the Phase 3 studies (BI strain versus non-BI strain). No relevant treatment differences in the incidence of either TEAEs or treatment-emergent SAEs were shown in subjects either with a BI strain or non-BI strain of *C. difficile*. The highest incidence of TEAEs and treatment-emergent SAEs occurred in the gastrointestinal disorders SOC. The treatment-emergent SAEs occurring at the highest incidence (≥2.0%) in fidaxomicin-treated subjects with a BI strain were *C. difficile* colitis (3.5%), megacolon (2.1%), sepsis (2.1%), and blood uric acid increased (2.1%).

Baseline strain type appeared to have no influence on the incidence of markedly abnormal hematology values. However, subjects with a BI strain of *C. difficile* had a higher incidence of markedly abnormally high glucose values than subjects with a non-BI strain of *C. difficile* in both the fidaxomicin and vancomycin groups.

### 7.8.9 Baseline Number of Unformed Bowel Movements

The safety of fidaxomicin was examined in subjects by baseline number of UBM (<median [6] vs. ≥median [6]). No relevant treatment group differences were observed in the overall incidence of TEAEs or treatment-emergent SAEs in subjects based upon the baseline number of UBM. The treatment-emergent SAE occurring at the highest incidence (≥2.0%) in fidaxomicin-treated subjects with <median number of UBM was pneumonia (2.8%) and in subjects with ≥median number of UBM was *C. difficile* colitis (1.7%).

Fidaxomicin-treated vs. vancomycin-treated subjects, respectively, with <median number of UBM had a higher incidence of markedly abnormally low lymphocyte values (7.3% vs. 1.0%) compared with subjects with ≥median UBM (2.0% vs. 2.9%). Having <median UBM appears to be associated with a higher incidence of markedly abnormally high glucose values than having ≥median UBM for both treatment groups.

### 7.8.10 Renal Impairment

No specific safety studies have been carried out in subjects with renal impairment. However, the safety of fidaxomicin was examined in subjects included in the Phase 3 clinical studies who had varying degrees of renal insufficiency, based on eCCL and characterized as either mild (51-79 mL/min), moderate (31-50 mL/min), or severe (≤30 mL/min). Most subjects had

mild renal insufficiency, but plasma levels of fidaxomicin and OP-1118 were not seen to be significantly affected by renal status based on eCCL.

No clinically significant treatment differences in the overall incidence of TEAEs were observed within subpopulations with mild, moderate, or severe renal insufficiency, but differences were seen in the overall incidence of treatment-emergent SAEs based on eCCL severity. In both fidaxomicin and vancomycin treated subjects, the highest incidence of treatment-emergent SAEs was seen in subjects with severe renal insufficiency and lowest incidence in subjects with mild renal insufficiency. This is not unexpected, given that subjects with severe renal insufficiency are usually elderly and/or have other underlying medical conditions.

The treatment-emergent SAEs occurring at the highest incidence (≥2.0%) in the fidaxomicin group for subjects with mild renal insufficiency were *C. difficile* colitis (3.9%) and abdominal pain (2.3%). For subjects with moderate renal insufficiency, the treatment-emergent SAEs occurring at the highest incidence were anemia, cardiac failure congestive, megacolon, pneumonia, blood uric acid increased, hyperkalemia, and renal failure (3.2% each). For subjects with severe renal insufficiency, the treatment-emergent SAEs occurring at the highest incidence were intestinal obstruction, pneumonia, sepsis, hyponatremia, and hypophosphatemia (4.1% each), and cardiac failure congestive, myocardial infarction, renal failure, pulmonary edema, and respiratory failure (2.7% each).

### 7.8.11 Disease Severity (ESCMID)

As there are no internationally accepted or validated scoring systems to assess severity of CDI, safety was assessed for subjects with severe and non-severe CDI at baseline, based upon the ESCMID severity categorization [Bauer, 2009b]. This definition is based on the elements of the diagnosis of CDI plus at least one of the following: temperature greater than 38.5°C, leukocyte count of greater than $15 \times 10^9$/L, or creatinine greater than 1.5 mg/dL. No relevant treatment differences were observed in the overall incidence of TEAEs or treatment-emergent SAEs within each subgroup. However, a higher incidence of TEAEs and treatment-emergent SAEs was reported in subjects with severe CDI than non-severe CDI in both treatment groups, as expected, given the more severe underlying disease state.

The treatment-emergent SAEs occurring at the highest incidence (≥2.0%) in the fidaxomicin group of subjects with severe CDI were sepsis (4.2%), pneumonia (3.5%), and cardiac failure congestive, GI hemorrhage, megacolon, *C. difficile* colitis, blood uric acid increased, hyperkalemia, hyponatremia, hypophosphatemia, and renal failure (2.1% each). For fidaxomicin subjects with non-severe CDI, the treatment-emergent SAE occurring at the highest incidence was *C. difficile* colitis (1.2%).

With respect to the incidence of markedly abnormal laboratory values, severe CDI appears to be associated with a higher incidence of markedly abnormally low lymphocyte values and markedly abnormally high glucose values than non-severe disease for both fidaxomicin and vancomycin subjects.

### 7.8.12 Hepatic Toxicity

Although not formally analyzed as a subgroup analysis, TEAEs were examined for subjects with hepatic toxicity (at least 1 toxicity Grade ≥2 for ALT, AST, or bilirubin at baseline) at baseline and without hepatic toxicity. The overall incidence of TEAEs was 64.7% (11/17 subjects) for fidaxomicin-treated subjects and 66.7% (14/21 subjects) for vancomycin-treated subjects with a Grade 2 or higher hepatic toxicity at baseline. These incidences were similar to those in subjects without hepatic toxicity (68.4% [374/547subjects] and 65.5% [368/562 subjects]).

The overall incidence of treatment-emergent SAEs was lower for fidaxomicin-treated subjects (41.2% [7/17 subjects]) than for vancomycin-treated subjects (52.4% [11/21 subjects]) with a Grade 2 or higher hepatic toxicity at baseline. These treatment-emergent SAE incidences were almost 2-fold higher than those in subjects without hepatic toxicity (25.2% [138/547 subjects] and 22.1% [124/562 subjects]).

### 7.8.13 Impact of Concomitant Therapies on Safety

As noted in Section 4.5, drug-drug interaction studies indicated no clinically meaningful interaction with CYP450 substrates or P-gp inhibitors or substrates. However, since subjects in the Phase 3 trials were frequently taking multiple concomitant therapies, the impact on safety was assessed for particular classes of concomitant therapies: specifically, anti-infectives and compounds that are P-gp inhibitors.

The mean duration of exposure to fidaxomicin and to vancomycin was 10.0 and 10.1 days each for subjects who used drugs that are P-gp inhibitors and 10.3 in both treatment groups for subjects who did not use P-gp inhibitors. A higher overall incidence of TEAEs and treatment-emergent SAEs was observed in subjects who used P-gp inhibitors than in subjects who did not for both fidaxomicin and vancomycin subjects. However, fidaxomicin use with P-gp inhibitors did not appear to increase the incidence of TEAEs compared to those seen with vancomycin. The treatment-emergent SAE that occurred at the highest incidence (>2.0%) in the fidaxomicin group of subjects who used P-gp inhibitors was blood uric acid increased (2.1%) compared to 0% in the vancomycin group. The treatment-emergent SAEs that occurred at the highest incidence in fidaxomicin subjects who did not use P-gp inhibitors were pneumonia and *C. difficile* colitis (1.5% each).

The abnormal clinical laboratory parameters reported at the highest incidence in both treatment groups were abnormally low lymphocyte values and abnormally high glucose values in subjects who used P-gp inhibitors during treatment compared with those not using P-gp inhibitors.

## 7.9 Safety Conclusions

In the Phase 3 studies, fidaxomicin and vancomycin showed a similar incidence of TEAEs, treatment-emergent SAEs, laboratory test abnormalities, and changes in vital signs and ECGs. Most of the TEAEs reported during the course of two large Phase 3 trials are compatible with the signs and symptoms of the disease and the most frequent observed

events (diarrhea, nausea, vomiting, infection, pseudomembranous colitis, abdominal pain) are commonly seen in CDI subjects.

However, evaluation of the safety of a medication in acutely ill subjects with a significant degree of comorbidity is complex. Safety assessment in CDI is complicated by the fact that the disease itself can induce events such as chills, GI bleeding episodes, and other symptoms that can add background noise to the TEAE profile. While there have been reports of treatment-emergent SAEs, including some with a fatal outcome, these appear to be consistent with the underlying clinical condition of the individual subjects and do not suggest a role of fidaxomicin, as shown by similar rates for these events in subjects treated with vancomycin.

The potential for fidaxomicin to prolong QTc interval has been carefully examined.
No signal of QT prolongation was identified in clinical or nonclinical studies (hERG or telemetry study in dogs). QTc parameters measured in Phase 3 comparative studies were similar between treatment groups, in terms both of the number of subjects with changes in QTc values meeting threshold levels and the mean and range of QTc interval changes from baseline to EOT. While some subjects in both groups did have QT prolongation recorded as TEAEs, it is considered that any observed QTc prolongation with fidaxomicin or vancomycin is likely to have resulted from fluid and electrolyte disturbance as a result of the diarrhea or to be related to underlying medications.

There is considerable experience with fidaxomicin treatment in subjects aged ≥65 years and no particular safety issues have been identified in this age group.

No dose adjustment is necessary in subjects with impaired renal function or in subjects with hepatic impairment.

Based on the safety data summarized above, the safety profile of fidaxomicin tablets given orally at a dosage of 200 mg q12h for 10 days is excellent, with overall safety in the Phase 3 trials closely resembling that of oral vancomycin.

# 8 RISK MANAGEMENT PLAN

No important or potential safety concerns have been identified for fidaxomicin. Routine pharmacovigilance will be carried out post-approval to provide reassurance of the safety of fidaxomicin and to facilitate the detection of signals suggesting a currently unidentified concern. TEAEs reported to the sponsor will be followed up to obtain full data and data will be regularly reviewed and presented in safety update reports.

# 9 ADDITIONAL PLANNED STUDIES

## 9.1 Pediatric Studies

A pediatric program is planned to ascertain the efficacy and safety of fidaxomicin in children aged from 2 years to 18 years of age. This program will be conducted as two studies as shown in Table 50. An oral suspension formulation for use in children unable to swallow tablets is under development and will be utilized in each study, as appropriate. Study 1 is currently planned to begin enrollment in 2011. The precise design of the program will be finalized after feedback from the FDA.

**Table 50. Planned Pediatric Studies**

| | **Study 1** | **Study 2** |
|---|---|---|
| **Objective** | **Safety and PK Study** | **Safety and Efficacy Study** |
| Ages | 2 years to 18 years | 2 years to 18 years |
| Fidaxomicin dosage | 32 mg/kg/day, in 2 divided doses, up to a maximum of 400 mg/day | |
| Number of patients | 20 patients | 120 patients (2:1 randomization) |
| Comparator drug | None | 40 mg/kg/day vancomycin, in 4 divided doses |
| Primary endpoints | Safety and tolerability<br>PK (plasma and fecal analysis) | Safety and efficacy (cure) |

## 9.2 Surveillance Program

Resistance to fidaxomicin is not expected to emerge rapidly based on *in vitro* testing and the analysis of clinical samples taken at baseline and at the point of failure or recurrence. However, Optimer will initiate a program to monitor the fidaxomicin MICs of clinical *C. difficile* isolates and evaluate any change in the wild type population. This surveillance program will evaluate the susceptibility profiles and genotypes of *C. difficile* isolates gathered and tested at multiple centers across the US. Anaerobic isolation and susceptibility are uncommonly performed by clinical microbiology laboratories, thus the number of sites capable of performing these studies are limited; however, six reference laboratories have been identified across the US to participate in this surveillance program. Approximately 450 clinical isolates per year will be collected and tested, beginning in 2011.

## 9.3 Interventional study

Optimer plans to conduct a post-approval, randomized clinical intervention trial to study the safety and efficacy of fidaxomicin versus vancomycin in CDI patients who have experienced one or more clinical recurrences within the previous three months. For those with two or more recurrences, a separate stratification will be performed. The definitions and endpoints of the Phase 3 trials will be used in the recurrence trial with emphasis on the next recurrence events, which will be followed up at one month and three months after therapy.

## 9.4 *In Vitro* Studies

*In vitro* studies are being performed on sporulation, germination and the inhibition of toxin production in *C. difficile*, including the hypervirulent BI strains and the classical VPI 10463 strain (a known very high-level toxin producer), to determine if fidaxomicin and OP-1118, at sub-MIC concentrations, can inhibit spore formation and toxin production. Studies to examine effect of drug on germination process are in progress.

# 10 SUMMARY

The current treatment options for CDI are limited, and are decreasing rather than expanding due to the medical communities' recommendations to avoid using vancomycin except when strictly necessary, in an effort to avoid the continuing emergence of MRSA, VRSA, and VRE strains [HICPAC Recommendations, 1995; Watanabe, 1997; ASHP position statement, 1998; Werner, 2008]. As a result, metronidazole is being used more commonly, but metronidazole has broad-spectrum activity against many anaerobic bacteria that are the normal residents of the colonic microflora so, although it is able to suppress *C. difficile*, metronidazole also exerts a deleterious effect on the normal flora. This can have detrimental effects and lead to high recurrence rates, with 20 to 50% of subjects who initially respond to metronidazole treatment suffering a clinical recurrence following the cessation of therapy [Kyne, 1999; Kyne, 2001]. Several studies have also shown that, especially in severe cases, metronidazole has fallen behind vancomycin in both acute cure and late relapses [Zar, 2007], with failure rates of 22% to 38% being reported [Kuipers, 2008]. This may be related to an increase in hypervirulent strains of *C. difficile* [Kuijper, 2008] that metronidazole is less active against, but there has also been antimicrobial 'creep' of resistance to metronidazole, with increases in the MIC of *C. difficile* strains isolated from recent clinical cases [Brazier, 2008; Citron, 2009], which can also account for the higher failure rates. The MIC 'creep' may be particularly relevant since metronidazole is nearly completely absorbed from the GI tract and thus fecal concentrations are reported to be unmeasurable in the absence of diarrhea and detectable, but only in the low µg/g range, during active diarrheal disease [Bolton, 1986].

As noted in Section 2.3, there is an urgent medical need for a new treatment that has potent, bactericidal activity against *C. difficile* but has minimal disruptive effects on other bacterial flora, has a low potential for resistance development and a low risk of inducing intestinal colonization with VRE, has a high rate of clinical cure but a low rate of clinical recurrence, and is safe and well-tolerated. The results seen in the clinical development program for fidaxomicin show that it meets all these criteria, with clinical cure rates that are non-inferior to vancomycin, and recurrence rates and global cure rates that are superior to vancomycin. Fidaxomicin also acts locally within the GI tract and has limited systemic absorption, leading to a very good safety profile that is comparable to that of vancomycin.

Due to its narrow spectrum of activity, fidaxomicin also appears to cause less disruption of the gut flora than other antibiotics [Louie, 2009], with the clinical studies demonstrating that fidaxomicin-treated subjects are less likely to develop recurrence, especially within the first two weeks after end of treatment, than those treated with vancomycin. This is possibly due to preservation of the normal flora that reduces overgrowth of *C. difficile* from spores in the bowel, which remain in the GI tract and could become a source of relapse of CDI once the treatment period is completed. Resistance to fidaxomicin is not expected to emerge rapidly based on *in vitro* testing and the analysis of clinical samples taken at baseline and at the point of failure or recurrence. However, Optimer will initiate a program to monitor the fidaxomicin MICs of clinical *C. difficile* isolates and evaluate any change in the wild type population.

Evaluating the safety of each regimen in such an acutely ill population with a significant degree of co-morbid states that are commonly seen in subjects with CDI is difficult. Thus reliance on the similarity in numbers and types of TEAEs between treatment groups is

perhaps the best method for the assessment of the tolerability of therapies directed against CDI. As shown in both the Phase 3 studies, the incidence of TEAEs, treatment-emergent SAEs, drug-related TEAEs, and discontinuations because of an TEAE was very similar in fidaxomicin-treated subjects and vancomycin-treated subjects. This is not unexpected since both compounds are minimally absorbed and so are expected to have limited systemic effects. There is no indication that fidaxomicin induces relevant prolongation of the QTc interval and analysis of GI bleeding TEAEs, leucopenia, and liver function in patients in the fidaxomicin group did not reveal any special concerns when underlying patient conditions and concomitant therapy were taken into consideration. In addition, no dose reductions are needed for the elderly, or in subjects with renal or hepatic impairment, and fidaxomicin has no clinically meaningful impact on the pharmacokinetics of drugs that were substrates for CYP enzymes, P-gp inhibitors or P-gp substrate (digoxin).

Therefore it can be concluded that the benefit/risk profile is positive and that fidaxomicin is ideally placed to become first line treatment for CDI and for reducing the risk of recurrences when used for treatment of initial CDI .

# 11 REFERENCES

Ackermann G, Loffler B, Adler D, et al. In vitro activity of OPT-80 against Clostridium difficile. Antimicrob Agents Chemother 2004;48(6):2280-2282.

Agresti A, Caffo BA. Simple and effective confidence intervals for proportions and difference of proportions result from adding two successes and two failures. The American Statistician. 2000;54:280-288.

Al-Nassir WN, Sethi AK, Li Y, et al. Both oral metronidazole and oral vancomycin promote persistent overgrowth of vancomycin-resistant enterococci during treatment of *Clostridium difficile*-associated disease. Antimicrob Agents Chemother. 2008;52(7):2403-2406.

Ariano RE, Zhanel GG, Harding GK. The role of anion-exchange resins in the treatment of antibiotic-associated pseudomembranous colitis. C Med Assoc J 1990;142(10):1049-1051.

ASHP therapeutic position statement on the preferential use of metronidazole for the treatment of *Clostridium difficile*-associated disease. Am J Health Syst Pharm. 1998;55(13):1407-1411.

Aslam S, Hamill RJ, Musher DM. Treatment of *Clostridium difficile*-associated disease: old therapies and new strategies. Lancet Infect Dis. 2005;5(9):549-57.

Barbut F, Richard A, Hamadi K, et al. Epidemiology of recurrences or reinfections of *Clostridium difficile*-associated diarrhea. J Clin Microbiol. 2000;38(6):2386-8.

Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. N Engl J Med. 2002;346(5):334-339.

Bartlett JG. New drugs for *Clostridium difficile* infection. Clin Infect Dis. 2006;43:428-431.

Bartlett JG. The case for vancomycin as the preferred drug for treatment of *Clostridium difficile* infection. Clin Infect Dis 2008; 46: 1489-92

Bauer MP, Veenendaal D, Verhoef L, Bloembergen P, van Dissel JT, Kuijper EJ. Clinical and microbiological characteristics of community-onset *Clostridium difficile* infection in The Netherlands. Clin Microbiol Infect. 2009a;15(12):1087-92.

Bauer MP, Kuijper EJ, van Dissel JT; European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for *Clostridium difficile* infection (CDI). Clin Microbiol Infect. 2009b;15(12):1067-79.

Beaurepaire C, Smyth D, McKay D. Interferon-γ regulation of intestinal epithelial permeability. J Interferon Cytokine Res. 2009;29(3):133-143.

Blanckaert K, Coignard B, Grandbastien B, et al. Update on *Clostridium difficile* infections. Rev Med Interne. 2008;29(3):209-214.

Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. Gut. 1986;27:1169-1172.

Brazier JS, Raybould R, Patel B, et al. Distribution and antimicrobial susceptibility patterns of *Clostridium difficile* PCR ribotypes in English hospitals, 2007-08. Euro Surveill. 2008;13(41):pii=19000.

Calfee DP. *Clostridium difficile*: a reemerging pathogen. Geriatrics. 2008;63(9):10-14, 21.

Centers for Disease Control and Prevention. Severe *Clostridium difficile*-associated disease in populations previously at low risk--four states, 2005. MMWR Morb Mortal Wkly Rep 2005; 54(47):1201-1205.

Chang TW, Bartlett JG, Gorbach SL, Onderdonk AB. Clindamycin-induced enterocolitis in hamsters as a model of pseudomembranous colitis in patients. Infect Immun. 1978;20(2):526-9.

Citron DM et al. Decreasing in vitro activities of vancomycin, metronidazole, and rifaximin and the REA types in contemporary strains of Clostridium difficile. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 25-28, 2008. Washington, DC.

Citron D, Babakhani F, Goldstein EJC, Nagaro K, Sambol S, Sears P, Shue YK, Gerding DN. Typing and susceptibility of bacterial isolates from the fidaxomicin (OPT-80) phase II study for *C. difficile* infection. Anaerobe. 2009;15:234-236.

Cloud J, Kelly CP. Update on *Clostridium difficile* associated disease. Curr Opin Gastroenterol. 2007;23(1):4-9.

CLSI M11-A7: Methods for Antimicrobial Testing of Anaerobic Bacteria; Approved Standard – Seventh Edition. January 2007.

Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald CL, 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 Disease Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5) [Epub ahead of print].

Credito KL, Appelbaum PC. Activity of OPT-80, a novel macrocycle, compared with those of eight other agents against selected anaerobic species. Antimicrob Agents Chemother. 2004;48(11):4430-4434.

de Lalla F, Nicolin R, Rinaldi E, Scarpellini P, Rigoli R, Manfrin V, Tramarin A. Prospective study of oral teicoplanin versus oral vancomycin for therapy of pseudomembranous colitis and *Clostridium difficile*-associated diarrhea. Antimicrob Agents Chemother. 1992;36(10): 2192-6.

Diehl KH, Hull R, Morton D, et al. A good practice guide to the administration of substances and removal of blood, including routes and volumes. J. Appl. Toxicol. 2001;21:15–23.

Ebright R, inventor; RNA-exit channel: target and method for inhibition of bacterial RNA polymerase. United States patent US 20060127905. Jun 15, 2006.

Fekety R, Silva J, Buggy B, et al. Treatment of antibiotic-associated colitis with vancomycin. J Antimicrob Chemother. 1984;14(Suppl D):97-102.

Fekety R. Guidelines for the diagnosis and management of *Clostridium difficile*-associated diarrhea and colitis. American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 1997;92(5):739-750.

Finegold SM, Molitoris D, Vaisanen ML, et al. *In vitro* activities of OPT-80 and comparator drugs against intestinal bacteria. Antimicrob Agents Chemother. 2004;48(12):4898-4902.

Fowler S. Successful use of feedback to improve antibiotic prescribing and reduce Clostridium difficile infection: a controlled interrupted time series. J. Antimicrob. Chemother. 2007:59(5): 990-995.

Freeman J, Stott J, Baines SD, et al. Surveillance for resistance to metronidazole and vancomycin in genotypically distinct and UK epidemic Clostridium difficile isolates in a large teaching hospital. J Antimicrob Chemother 2005;56(5):988-989.

Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J, Jr. *Clostridium difficile*-associated diarrhea and colitis. Infect Control Hosp Epidemiol 1995; 16(8):459-477.

Gualtieri M, Villain-Guillot P, Latouche J, Leonetti JP, Bastide L. Mutation in the Bacillus subtilis RNA polymerase beta' subunit confers resistance to lipiarmycin. Antimicrob Agents Chemother. 2006;50(1):401-402.

Guerrant RL, Hughes JM, Lima NL, Crane J. Diarrhea in developed and developing countries: magnitude, special settings, and etiologies. Rev Infect Dis. 1990;12(Suppl 1): S41-50.

Hecht DW, Galang MA, Sambol SP, et al. In vitro activities of 15 antimicrobial agents against 110 toxigenic Clostridium difficile clinical isolates collected from 1983 to 2004. Antimicrob Agents Chemother 2007;51(8):2716-2719.

HICPAC Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). Am J Infect Control. 1995;23(2):87-94.

Johnson S, Adelmann A, Clabots CR, Peterson LR, Gerding DN. Recurrences of *Clostridium difficile* diarrhea not caused by the original infecting organism. J Infect Dis 1989;159:340-3.

Karlowsky JA, Laing NM, Zhanel GG. In vitro activity of OPT-80 tested against clinical isolates of toxin-producing *Clostridium difficile*. Antimicrob Agents and Chemother. 2008;52(11):4163-4165.

Kelly CP, Pothoulakis C, LaMont, JT. *Clostridium difficile* colitis. N Engl J Med. 1994;330(4): 257-262.

Kelly CP, LaMont JT. *Clostridium difficile*-more difficult than ever. N Engl J Med. 2008; 359(18):1932-1940.

Kelly CP, LaMont JT. Treatment of antibiotic-associated diarrhea caused by Clostridium difficile. UpToDate Online. 18.1. January 2010.

Killgore G, Thompson A, Johnson S, et al. Comparison of seven techniques for typing international epidemic strains of *Clostridium difficile*: restriction endonuclease analysis, pulsed-field gel electrophoresis, PCR-ribotyping, multilocus sequence typing, multilocus variable-number tandem-repeat analysis, amplified fragment length polymorphism, and surface layer protein A gene sequence typing. J Clin Microbiol. 2008;46(2):431-437.

Kreutzer EW, Milligan FD. Treatment of antibiotic-associated pseudomembranous colitis with cholestyramine resin. Johns Hopkins Med J 1978;143(3):67-72.

Kuijper EJ, Coignard B, Tull P on behalf of the ESCMID Study Group for *Clostridium difficile* (ESGCD), EU Member States and the European Centre for Disease Prevention and Control (ECDC). Emergence of Clostridium difficile-associated disease in North America and Europe. Clin Microbiol Infect. 2006;12(Suppl 6):2-18.

Kuijper EJ, van Dissel JT, Wilcox MH. *Clostridium difficile*: changing epidemiology and new treatment options. Curr Opin Infect Dis. 2007;20:376-383.

Kuijper EJ, Barbut F, Brazier JS, et al. Update of *Clostridium difficile* infection due to PCR ribotype 027 in Europe, 2008. Eurosurveillance. 2008;13(31):1-7.

Kuipers EJ, Surawicz CM. *Clostridium difficile* infection. The Lancet. 2008;371:1486-1488.

Kurabachew M, Lu SH, Krastel P, et al. Lipiarmycin targets RNA polymerase and has good activity against multidrug-resistant strains of *Mycobacterium tuberculosis*. J Antimicrob Chemother. 2008;62(4):713-719.

Kyne L, Merry C, O'Connell B, et al. Factors associated with prolonged symptoms and severe disease due to *Clostridium difficile*. Age Ageing. 1999;28(2):107-113.

Kyne L, Warny M, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhea. Lancet. 2001;357:189-193.

Lanis JM, Barua S, Ballard JD. Variations in TcdB Activity and the Hypervirulence of Emerging Strains of *Clostridium difficile*. PLoS Pathog. 2010;6(8): e1001061.

Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46(1-3):3-26.

Loo VG, Poirier L, Miller MA et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med 2005; 353(23):2442-2449.

Lorenz W, Schmal A, Schult H, et al. Histamine release and hypotensive reactions in dogs by solubilizing agents and fatty acids: Analysis of various components in cremophor El and development of a compound with reduced toxicity. Agents and Actions 1982;12:64-80.

Louie T, Gerson M, Grimard D, et al. Results of a Phase III Trial Comparing Tolevamer, Vancomycin and Metronidazole in Patients with *Clostridium difficile*-Associated Diarrhea (CDAD). Poster 3826, ICAAC 2007.

Louie TJ, Emery J, Krulicki W, Byrne B, Mah M. OPT-80 Eliminates *Clostridium difficile* and is sparing of *Bacteroides* species during treatment of *C. difficile* infection. Antimicrob Agents Chemother. 2009;53(1):261-263.

Maroo S, LaMont JT. Recurrent *Clostridium difficile*. Gastroenterology 2006; 130(4):1311-1316.

McFarland LV, Surawicz CM, Greenberg RN et al., A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease. JAMA 1994;271(24):1913-1918.

McFarland LV. Alternative treatments for *Clostridium difficile* disease: what really works. J Med Microbiol 2005;54:101-111.

McFarland LV. Epidemiology of infectious and iatrogenic nosocomial diarrhea in a cohort of general medicine patients. Am J Infect Control. 1995;23(5):295-305.

Miller M, Gravel D, Mulvey M et al. Hospital-acquired *Clostridium difficile* infection in Canada: patient age and infecting strain type are highly predictive of severe outcome and mortality. Clinical Infectious Diseases 2010;50:194-201.

Missaghi B, Valenti AJ, Owens RC Jr. *Clostridium difficile* infection: a critical overview. Curr Infect Dis Rep. 2008;10(3):165-73.

Monaghan T, Boswell T, Mahida YR. Recent advances in *Clostridium difficile*-associated disease. Gut. 2008;57:850-860.

Musher DM, Aslam S, Logan N et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. Clin Infect Dis 2005; 40(11):1586-1590.

Mylonakis E, Ryan ET, Calderwood SB. *Clostridium difficile*-associated diarrhea: a review. Arch Intern Med. 2001;161(4):525-33.

Nelson RL. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. Cochrane Database of Systematic Reviews. 2007; Issue 3.

Nelson RL. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. Cochrane Database of Systematic Reviews 2008; Issue 4.

Nerandzic MM, Mullane K, Miller M, Babakhani F, Donskey CJ. Acquisition and overgrowth of vancomycin-resistant Enterococci in patients treated with either fidaxomicin or vancomycin for *C. difficile* infection. Presented at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy. 2009.

Peláez T, Alcalá L, Alonso R, et al. Reassessment of *Clostridium difficile* susceptibility to Metronidazole and Vancomycin. Antimicrob Agents Chemother. 2002;46(6):1647–1650.

Pepin J, Alary ME, Valiquette L et al. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. Clin Infect Dis 2005; 40(11):1591-1597.

Pepin J, Valiquette L, Gagnon S, Routhier S, Brazeau I. Outcomes of *Clostridium difficile*-associated disease treated with metronidazole or vancomycin before and after the emergence of NAP1/027. Am J Gastroenterol 2007; 102(12):2781-2788.

Podolsky ML, Lukas VS (Eds). The Care and Feeding of an IACUC. CRC Press, Boca Raton, FL 1999:187-188.

Redelings MD, Sorvillo F, Mascola L. Increase in *Clostridium difficile*-related mortality rates, United States, 1999-2004. Emerg Infect Dis 2007; 13(9):1417-1419.

Rouphael NG, O'Donnell JA, Bhatnagar J et al. *Clostridium difficile*-associated diarrhea: an emerging threat to pregnant women. Am J Obstet Gynecol 2008; 198(6):635-636.

Sears P, Babakhani FK, Citron DM, et al. Typing and susceptibility of Bacteroides isolates from the OPT-80 (PAR-101) Phase 2A study for C. difficile-associated diarrhea. Presented at the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 25-28, 2008. Washington, DC.

Sergio S, Pirali G, White R, Parenti F. Lipiarmycin, a new antibiotic from *Actinoplanes* III. Mechanism of Action. J Antibiotics. 1975;28(7):543-549.

Stabler RA, Valiente E, Dawson LF, et. al. In-depth genetic analysis of *Clostridium difficile* PCR-ribotype 027 strains reveals high genome fluidity including point mutations and inversions. Gut Microbes. 2010;1(4): 269-276.

Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent Clostridium difficile disease: use of high-dose vancomycin combined with Saccharomyces boulardii. Clin Infect Dis 2000;31(4):1012-1017.

Talpaert M, Campagnari F, Clerici L. Lipiarmycin, an antibiotic inhibiting nucleic acid polymerase. Biochem Biophys Res Commun. 1975;63(1):328-334.

Tannock GW, Munro K, Taylor C, et al. A new macrocyclic antibiotic, fidaxomicin (OPT-80), causes less alteration to the bowel microbiota of Clostridium difficile-infected patients than does vancomycin. Microbiology 2010;156(11):3354-9.

Taylor NS, Bartlett JG. Binding of Clostridium difficile cytotoxin and vancomycin by anion exchange resins. J Infect Dis 1980;141(1):92-97.

Teasley DG, Gerding DN, Olson MM, Peterson LR, Gebhard RL, Schwartz MJ, et al. Prospective randomised trial of metronidazole versus vancomycin for Clostridium-difficile-associated diarrhea and colitis. Lancet. 1983;2(8358):1043-1046.

Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet. 2005;366(9491):1079-1084.

Watanabe T, Ohashi K, Matsui K, et al. Comparative studies of the bactericidal, morphological and post-antibiotic effects of arbekacin and vancomycin against methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother. 1997;39(4):471-476.

Weiss K. Toxin-binding treatment for *Clostridium difficile*: a review including reports of studies with tolevamer. Int J Antimicrob Agents. 2009;33(1):4-7.

Wenisch C, Parschalk B, Hasenhündl M, Hirschl M, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. Clin Infect Dis. 1996;22(5):813-8.

Werner G. Emergence and spread of vancomycin resistance among Enterococci in Europe. Eurosurveillance. 2008;13(47):pii=19046.

Westfall PH and Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. Journal of Statistical Planning and Inference. 2001;99:25-40.

Wilcox MH. Cleaning up *Clostridium difficile* infection. Lancet. 1996;348(9030):767-768.

Wistrom J, Norrby SR, Myhre EB, et al. Frequency of antibiotic-associated diarrhea in 2462 antibiotic-treated hospitalized patients: a prospective study. J Antimicrob Chemother. 2001;47(1): 43-50.

Wullt M, Odenholt I. A double-blind randomized controlled trial of fusidic acid and metronidazole for treatment of an initial episode of *Clostridium difficile*-associated diarrhea. J. Antimicrob Chemother. 2004;54(1):211-6.

Yoon SS, Brandt LJ. Treatment of refractory/recurrent *C. difficile*-associated disease by donated stool transplanted via colonoscopy: a case series of 12 Patients. J Clin Gastroenterol. 2010;May 11 [Epub ahead of print]

Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007;45(3):302-7.

Zilberberg MD, Shorr AF, Kollef MH. Increase in adult *Clostridium difficile*-related hospitalizations and case-fatality rate, United States, 2000-2005. Emerg Infect Dis 2008; 14(6):929-931.

Zimmerman MJ, Bak A, Sutherland LR. Treatment of *Clostridium difficile* infection. Aliment Pharmacol Ther. 1997;11:1003-1012.

# APPENDIX: TREATMENT EMERGENT SAES WITH A GI BLEEDING COMPONENT

| Treatment Study Demographics | SAE Term Outcome of SAE Event | Study Day of GI Bleeding Event | Summary |
|---|---|---|---|
| **Fidaxomicin** | | | |
| Fidaxomicin 101.1.C.003 43 years White Female | **Toxic megacolon** Resolved | 14 | History of acute myelogenous leukemia s/p stem cell transplantation followed by CDI. At enrollment, x-ray suggested inflammatory changes of colon. On Day 2, CT confirmed pancolitis and/or toxic megacolon. Study drug was discontinued and subject underwent urgent subtotal colectomy with endoileostomy. Her post-op course was complicated by worsening renal failure requiring dialysis and graft versus host disease (GVHD). On Day 14, her ostomy output increased, with large volumes of **stool (initially with blood, later melanotic**). Desmopressin and later octreotide was used to slow GI bleeding. Required multiple blood and platelet transfusions. |
| Fidaxomicin 101.1.C.003 86 years White Male | **GI hemorrhage** Fatal | 21/29 | History of recent **pre-study GI bleed**, diverticulosis. Admitted with diarrhea with pseudomembranous colitis. Study drug discontinued Day 9 due to treatment failure. **Recurrent GI bleed** on Day 21 treated with blood transfusion; source of bleed not identified despite upper endoscopy and colonoscopy x 2. Co-morbidities included poor oral intake with severe malnutrition, worsening respiratory status, acute renal failure (ARF), urinary tract infection (UTI), atrial fibrillation (AF), recent deep vein thrombosis (DVT) with placement of inferior vena cava filter, a history of bladder cancer, and an intrarenal aortic aneurysm. The subject was discharged to home hospice care on Day 28 with comfort care measures. Death at home Day 29 reportedly due to recurrent GI bleed. |
| Fidaxomicin 101.1.C.003 64years White Male | ***C diff* colitis** Recovered | ~9-20 | History of recent coronary artery bypass graft re-hospitalized for post-op complications of congestive heart failure (CHF), *Staphylococcus epidermidis* infection, ARF and diarrhea. Enrolled in study and sent home with study drug. Returned to emergency room on Day 2 with abdominal pain, ascites and anuria. Computed tomography (CT) revealed severe pancolitis. On Day 8 underwent subtotal colectomy and ileostomy. Post-op course complicated by worsening CHF, chronic obstructive pulmonary disease (COPD), renal insufficiency, pneumothorax s/p central line placement, and DVT treated with heparin and then coumadin. Received blood transfusion for **bleeding from ostomy** prior to discharge on Day 20. |
| Fidaxomicin 101.1.C.003 66 years White Male | **GI hemorrhage** Recovered | 23 | Developed CDI following hospitalization for **pre-study GI bleed**. Co-morbidities include CHF, COPD, diabetes mellitus (DM), hepatic encephalopathy and pancytopenia due to chronic alcohol abuse. CDI cured without recurrence. GI bleed (**hematemesis**) on Day 23 treated with Vitamin K. Endoscopy revealed Barrett's esophagus and vascular abnormality in the pylorus. |

| Treatment Study Demographics | SAE Term Outcome of SAE Event | Study Day of GI Bleeding Event | Summary |
|---|---|---|---|
| Fidaxomicin 101.1.C.003 61years White Female | **GI hemorrhage** Recovered | 11 | S/P colostomy. Received only 4 doses study drug; deemed failure. GI bleeding on Day 11 described as "50mL **blood from ostomy** after turning". On SQ enoxaparin. |
| Fidaxomicin 101.1.C.003 59 years White Female | **GI hemorrhage** Recovered | 3 | History of ischemic bowel s/p resection; admitted for reversal of ileostomy complicated by post-op MI and CDI. Study drug discontinued after only 3 doses; subject switched to metronidazole and vancomycin. On aspirin and clopidogrel. GI bleeding (**hematochezia**) on Day 3, recovered. Endoscopy revealed multiple erosions, healing gastric ulcers, esophagitis and duodenitis. Subject expired Day 28 due to aspiration pneumonia, sepsis and respiratory failure (refused intubation). |
| Fidaxomicin 101.1.C.004 80 years White Female | **Diarrhoea haemorrhagic** Recovered | 23 | Initial CDI cured. Subject admitted on Day 23 with fever, abdominal pain and **bloody diarrhe**a, considered recurrence of CDI. |
| Fidaxomicin 101.1.C.004 38 years White Female | **Diarrhoea haemorrhagic** Recovered | 30 | Initial CDI cured. Received amoxicillin for tooth abscess. Readmitted with **bloody diarrhea** on Day 30, considered recurrence of CDI. |
| **Vancomycin** | | | |
| Vancomycin 101.1.C.003 92 years White Female | **Ischemic colitis** Recovered | 21 | Prior recent hospitalizations for *C perfringe*s bacteremia (presumed gall bladder source), portal vein thrombosis, pancreatitis and nosocomial pneumonia with development of CDI. Enrolled in study and completed dosing with presumed cure. Discharged to nursing home. Found unresponsive on Day 21, was DNR, large **bloody stools** noted. Death on Day 24 attributed to ischemic colitis and MI. |
| Vancomycin 101.1.C.003 68 years Black Female | **Metabolic acidosis, ARF, bacteremia, hyperuricemia** Recovered | 18 | History of ARF, DM, marked weight loss, AF, hypertension, and recent UTI, cerebrovascular accident and GI bleed. Hospitalized for CDI and started on study drug, coumadin, aspirin and metformin. On Day 18, rehospitalized for poor oral intake, diarrhea, abdominal pain, **blood in stool**, and oliguria. Blood cultures positive for gram negative bacilli. Worsening ARF treated with dialysis. Metformin discontinued due to hyperuricemia. Received transfusions of multiple blood products for neck hematoma s/p central line placement. |
| Vancomycin 101.1.C.003 40 years White Male | **Meningitis** Recovered | 2-10 | History of Hodgkin's lymphoma s/p chemotherapy and both autologous and allogeneic stem cell transplants. Admitted with staph bacteremia and developed CDI. During study drug dosing, had **blood in stools** possibly due to internal hemorrhoids. On Day 7, developed a headache, work-up consistent with meningitis, treated with IV acyclovir, ceftriaxone and vancomycin. On Day 17, developed recurrent severe nausea and vomiting with profuse watery diarrhea with negative test for *C diff*, treated with vancomycin. |

| Treatment Study Demographics | SAE Term Outcome of SAE Event | Study Day of GI Bleeding Event | Summary |
|---|---|---|---|
| Vancomycin<br>101.1.C.003<br>68 years<br>White Female | **Large intestine perforation**<br>Resolved with sequelae | 44 | History of inflammatory bowel disease on steroid, COPD and recent UTI. Completed study drug therapy for CDI. Following successful treatment, subject had diarrhea and a repeat positive toxin test, treated with oral vancomycin and probiotics. On Day 31, readmitted with severe lower abdominal pain, CT findings consistent with **toxic megacolon with perforated transverse colon**, managed with total colectomy and blood product transfusions. On Day 39, started on heparin for DVT. **Bloody stool from ostomy and rectum** on Day 44 after re-initiation of oral nutrition. Heparin drip discontinued and Vitamin K administered. Subject recovered. |
| Vancomycin<br>101.1.C.003<br>68 years<br>White Female | **Dyspnea**<br>Ongoing | 9 | History of multiple medical problems including obstructive sleep apnea, coronary artery disease, ↑PT/INR, rheumatoid arthritis treated with steroids, serum chemistry abnormalities and foot abscess with MRSA. Admitted with nausea, vomiting, diarrhea and hypotension, diagnosed with CDI. **Hemoccult positive stools** and low hematocrit noted during study drug dosing. Subject refused further GI work-up. Transfused 2 units blood. On Day 14, bilateral thrombi in thighs noted, treated with inferior vena cava filter and anticoagulants. Readmitted on Day 32 for syncope, paroxysmal supraventricular tachycardia and urosepsis. Died on Day 46 of urosepsis. |
| Vancomycin<br>101.1.C.003<br>41 years<br>Hispanic Male | **Large intestine perforation**<br>Fatal | 6/17 | History of metastatic T-cell lymphoma with recent chemotherapy, GI bleed, upper GI ulcers, hematochezia, hemorrhoids, pneumonia. Developed CDI. On Day 6 of study drug, developed large amount of **red, watery stools** with hemoglobin 7.9 treated with blood transfusions. On Day 17, developed **bright red blood per rectum** with syncopal episode. Esophageogastroduodenoscopy revealed ulceration of stomach and esophagus. On Day 18, experienced acute abdominal pain and underwent emergency colectomy for **perforated transverse colon**. Histopath revealed evidence of lymphomatous involvement of transverse colon and esophageal biopsies. On Day 24, he began receiving comfort care only and expired due complications of perforated transverse colon. |
| Vancomycin<br>101.1.C.003<br>62 years<br>White Male | **GI hemorrhage**<br>Recovered | 17 | History of chronic renal failure, diabetes and peripheral vascular disease s/p recent pop-tib bypass and aspirin/heparin use. CDI cured with recurrence. C**offee-ground emesis** on Day 17 treated with blood transfusion. Endoscopy negative. |
| Vancomycin<br>101.1.C.004<br>85 years<br>White Female | **Pneumonia**<br>**Faeculent vomiting**<br>**Renal failure**<br>Fatal | 5 | History of newly diagnosed myeloma, recently admitted with pneumonia, developed CDI. On Day 5 of study drug dosing, developed worsening respiratory failure and oliguria. On Day 7, faeculent and possibly **blood-stained vomiting**, diarrhea, possible **melena** and abdominal bloating were reported. Subject had a drop in hematocrit and became hypotensive. She expired on Day 7 due to sepsis and multi-organ failure. |

| Treatment Study Demographics | SAE Term Outcome of SAE Event | Study Day of GI Bleeding Event | Summary |
|---|---|---|---|
| Vancomycin<br>101.1.C.004<br>49 years<br>White Male | **Oesophageal varices haemorrhage**<br>Recovered | 11 | History of alcoholic liver disease/cirrhosis, esophageal varices, thrombocytopenia, and hematemesis. CDI cured without recurrence. Recurrent "**hematemesis/melena** secondary to variceal bleeding" on Day 28. Treated with variceal banding and blood transfusion. |
| Vancomycin<br>101.1.C.004<br>82 years<br>White Male | **Hematochezia**<br>Recovered | 5 | History of gastritis and gastroesophageal reflux disease, recent DVT and aspirin use. **Hematochezia** reported on Day 5. CDI treatment failure. |
| Vancomycin<br>101.1.C.004<br>50 years<br>Black Male | **Malnutrition**<br>**Epistaxis**<br>**Renal failure**<br>**Septic shock**<br>Fatal | 27 | History of hepatitis C cirrhosis, esophageal varices, coagulopathy, anemia, ARF. Subject was enrolled due to a positive C diff rapid test but then discontinued from the study on Day 4 when two repeat C diff toxin assays came back negative. The subject was hospitalized on Day 28 for malnutrition; insertion of a Dobhoff tube resulted in epistaxis. Attempts to administer medications rectally resulted in **rectal bleeding**. A positive *C diff* test was obtained, and he was treated with vancomycin. Ischemic bowel was suspected. He was made a Do-Not-Resuscitate (DNR) and expired on Day 32 due to septic shock and cardiopulmonary arrest. |