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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
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Review Completion Date	April 9, 2011
Established Name	Fidaxomicin
(Proposed) Trade Name	Dificid
Therapeutic Class	Macrolide Antibacterial
Applicant	Optimer Pharmaceuticals, Inc.
Formulation	Tablet
Dosing Regimen	200 mg every 12 hours
Indication	Treatment of <i>Clostridium difficile</i> associated diarrhea and prevention of recurrences
Intended Population	Adult

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ABBREVIATIONS

BA	Bioavailability
CDAD	<i>Clostridium difficile</i> associated diarrhea
CDI	<i>Clostridium difficile</i> infection
EOT	End of treatment
GI	Gastrointestinal
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
MIC	Minimal Inhibitory Concentration
PAE	Post-antibiotic effect
PK	Pharmacokinetic
SOC	System organ class allocation
TEAE	Treatment emergent adverse event
UBMs	Unformed bowel movements

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on clinical efficacy and safety data submitted by the Applicant from two randomized, double blind, active controlled clinical trials, there is adequate evidence to recommend the approval of fidaxomicin as a safe and efficacious treatment for *Clostridium difficile* associated diarrhea (CDAD).

1.2 Risk Benefit Assessment

In two phase 3 trials fidaxomicin has demonstrated noninferiority to vancomycin for the primary endpoint of clinical cure and superiority to vancomycin for the secondary endpoint of global cure. Global cure was defined as the number of subjects in each treatment group who had been evaluated as cured and who did not have a recurrence up to 21 days after the last dose of study drug. However, for patients with CDAD due to the BI/NAP1/027 strain, fidaxomicin did not demonstrate superiority in global cure owing to an increase in recurrence rates in fidaxomicin patients infected with this strain.

The non-inferiority was concluded based on the prespecified noninferiority (NI) margin (10%). In each trial the lower bound of the 95% confidence interval (CI) around the difference in clinical response rates (fidaxomicin - comparator) was greater than -10. Superiority in global cure rates was demonstrated by the lower limit of the CI greater than 0 in both phase 3 trials.

With regard to safety, fidaxomicin appears to be safe and well tolerated. There were no differences in the incidence of deaths (6.4% and 6.5%) and treatment-emergent serious adverse events (25.7% and in 23.2%) in the fidaxomicin and vancomycin arms. There was a numerical imbalance in adverse events related to gastrointestinal hemorrhage (3.5% vs. 1.7%) and leukopenia (4.1% vs. 1.7%) between fidaxomicin and vancomycin groups. However, the overall number of events was small and no causal relationship between fidaxomicin and these events could be established. Postmarketing monitoring of adverse events may provide additional information on the safety profile of fidaxomicin.

In summary, the data submitted by the Applicant demonstrate the overall similar safety profile of fidaxomicin and the comparator, vancomycin and provide evidence for approval of fidaxomicin for the treatment of CDAD.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Two pediatric studies will be requested:

Study 1 will be safety and PK study in children aged 2 to 18 years. A total 30 patients evenly divided in three age groups: 2-5, 6-11, and 12-18 years of age will be enrolled in the study. The study will provide PK analysis and Descriptive Statistics.

Study 2 will be a safety and efficacy study. The applicant proposed (b) (4) (b) (4) the division proposes a study with sufficient power to meet an NI margin of 15%

Of note, the final design of the studies has not been agreed upon by the time of the completion of this review.

In addition, a study to monitor clinical isolates of *C. difficile* for the development of higher minimal inhibitory concentrations (MIC) was recommended.

During fidaxomicin advisory committee the Applicant indicated that a study of efficacy of fidaxomicin in patients with multiple previous CDAD recurrences had been planned. This study should also be considered for inclusion as a postmarketing commitment.

2 Introduction and Regulatory Background

2.1 Product Information

Fidaxomicin (also known as OPT-80, PAR-101 and tiacumicin B) is a macrolide antibiotic. Fidaxomicin is characterized by an 18-membered macrocyclic ester structure, has a molecular weight of 1,058 and a chemical formula of $C_{52}H_{74}C_{12}O_{18}$. The mechanism of action of fidaxomicin is inhibition of bacterial ribonucleic acid (RNA) polymerase.

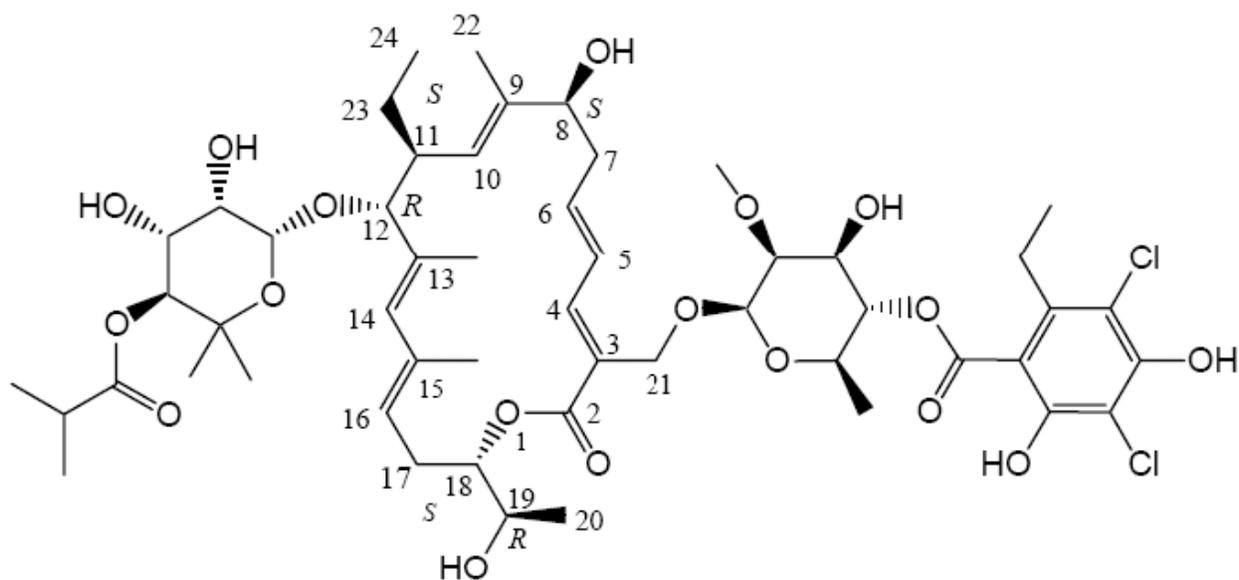


Figure 1 Structure of fidaxomicin

The drug has not been marketed anywhere in the world.

- Generic name: fidaxomicin
- Proposed Trade Name: Dificid
- Chemical class: New Molecular Entity
- Pharmacologic class: Macrolide Antibacterial
- Dosing regimen: 200 mg tablet twice daily for 10 days with or without food

2.2 Tables of Currently Available Treatments for Proposed Indications

For the indication of *Clostridium difficile* infection, vancomycin is the only medication approved by the FDA.

2.3 Availability of Proposed Active Ingredient in the United States

Fidaxomicin is a new molecular entity (NME) that is only available as an investigational agent.

2.4 Important Safety Issues with Consideration to Related Drugs

Fidaxomicin is a macrolide antibacterial. Considering its minimal absorption, fidaxomicin may not have the same spectrum of side effects that are characteristic of other macrolides. However, the following macrolide-class adverse reactions may be observed with fidaxomicin:

- Gastrointestinal disorders including nausea, vomiting, melena, diarrhea, and anorexia
- Hepatobiliary disorders

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- Drug-drug interactions including interactions with P-glycoprotein inhibitors and inhibition of cytochrome P450 enzymes

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The presubmission regulatory history and milestones related to the current NDA submission are summarized as follows:

- August 2003 IND 64,435 was submitted by Optimer Pharmaceutical, Inc. to develop OPT-80 for the treatment of *Clostridium Difficile* associated diarrhea (CDAD).
- In October 2003 Fidaxomicin was granted fast track designation for treatment of *Clostridium difficile*- Associated Diarrhea (CDAD) by the Division of Anti-Infective Drug Products. The designation was based on fidaxomicin's potential to avoid the side effects of currently accepted treatments and/or prevent relapses of CDAD.
- May 2006 The first Phase 3 study (101.1.C.003) initiated
- April 2007 The second Phase 3 study (101.1.C.004) initiated
- July 2007 The End of Phase II Meeting held
- August 2008 Enrollment in Study 101.1.C.003 completed
- September 2009 The results from the first Phase 3 study were discussed; Global Cure changed from exploratory to secondary endpoint for the ongoing Phase 3 study (101.1.C.004).
- December 2009 Enrollment in Study 101.1.C.004 completed
- July 2010 An agreement on 10% non-inferiority margin reached; there was concurrence that a thorough QTc study is not practical or necessary
- Nov 30, 2010 The final portion of the rolling submission for NDA 201,699 was received

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was based on the electronic common technical document (eCTD) format and overall well organized. The submission was easy to navigate and needed information was easy to find.

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A total of 118 case reports form representing a 10% random sample of phase 3 trials population was reviewed. The review prompted additional information requests, including, among others:

- Case reports of subjects identified as non-recurrent despite administration of medications active against CDAD disallowed by the protocol. The list of 62 subjects with additional CRFs was provided by the applicant in response to the request.
- Clarifications of the classifications of outcomes for 30 subjects who died during the study but were declared globally cured and for 67 subjects assessed as globally cured with their recurrence assessment day before study day 36 and less than 25 days after the last treatment day.
- Additional case report forms, case narratives, and medical records for subjects with adverse events related to gastrointestinal hemorrhage.
- Clarifications regarding the data collection of subject's daily stool frequency, timing or volume and handling of missing data

The applicant provided the responses in a timely fashion without delaying the review.

3.2 Compliance with Good Clinical Practices

The studies protocols and amendments were evaluated and approved by local and/or central Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs). The studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that were consistent with Good Clinical Practice (GCP), International Conference on Harmonization (ICH) guidelines, and applicable regulatory requirements. Subjects provided written consent to participate in the study during the pre-randomization phase of the study after having been informed of the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

Site inspections by the Division of Scientific Investigations (DSI) were performed for 1 domestic and 3 foreign clinical sites. DSI also conducted an inspection of the applicant's clinical monitoring facility. Based on preliminary findings of these inspections, there were no significant issues identified that would affect the safety or efficacy findings of this review.

3.3 Financial Disclosures

The applicant certified that there were no financial arrangements with clinical investigators that could affect the outcome of the study as defined in 21 CFR 54.2 (a) and that the clinical investigators did not disclose any proprietary interest of significant equity in the applicant as defined in 21 CFR 54.2 (b). The applicant also certified that no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Fidaxomicin is a purified fermentation product produced by the organism *Dactylosporangium aurantiacum*. (b) (4)

Fidaxomicin tablets are white to off-white film-coated, (b) (4) tablets; each tablet is debossed with “FDX” on one side and “200” on the other side.

The submission has provided sufficient information to assure the strength, purity, stability and quality of the drug product. For more details the reader is referred to Chemistry Manufacturing and Controls review for fidaxomicin.

4.2 Clinical Microbiology

C. difficile strain isolation was performed for all subjects in the Phase 3 trials at baseline, at failure for primary failures, and at recurrence for subjects with recurrences. These strains were tested for susceptibility to fidaxomicin, vancomycin, metronidazole, and rifaximin, and typed using the restriction endonuclease analysis (REA) method. This typing method classifies the strains into the major epidemic groups (e.g., REA groups, BI, J, K, etc.) or alternatively, not belonging to one of the major epidemic groups, in which case the strain was classified as “non-specified REA group”.

In both Phase 3 trials, the MIC₉₀ of fidaxomicin for most *C. difficile* strain isolates ranged from 0.125 to 0.25 mcg/mL. Higher fidaxomicin MICs were observed for BI strain isolates (MIC₉₀=0.5, range 0.015-1.0). An MIC of 1 µg/mL was the highest MIC observed at baseline. BI isolates had higher MICs for all antibiotics tested.

The main metabolite of fidaxomicin, OP-1118, has an MIC₉₀ of 8 µg/mL, 32-fold higher than that of the parent. No differences were seen in susceptibility from different geographic locations. *In vitro* data demonstrated that in the presence of fecal material, MIC values of fidaxomicin and OP-1118 increased by 8-fold and 4-fold, respectively. The increased fidaxomicin and OP-1118 MIC values were attributed to likely fecal binding of the drug.

Fecal concentrations of fidaxomicin have been shown to be more than 5000 times the MIC of *C. difficile* (see Table 1). Average fidaxomicin fecal concentrations were in excess of 1000 µg/g. Metabolite (OP-1118) concentrations were approximately half that of the parent compound. In study 101.1.C.003 mean fidaxomicin fecal concentrations in clinical failures were to some extent lower when compared with clinical cures. There

were no differences in fecal concentrations between cures and failures in study 101.1.C.004.

Table 1 Mean (Range) Fidaxomicin and OP-1118 Fecal Concentrations (mcg/g) in Phase 3 Studies at the EOT visit

		Study 101.1.C.003		Study 101.1.C.004	
Outcome	Statistic	Fidaxomicin	OP-1118	Fidaxomicin	OP-1118
Cure	n > LLOQ ¹	97	95	72	72
	Mean	1260.0	835.8	1584.0	860.4
	Range	(31.7, 4640.0)	(63.4, 4170.0)	(182.0, 4790.0)	(131.0, 2440.0)
Failure	n > LLOQ	5	4	5	4
	Mean	548.1	178.5	1925.0	633.6
	Range	(43.0, 1530.0)	(95.5, 328.0)	(5.0, 7630.0)	(99.3, 1720.0)
Recurrence	n > LLOQ	14	14	7	7
	Mean	1034.1	498.6	1099.7	744.4
	Range	(102.0, 1990.0)	(63.4, 1350.0)	(305.0, 2550.0)	(131.0, 2290.0)

Adapted from 101.1.C.003 and 101.1.C.004 study reports, table 32

¹LLOQ = lower limit of quantification

There was one subject in the fidaxomicin arm of study 101.1.C.004 (subject 185001), enrolled with a strain having a fidaxomicin MIC of 0.06 mcg/mL. The subject was cured but culture-positive at the end of therapy with the same strain with the same fidaxomicin MIC at the end of therapy as at the start. The subject's CDAD recurred 6 days after the last dose of study drug, and the strain isolated at that time had an MIC of 16 mcg/mL.

Possible explanations include the development of reduced susceptibility to fidaxomicin during the study versus re-infection with a strain having an innately lower susceptibility to fidaxomicin. 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. Similar mutation was identified at Optimer in a spontaneous laboratory-derived *C. difficile* mutant displaying decreased susceptibility to fidaxomicin.

The post-antibiotic effect (PAE) of fidaxomicin was estimated at approximately 10 hours for two laboratory strains and 5.5 hours for a clinical isolate following treatment at 4 times the MIC, with the PAE of OP-1118 being approximately 3 hours. The PAE for vancomycin was less than 1 hour. Fidaxomicin remained detectable in the feces for up to 5 days.

Fidaxomicin is active against some Gram-positive anaerobes, including *Peptostreptococcus* species and non-difficile clostridia. MIC for *Enterococcus* species ranged from 2 to 16 mcg/mL. Fidaxomicin is reported to have virtually no activity against Gram-negative organisms, with MIC₅₀ values universally above 100 mcg/mL. Fidaxomicin has no activity against yeasts.

Medical Reviewer comments: There is a notable variability in fecal concentrations of fidaxomicin and its metabolite. Of note, in vivo baseline fidaxomicin MIC was up to 1 mcg/mL and fidaxomicin MIC was shown to increase 4-fold in the presence of fecal material. It is unclear whether the variability of fidaxomicin concentrations may have contributed to suboptimal clinical response in some cases. Overall, the values of fecal concentrations in clinical cures and failures overlapped and the number of failed subjects with measured fecal concentrations was small.

Ffidaxomicin remained detectable in the feces for up to 5 days. It is conceivable that the exposure to sub-therapeutic fidaxomicin concentrations may contribute to the development of resistance.

4.3 Preclinical Pharmacology/Toxicology

The safety of fidaxomicin has been evaluated in general toxicology (up to 3 months repeated dosing in the dog), genotoxicity and reproductive toxicity studies. No fidaxomicin-related toxicities were found at fidaxomicin plasma or fecal exposure levels considerably higher than plasma concentrations observed in humans at the therapeutic dose. Additionally, No-Observed-Adverse-Effect-Levels (NOAEL) were achieved in the definitive toxicology studies at fidaxomicin exposure levels which are at least 100-fold (dog 3-month toxicity) or 30-fold (rat and rabbit reproductive toxicity) above the human plasma concentrations at the therapeutic dose.

One month oral gavage studies in rats and monkeys showed minimal toxicities at the maximum feasible dose of 90 mg/kg. Intravenous studies in rats for 14 days with 3 different vehicles were conducted. No fidaxomicin-related toxicities were noted at the maximum feasible doses (<4 mg/kg as an i.v. bolus). A 3 month oral capsule study in the dog showed no toxicity at the maximum feasible dose of approximately 1 g/kg/day.

Cardiologic effects were minimal as tested in the hERG assay, telemeterized dogs (single 1 mg/kg intravenous dose), and in oral dog and monkey toxicology studies. No other respiratory, CNS or renal toxicities were identified in the safety pharmacology or general toxicology studies.

Segment I and II reproductive toxicity studies were conducted in rats and rabbits. Fidaxomicin had no effects on fertility or development through implantation in the rat at intravenous doses up to 6.3 mg/kg. In the rat by the intravenous route in 1% solutol HS15, when administered during the period of organogenesis, fidaxomicin had no effect on maternal or fetal parameters at the highest dose tested, 12.6 mg/kg. In the rabbit, the highest dose tested, 7.0 mg/kg, was a no observed adverse effect level (NOAEL) for both dams and offspring.

Fidaxomicin and its main metabolite, OP-1118, were negative for genotoxicity in the Ames bacterial assay. In the chromosomal aberration assay, fidaxomicin was positive,

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while OP-11118 was negative. Fidaxomicin was negative in the rat micronucleus assay.

Medical Reviewer comments: the fidaxomicin animal toxicology program appears to be adequate and did not raise any specific concerns with regard to fidaxomicin safety, including reproductive safety.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Fidaxomicin is bactericidal and acts via inhibition of RNA synthesis by bacterial RNA polymerase through inhibition of transcriptional initiation. 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.

4.4.2 Pharmacodynamics

Fidaxomicin exhibits minimal absorption and directs its activity against bacteria locally within the gastrointestinal tract. Microbiology data are addressed in section 4.2.

4.4.3 Pharmacokinetics

Absorption: Fidaxomicin is minimally absorbed from the gastrointestinal tract due to poor permeability and poor solubility. Plasma concentrations of fidaxomicin were observed at 15 minutes post-dose across the range of doses studied and were detectable up to 24 hours post-dose. In healthy volunteers after a 200-mg dose the mean C_{max} was 9.88 ng/mL. Systemic exposure of metabolite OP-1118 was approximately 2 times that of the parent compound.

In Phase 3 patients treated with fidaxomicin 200 mg PO every 12 hours there was a trend towards higher levels (2 to 6-fold for fidaxomicin and metabolite OP-1118) than those observed in healthy subjects. No evidence of notable accumulation of fidaxomicin was observed, based on the similarity between the Day 1 and Day 10 plasma concentrations across both Phase 3 studies.

Fidaxomicin was administered with a high-fat meal and under fasting conditions. The C_{max} of fidaxomicin and OP-1118 were decreased by 21.5% and 33.4%, respectively, with the high fat meal. AUC_{0-t} remained unchanged. This decrease in C_{max} is not clinically significant, and thus, fidaxomicin may be administered with or without food.

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Distribution: Fidaxomicin is mainly confined to the GI tract following PO administration.

Metabolism: The main route of fidaxomicin metabolism is conversion to the primary and active metabolite OP-1118 by hydrolysis of the isobutyl ester. OP-1118 possesses antibacterial activity that is weaker than the parent compound; its MIC₉₀ against *C. difficile* is 32-fold higher than that of fidaxomicin.

In addition, fidaxomicin has been shown to non-enzymatically isomerize to Tiacumicin C and Tiacumicin F in vitro. 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. CYP enzymes do not appear to play a significant role in the metabolism of fidaxomicin or formation of OP-1118.

Excretion: Fidaxomicin is mainly excreted in the feces. Following single doses of 200 and 300 mg in healthy adults (n=11), approximately 26.4% of the dose was recovered in stool as fidaxomicin and 66.2% as OP-1118. Concentrations of fidaxomicin remained detectable in the feces for up to 5 days. Total fecal recovery of fidaxomicin in a healthy volunteer single dose study (OPT-80 1A SD) was over 92%.

Intrinsic Factors

Based on the applicant's analysis of Phase 3 patients, age (≥ 65 years versus < 65 years), gender (male versus female), and renal impairment (creatinine clearance of 51-79 mL/min, 31-50 mL/min, and ≤ 30 mL/min) did not significantly impact plasma concentrations of fidaxomicin and OP-1118.

PK data from 12 phase 3 subjects with hepatic impairment obtained on Day 1 and Day 10, 3-5 hours post dose, show mean fidaxomicin and OP-1118 plasma concentrations 1.3 to 2.5 times higher than those observed in subjects with liver function test results of toxicity Grade 1 or lower. Hepatic impairment was defined as at least at least one toxicity Grade ≥ 2 for ALT, AST, or bilirubin at baseline. The observed increase in plasma concentrations was still in the low ng/mL range and appears not to be clinically meaningful. No dosage adjustment is necessary in patients with hepatic impairment.

5 Sources of Clinical Data

The safety and efficacy of fidaxomicin has been evaluated in three Phase 1 studies in healthy subjects (Study OPT-80 1A-SD - a single dose, dose escalation study; Study OPT-80 1B-MD - a multiple dose, dose escalation study; Study OPT-80-005 - a food effect study), a Phase 2A dose-finding study conducted in subjects with CDAD (Study OPT-80 Phase 2A), and two Phase 3 studies conducted in subjects with CDAD (Study 101.1.C.003 [OPT-80-003] and Study 101.1.C.004 [OPT-80-004]) (Table 2).

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An additional 3 clinical studies (OPT-80-007, OPT-80-008, and OPT-80-009) were conducted to evaluate the drug-drug interaction effects of fidaxomicin; however, per agreement with the Division (b) (4) these studies were excluded from this ISS.

Table 2 Tables of Studies/Clinical Trials

Type of Study	Study Identifier Study Dates	Objectives of the study	Study design and type of control	Test product; Dose regimen; Route of administration	No of subjects treated	Diagnosis	Duration of treatment
BA and PK	OPT-80-005 08/07/09-09/21/09	To investigate the BA of fidaxomicin when administered with or without a high-fat meal. Secondary objectives were to analyze the levels of fidaxomicin and its major metabolite (OP-1118) in plasma, urine and feces and to further investigate the PK of a single 200mg dose of fidaxomicin in 6 subjects	In first 6 subjects: a single-dose, 1-period study In remaining subjects, a randomized, single-dose, 2-period, 2-way crossover study No control	Fidaxomicin 200-mg tablets; 200 mg or 400 mg; oral	34	Healthy subjects	Single dose
PK and Safety	OPT-80 1A-SD 09/30/03-11/12/03	To determine the safety, tolerability, and PK of fidaxomicin following a single oral dose	Single dose, double-blind, randomized, placebo-controlled, dose escalation study	Fidaxomicin capsules; 100 mg 200 mg 300 mg 450 mg	16: 12 fidaxomicin – 4 in each dose group, 4 placebo	Healthy subjects	Single dose
PK and Safety	OPT-80 1B-MD 04/29/04-06/21/04	To determine the safety, tolerability, and PK of fidaxomicin following administration of a series of oral doses	Multiple dose, double-blind, randomized, placebo-controlled, dose escalation study	Fidaxomicin Capsules: 150 mg 300 mg 450 mg	24: 18 fidaxomicin – 6 per dose group; 6 placebo	Healthy subjects	10 days
PK and Safety	OPT-80-007 06/01/10-06/16/10	To examine the effect of a single dose of cyclosporine on the single dose PK of fidaxomicin and to compare the safety and tolerability of a single dose of fidaxomicin in the presence of a single dose of cyclosporine	Open-label, two-period, randomized crossover study No control	Fidaxomicin 200 mg tablets; 200 mg; Cyclosporine 100 mg capsules; 200 mg;	14	Healthy subjects	Fidaxomicin: 11 days Digoxin: One dose
PK and Safety	OPT-80-008 05/26/10-	To examine the effect on the single dose PK of digoxin in the presence of steady-state fidaxomicin and to compare the safety and tolerability	Open-label, mono-sequence crossover study	Fidaxomicin 200 mg tablets; 200 mg q12h Digoxin 0.25 mg	14	Healthy subjects	Fidaxomicin: 11 days Digoxin: One

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	07/01/10	of steady-state fidaxomicin with a single-dose of digoxin	No control	tablet; 0.5 mg			dose
PK and Safety	OPT-80-009 5/24/10-07/16/10	To examine the effect of steady-state fidaxomicin on the single-dose PK of a cocktail of 3 drugs, warfarin, omeprazole, and midazolam; and to compare the safety and tolerability of steady-state fidaxomicin alone and with warfarin, omeprazole, and midazolam	Open-label, mono sequence crossover study No control	Fidaxomicin 200 mg q12h; Warfarin 10 mg tablet; Omeprazole 20 mg tablet; Midazolam syrup; 5 mg/l	24	Healthy subjects	Fidaxomicin 10 days; Other drugs: One dose
Efficacy and Safety	OPT-80 Phase 2A 11/26/04-07/25/05	To investigate the safety, conduct a clinical evaluation, and establish an effective dose of fidaxomicin in subjects with mild to moderate CDAD	Open-label, randomized, dose ranging study No control	Fidaxomicin 50 mg capsules; 50 mg q12h, 100 mg q12h, 200 mg q12h	48	Patients with CDAD	10 days
Efficacy and Safety	101.1.C.003 05/09/06-08/21/08	To investigate the safety and efficacy of fidaxomicin versus vancomycin in subjects with CDAD. Cure rates at end of therapy (primary outcome) and recurrence rates (secondary outcome) were compared	Randomized double-blind, comparative study versus vancomycin	Fidaxomicin 200 mg over-encapsulated tablets; 200 mg q12h Vancomycin 125 mg over-encapsulated capsules; 125 mg q6h	623: 323 vancomycin 300 fidaxomicin	Patients with CDAD	10 days
Efficacy and Safety	101.1.C.004 4/19/07-12/11/09	To investigate the safety and efficacy of fidaxomicin versus vancomycin in subjects with CDAD. Cure rates at end of therapy (primary outcome) and recurrence and global cure rates (secondary outcomes) were compared	Randomized double-blind, comparative study versus vancomycin	Fidaxomicin 200 mg over-encapsulated tablets; 200 mg q12h; oral Vancomycin 125 mg over-encapsulated capsules; 125 mg q6h; oral	524: 260 vancomycin 264 fidaxomicin	Patients with CDAD	10 days

BA = bioavailability; CDI = Clostridium difficile Infection; PK = pharmacokinetic

5.2 Review Strategy

The efficacy and safety assessment of fidaxomicin will be mostly based on the results of two Phase 3 clinical trials. The review will discuss the results of individual trials as well as information from integrated summary of efficacy and safety when deemed appropriate. The efficacy and safety review was completed by Dmitri Iarikov, MD, PhD. Statistical analyses for efficacy were conducted by Rima Izem, Ph.D.

5.3 Discussion of Individual Studies/Clinical Trials

Both Phase 3 trials were similar in design: randomized, double-blind, comparative studies using vancomycin as the comparator. The studies used similar inclusion criteria and efficacy endpoint definition. Study 101.1.C.004 included subjects from European countries in addition to US and Canadian subjects, while study 101.1.C.003 included only US and Canadian subjects.

6 Review of Efficacy

Efficacy Summary

The FDA review results confirm the applicant's conclusions that in both phase 3 trials fidaxomicin demonstrates noninferiority to vancomycin for the primary endpoint of clinical cure and superiority to vancomycin for the secondary endpoint of global cure. Global cure was defined as the number of subjects in each treatment group who had been evaluated as cured and who did not have a recurrence up to 21 days after the last dose of study drug. However, for BI/NAP1/027 strain, fidaxomicin did not demonstrate superiority in global cure when compared with vancomycin.

Clinical cure rates in study 101.1.C.003 were 88% and 84% in the fidaxomicin and vancomycin groups respectively, with 95% CI of 4.2 (-1.4, 9.7). In study 101.1.C.004 clinical cure rates were 86% and 85% in the fidaxomicin and vancomycin groups respectively with 95% CI of 0.2(-5.9, 6.4). The confidence interval reflects the difference between cure rates in the fidaxomicin and vancomycin arms.

The analysis of global cure rates demonstrated superiority of fidaxomicin. The global cure rates for the fidaxomicin and vancomycin treatment arms were 71% and 57%, respectively with 95% CI of 13.1% (95% CI 5.0% - 21.2%) in study 101.1.C.003 and 72% and 59% with 95% CI of 13.3% (95% CI 4.5%-22.0%) in study 101.1.C.004.

For the virulent BI strain, the fidaxomicin arm did not demonstrate superiority in global cure when compared with vancomycin. The 95% CI include 0 in both phase 3 trials and global cure rates for BI strain in the pooled analysis was 61% and 58% in the fidaxomicin and vancomycin groups respectively with 95% CI of 2.5% (-8.8%, 13.8%). It

appears that higher recurrence rates among fidaxomicin patients infected with the BI strain are responsible for this result.

6.1 Indication

Fidaxomicin is proposed for the treatment of *Clostridium difficile* associated diarrhea (CDAD).

6.1.1 Methods

Two randomized, double blind, identically designed phase 3 trials were conducted. Subjects with >3 unformed stools positive for either *C. difficile* toxin A or B, or both, were stratified for enrollment based upon whether they had a single prior episode of CDAD or no previous CDAD occurrence within the last 3 months. Subjects were randomized to receive either fidaxomicin or vancomycin for 10 days. Fidaxomicin subjects received one 200-mg capsules 2 times daily (BID) with intermittent matching placebo doses. Vancomycin subjects received one 125-mg capsule QID.

The methodology of the trials is presented below.

Study Objectives: The objective of this study is to show that a 10-day course of fidaxomicin 200 mg PO Q 12h is not inferior at the End of Therapy to a 10-day course of vancomycin 125 mg PO q6h for the treatment of CDAD.

Inclusion Criteria

- 1) Male or female inpatients or outpatients, who were 16 years of age or older and who had *C. difficile* infection as defined by:
 - a) Diarrhea defined as a change in bowel habits with >3 unformed bowel movements (UBMs); or >200 mL of unformed stool (for subjects having rectal collection devices) in the 24 hours before randomization
 - b) Presence of either toxin A or B of *C. difficile* in the stool within 48 hours of randomization for metronidazole failures (see inclusion criterion 5), or within 96 hours of randomization for subjects with ≤24 hours pretreatment of CDAD. Note that the age criterion was different for German sites, where the minimum age for inclusion was 18.
- 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.
- 3) All subjects were required to sign an Informed Consent Form.

- 4) Opiates were permitted as needed (PRN) 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 who continued to meet the definition of diarrhea without any significant clinical improvement and remained toxin positive could be enrolled in the study.

Exclusion Criteria

Individuals who met any of the following criteria were excluded from the study:

- 1) Life-threatening or fulminant *C. difficile* infection (white blood cell [WBC] count $>30 \times 10^9/L$, temperature $>40^\circ C$ (Celsius), 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 determined there was a clinical imperative to begin treatment before receiving laboratory results for stool toxin, up to 4 doses, but no more than 24 hours of treatment with metronidazole and/or vancomycin were allowed. While pretreated subjects could be enrolled (as long as they had received no more than 24 hours of previous therapy), it was preferred that subjects not have received prior CDAD treatment during the current admission.
- 7) The anticipated need to continue other antibacterials 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 drugs 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 CDAD within the past 3 months; subjects presenting with the first recurrence within 3 months could be enrolled
- 13) Subjects the investigator believed were inappropriate for the trial, e.g., subjects with known hypersensitivity to vancomycin

Medical Reviewer comments: The selection of the comparator and proposed dosing and duration of treatment are consistent with current recommendations for treatment of CDAD and with the vancomycin label. Inclusion and exclusion criteria appear to be appropriate.

Time and Events Schedule

- Day 1: Once randomized, day 1 evaluation included physical examination, ECG, clinical laboratory tests, PK blood samples and stool samples (Appendix 1).
- Days 2-9: subjects were interviewed daily up to EOT visit (± 2 days). These interviews may have been conducted by telephone.
- Days 10-11: EOT visit. Subjects could take greater than 11 days of study drug if they missed doses. The most tablets that could have been received by any subject were 11 days' worth.
- Days 12-31: Subjects were contacted 2 to 4 days after the last dose of study drug to determine clinical response and then weekly thereafter (Day 17 ± 1 day, Day 24 ± 1 day, Day 31 ± 1 day) until recurrence or post-study visit.
- Days 36-40: Post-study visit
- Early termination and unscheduled visits for recurrences were conducted as necessary

Medical Reviewer comments: Time of assessments and duration of follow-up seem to be reasonable. The majority of recurrences are expected to occur during the first two weeks after completion of CDAD treatment. It has to be kept in mind, however, that a 25-day follow-up period may not capture all recurrences. Finally, as will be discussed later, the protocol allowed a conclusion of non-recurrence for subjects who did not have diarrhea at study day 31 assessment, thus effectively shortening follow-up to 20-21 days after the last dose of study drug.

Analysis Populations

- The enrolled population was the group of subjects who signed the Informed Consent Form
- The safety population was the group of subjects who received at least 1 dose of study drug and had at least 1 safety assessment after dosing
- The mITT population for cure was the group of subjects with CDAD as defined in inclusion criteria and who received at least 1 dose of study medication.
- The mITT population for recurrence was the group of subjects in the mITT population for Cure who were classified as cured at the end of therapy.
- The PP population for cure was the group of subjects included in the mITT population who met the following criteria:
 - Had CDAD confirmed by positive toxin assay

- Met all inclusion criteria and no exclusion criteria (unless failures to meet the former and meeting any of the latter were documented and approved by the applicant)
- Received a sufficient course of therapy: To assess study medication results, an adequate course of treatment was required. For failures, at least 3 complete days of therapy (6 active doses of fidaxomicin or 12 active doses of vancomycin) were required. For cures, ≥ 8 complete days of therapy (16 active doses of fidaxomicin or 32 active doses of vancomycin) were required.
- Had an EOT clinical evaluation
- Did not have significant protocol violations including use of concomitant CDAD therapy or other drugs, which could have confounded the assessment of efficacy, or other significant protocol violations as judged by a blinded assessment before study unblinding

Subjects who had a positive toxin test within 96 hours (4 days) of randomization were accepted into the mITT and PP populations if they had received less than or equal to 24 hours of *C. difficile* therapy and met the other criteria for inclusion into these populations. Subjects who received more than 24 hours of *C. difficile* therapy (e.g., metronidazole failure subjects) were required to have had a positive toxin test within the 48-hour window before randomization.

The following were general rules for incorrect study medication receipt and incorrect stratum (no prior episode versus prior episode) assignment:

- Incorrect study medication receipt: In the event that a subject was randomized to 1 treatment group but received the opposite treatment, the subject was analyzed according to the treatment received.
- Incorrect stratum assignment: A subject who was randomized to the wrong stratum was analyzed according to the stratum documented by the internal Case Record Form (iCRF). This did not disqualify the subject from the PP analysis.
- For protocol 101.1.C.003- A subject who received study medication without having been randomized through the interactive voice response system (IVRS) was included in the analysis populations as defined above.

Efficacy Measures

The objective of this study was to demonstrate that a 10-day course of fidaxomicin 200 mg PO q12h was non-inferior to a 10-day course of vancomycin 125 mg PO q6h for the treatment of CDAD. The primary efficacy endpoint was the cure rate at the EOT visit. A non-inferiority design was used to demonstrate the efficacy of fidaxomicin. To demonstrate the non-inferiority of fidaxomicin the lower limit of the 2-sided 95% CIs should be $> -10\%$. If the lower limit of the CI was greater than 0, the statistical superiority of fidaxomicin to vancomycin is demonstrated.

Primary Efficacy Measure

Primary cure rates at the EOT visit (± 2 days) were used for the principal comparison between treatments. The following clinical responses were used to categorize each subject regarding cure and failure. This assessment was made at the EOT visit (± 2 days), or early withdrawal from the study, and was determined by the investigator:

Cure

Subjects who, in the opinion of the investigator, required no further CDAD therapy 2 days after completion of study medication were considered cured. Subjects who had 3 or fewer unformed stools for 2 consecutive days and remained well before the time of study medication discontinuation were considered cured.

Alternatively, subjects who at the end of treatment had a marked reduction in the number of unformed stools but who had residual and mild abdominal discomfort interpreted by the investigator as recovering bowel could be considered cured at that time providing no new anti-infective CDAD therapy was required. Subjects who were considered cured based on stabilization and improvement in CDAD signs and symptoms were evaluated 2 to 3 days after the end of therapy. In the event that their signs or symptoms of CDAD worsened, subjects were to be designated primary failures. If they remained stable and were not considered to require further CDAD therapy to maintain their stable state, they were to be followed for recurrence as cures.

Subjects who had rectal collection devices and who were passing liquid stools periodically during the day were considered to have resolution of diarrhea when the volume (over a 24-hour period) was decreased by 75% compared with the volume observed at admission or when the subject was no longer passing liquid stools.

Modified Definition of Cure

In the modified definition of cure used in the sensitivity analysis, subjects who do not meet the criteria of 3 or fewer unformed stools for 2 consecutive days (maintained to the end of the end of therapy) will be considered failures regardless of any other data used at TOC. The sensitivity analysis for the primary efficacy analysis will be the same analysis as described in the primary efficacy analysis, with the modified definition of cure rate as a response variable.

Failure

Subjects who in the opinion of the investigator required additional CDAD therapy were considered failures.

The investigator based clinical impressions of the need for additional therapy on subjects' status including:

- Fever $>38.0^{\circ}\text{C}$, not attributable to another clear etiology (e.g., pneumonia)

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- Elevated WBC count >13,000/ μ L not attributable to another clear etiology (e.g., pneumonia)
- Abdominal pain of moderate or greater severity lasting 1 hour or more and/or abdominal tenderness of at least moderate severity, including any peritoneal signs

As defined in the protocol, subjects who entered the study without signs or symptoms of CDAD other than diarrhea were evaluated as failures on the basis of continued diarrhea alone.

Secondary Efficacy Measure

Recurrence rate

The secondary efficacy endpoint for both studies was the recurrence rate of CDAD within 28 days (\pm 2 days) after the last dose of study therapy. Subjects who remained in the study throughout the post-study days (Study Days 36-40) or who had a recurrence before that time were evaluated for recurrence and non-recurrence by using the following definitions:

- Recurrence – The re-establishment of diarrhea to an extent (frequency of passed unformed stools) that was greater than that noted on the last day of study medication with the demonstration of either toxin A or B or both of *C. difficile* and that, in the investigator's opinion, required retreatment with CDAD anti-infective therapy. Subjects being considered for recurrence must have had positive toxin demonstrated in the stool. If a rapid screening test was used and failed to demonstrate toxin, a confirmatory test using a non-rapid kit method was to be used.
- Non-recurrence – The maintenance of a non-diarrheal state up to and through the post-study visit. Subjects who developed other causes of diarrhea associated with a negative *C. difficile* stool toxin test were not considered to have a recurrence.

Missing values in the investigators' classification of recurrence or non-recurrence were imputed with a recurrence classification. Exceptions to this were missing values for subjects followed for more than 25 days after the date of clinical cure with complete Day 17, Day 24, and Day 31 subject assessments (7, 14, and 21 days post-therapy, respectively) without indication of resuming diarrhea which will be classified as non-recurrence.

Medical Reviewer comments: definitions of cure, failure, and recurrences are acceptable. However, since Day 31 was the time point allowing the conclusion of non-recurrence, this day will be used to determine the duration of follow-up for the purpose of global cure assessment.

Global cure rate

Global cure rate was an exploratory efficacy measure for study 101.1.C.003 and a secondary efficacy measure for study 101.1.C.004. Global cure rate was defined as the number of subjects in each treatment group who had been evaluated as cured and who did not have a recurrence.

Time-to-resolution of diarrhea

Time-to-resolution of diarrhea (TTROD) was an exploratory efficacy measure in both studies. TTROD was defined as the number of days and hours from the start of study medication until the earliest resolution of diarrhea. The earliest resolution of diarrhea was assessed during subject interviews by review of subjects' personal records for the day and by the time and quality (formed versus unformed) of bowel movements. The earliest resolution of diarrhea endpoint was recorded as the first of 2 consecutive days of ≤ 3 unformed bowel movements maintained at ≤ 3 UBM per day through the end of therapy.

TTROD was difficult to assess in subjects with rectal tubes because the time of stool production was imprecise. Initially, earliest resolution of diarrhea was defined by reduction ($\geq 75\%$) in 24-hour volume of stool sustained until Day 10 (EOT) compared to volume of stool at admission, or by the fact that a subject was no longer passing liquid stools. However, subjects may have required rectal tubes intermittently. Therefore, in a subsequent protocol amendment, an arbitrary conversion of the volume of liquid stool to UBM was defined as 60 mL liquid stool = 1 UBM. The earliest resolution of diarrhea was evaluated as described above on consecutive days, when the volume of liquid stool was ≤ 180 mL/24h.

Microbiological Measures

Subjects were requested to provide stool samples before the first dose of study medication, at EOT or early termination, and at recurrence.

Fecal samples (at entry and for treatment failures and recurrences) were tested for toxins A and B. In the event that this test was negative by a rapid screening test, a confirmatory test using a non-rapid assay (e.g., enzyme-linked immunosorbent assay [ELISA]) was permitted to consider such stools negative. These samples were also cultured for susceptibility and subjected to REA typing^{1,2}.

6.1.2 Demographics

The demographic profile was similar in the two Phase 3 studies, 101.1.C.003 and 101.1.C.004 (Table 3). Most subjects in both studies were white and females. There were slightly more females enrolled into study 101.1.C.004, and the average age of subjects in the 101.1.C.004 study was 2 years higher than in study 101.1.C.003.

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

	101.1.C.003		101.1.C.004	
	Fidaxomicin (N=287)	Vancomycin (N=309)	Fidaxomicin (N=252)	Vancomycin (N=257)
Sex, n (%)				
Female	164 (57.1)	169 (54.7)	148 (58.7)	162 (63.0)
Male	123 (42.9)	140 (45.3)	104 (41.3)	95 (37.0)
Race, n (%)				
White	252 (87.8)	267 (86.4)	232 (92.1)	238 (92.6)
Black	30 (10.5)	33 (10.7)	17 (6.7)	17 (6.6)
Asian	4 (1.4)	7 (2.3)	2 (0.8)	1 (0.4)
Other ^a	1 (0.3)	2 (0.6)	1 (0.4)	1 (0.4)
Age (yrs)				
N	287	309	252	257
Mean±SD	60.3±16.9	62.9±16.9	64.3±17.9	62.5±18.4
Median	61.0	64.0	67.5	65.0
Range	18, 94	19, 94	18, 94	19, 93
Weight (kg)				
N	287	308	251	257
Mean±SD	78.1±24.2	76±21.3	71.44±20.7	70.88±19.8
Median	74.1	73.0	68.00	67.00
Range	36.4, 230.6	36, 242.3	32.0, 231.6	32.8, 181.4
Height (cm)				
N	287	308	251	256
Mean±SD	167.1±11.1	166.9±12.1	167.07±9.7	165.76±10.97
Median	167.0	167.6	166.00	165.00
Range	124, 193	129.5, 198	146.0, 195.6	114.0, 208.0
BMI(kg/m ²) ^b				
N	287	308	251	256
Mean±SD	27.9±8.1	27.3±7.4	25.5±6.30	25.7±6.7
Median	26.3	26.0	24.2	24.9
Range	15.9, 79.6	15.4, 83.6	12.5, 63.8	12.8, 51.9

^a Other includes: American Indian and Alaska native.

^b Calculated body mass index (BMI) is defined as (weight in kg)/(height in meters)².
BMI – body mass index; SD = standard deviation

Adapted from Table 3.1-1 ISE

Within each study, the treatment groups were generally comparable for baseline characteristics. More subjects in the 101.1.C.004 study were inpatients compared to subjects in study 101.1.C.003 (Table 4). In addition a larger proportion of subjects in the 101.1.C.004 study had previously used antibiotics for CDAD (87.4%), compared to study 101.1.C.003 (44.8%). 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 4 Summary of Baseline Characteristics in the Phase 3 Studies
(mITT Population)**

	101.1.C.003		101.1.C.004	
	Fidaxomicin (N=287)	Vancomycin (N=309)	Fidaxomicin (N=252)	Vancomycin (N=257)
Subject status, n (%)				
Inpatient	167 (58.2)	187 (60.5)	174 (69.0)	173 (67.3)
Outpatient	120 (41.8)	122 (39.5)	78 (31.0)	84 (32.7)
Stratum, n (%)				
No Prior Episode	239 (83.3)	255 (82.5)	212 (84.1)	221 (86.0)
Single Prior Episode	48 (16.7)	54 (17.5)	40 (15.9)	36 (14.0)
Daily Bowel Movements				
N	287	309	251	257
Mean ±SD	8.1±4.2	8.3±5.4	7.5±4.4	7.5±4.3
Median	7.0	6.0	6.0	6.0
Min, Max	4, 32	4, 50	4, 30	4, 30
Baseline disease severity ^a , n (%)				
Mild	64 (22.3)	80 (25.9)	77 (30.6)	95 (37.0)
Moderate	111 (38.7)	106 (34.3)	82 (32.5)	73 (28.4)
Severe	112 (39.0)	123 (39.8)	90 (35.7)	88 (34.2)
Missing	0	0	3 (1.2)	1 (0.4)
<i>C. difficile</i> Toxin, n (%)				
Positive	287 (100)	309 (100)	252 (100)	257 (100)
Negative	0	0	0	0
CDI Indication, n (%)				
Diarrhea Alone	49 (17.1)	68 (22.0)	188 (74.6)	192 (74.7)
Diarrhea and Other Symptoms	238 (82.9)	241 (78.0)	64 (25.4)	65 (25.3)
Prior Use of CDI Antibiotics, n (%)				
Prior Use	128 (44.6)	139 (45.0)	225 (89.3)	220 (85.6)
No Prior Use	159 (55.4)	170 (55.0)	27 (10.7)	37 (14.4)
Metronidazole Failure, n (%)				
Yes	13 (4.5)	17 (5.5)	12 (4.8)	8 (3.1)
No	274 (95.5)	292 (94.5)	240 (95.2)	249 (96.9)

^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

Source: Sponsor's Table 3.1-2 ISE

Medical Reviewer comments: More subjects in 101.1.C.004 compared to 101.1.C.003 trial were inpatients (68.2% vs. 59.4%), had diarrhea alone as a CDAD indication (74.7% vs. 19.6%), and had a history of prior antibiotic use (87.4% vs. 44.8%). These differences should not affect the evaluation of fidaxomicin efficacy since subjects' baseline characteristics in treatment groups are comparable.

6.1.2 Subject Disposition

The number of patients in the prespecified analysis populations is shown in Table 5.

Table 5 Summary of Subject Populations

Study Population	Vancomycin (N=327) n (%)	Fidaxomicin (N=302) n (%)	Vancomycin (N=265) n (%)	Fidaxomicin (N=270) n (%)
Randomized	327 (100.0)	302 (100.0)	265 (100.0)	270 (100.0)
Safety	323 (98.8)	300 (99.3)	260 (98.1)	264 (97.8)
MITT for cure	309 (94.5)	287 (95.0)	257 (97.0)	252 (93.3)
Per Protocol for cure	283 (86.5)	265 (87.7)	235 (88.7)	216 (80.0)
MITT for Recurrence	265 (81.0)	253 (83.8)	223 (84.2)	221 (81.9)
Per Protocol for Recurrence	221 (67.6)	211 (69.9)	182 (68.7)	180 (66.7)

Adapted from Trial 101.1.C.004, Study Report Body, Table 11, Trial 101.1.C.003, Study Report Body, Table 4

In study 101.1.C.003, 629 subjects were enrolled and randomized, with 623 receiving study drug (323 on vancomycin and 300 on fidaxomicin). A total of 54 subjects (32 [9.9%] vancomycin and 22 [7.3%] fidaxomicin) withdrew from the study during the treatment phase and 35 withdrew after end of therapy (EOT) during the follow-up phase (20 [6.2%] vancomycin and 15 [5.0%] fidaxomicin). The most frequent reason for prematurely discontinuing study drug was AEs, with a similar percentage observed in both treatment groups.

In study 101.1.C.004, 535 subjects were enrolled and randomized, with 524 receiving study drug (260 on vancomycin and 264 on fidaxomicin). More subjects in this study than in study 101.1.C.003 withdrew from the study during the treatment phase: 34 [13.1%] vancomycin and 45 [17.0%] fidaxomicin) and 29 withdrew after EOT during the follow-up phase (17 [6.5%] vancomycin and 12 [4.5%] fidaxomicin). The most frequent reason for prematurely discontinuing study drug was AEs (which was the most common reason for withdrawal in study 101.1.C.003 as well), with a similar percentage observed in both treatment groups (Table 6).

Table 6 Subject Disposition and Reasons for Discontinuation in Phase 3 trials

	101.1.C.003			101.1.C.004		
	Fidaxomicin (N=302)	Vancomycin (N=327)	Total (N=629)	Fidaxomicin (N=270)	Vancomycin (n=265)	Total (N=535)
No. of subjects who were enrolled and randomized	302	327	629	270	265	535
No. of subjects who were randomized and received study medication	300	323	623	264	260	524
No. of Subjects Completing at least 80% of study medication	266	280	546	227	234	461
No. of subjects completing end of therapy visit (including withdrawal subjects with at least 3 days of study drug due to clinical failure)	280	295	575	233	234	467
No. of subjects prematurely withdrawn from the study during the treatment phase; reason for early termination	22 (7.3)	32 (9.8)	54 (8.6)	45 (16.7)	34 (12.8)	79 (14.8)
Adverse event	12 (4)	15 (4.6)	27 (4.3)	15 (5.6)	16 (6)	31 (5.8)
Subject choice	6 (2)	7 (2.1)	13 (2.1)	10 (3.7)	10 (3.8)	20 (3.7)
Clinical failure	NA	NA	NA	8 (3)	3 (1.1)	11 (2.1)
Effective concomitant CDI therapy	0	5 (1.5)	5 (0.8)	0	0	0
Protocol violation	0	3 (0.9)	3 (0.5)	3 (1.1)	2 (0.8)	5 (0.9)
Non-compliance	2 (0.7)	1 (0.3)	3 (0.5)	8 (3)	3 (1.1)	11 (2.1)
Lost to follow-up	1 (0.3)	1 (0.3)	2 (0.3)	0	0	0
Treatment failure (less than 3 days of therapy)	1 (0.3)	0	1 (0.2)	0	0	0
Not having a robust enough response	NA	NA	NA	1 (0.4)	0	1 (0.2)
No. of subjects prematurely withdrawn from the study during the follow-up phase; reason for withdrawal	15 (5)	20 (6.1)	35 (5.6)	12 (4.4)	17 (6.4)	29 (5.4)
Adverse event	6 (2.)	8 (2.4)	14 (2.2)	8 (3.0)	7 (2.6)	15 (2.8)
Subject's choice	3 (1.0)	3 (0.9)	6 (1)	1 (0.4)	2 (0.8)	3 (0.6)
Treatment failure (less than 3 days of therapy)	NA	NA		1 (0.4)	0	1 (0.2)
Lost to follow-up	0 (0)	3 (0.9)	3 (0.5)	1 (0.4)	6 (2.3)	7 (1.3)
Protocol violation	1 (0.3)	0	1 (0.2)	1 (0.4)	2 (0.8)	3 (0.6)
Effective concomitant therapy	3 (1)	4 (1.2)	7 (1.1)	0	0	0
Non-compliance	1 (0.3)	1 (0.3)	2 (0.3)	0	0	0
Reason not specified	1 (0.3)	1 (0.3)	2 (0.3)	0	0	0
No. of subjects completing entire study (cure + recurrence)	265 (87.7)	275 (84.1)	540 (85.9)	214 (79.3)	214 (80.7)	428 (80)

NOTE: A subject can have multiple reasons for study termination. NA = not applicable (i.e. category was not included in the study as an option)

Adapted from Source Tables: Trial 101.1.C.003, Study Report Body, Table 3
Trial 101.1.C.004, Study Report Body, Table 10

Medical Reviewer comments: According to the reviewer analysis, there were 8 and 3 subjects in the fidaxomicin and vancomycin group in study 101.1.C.003 and 5 and 2 subjects in the fidaxomicin and vancomycin group in study 101.1.C.004 who were withdrawn during the treatment phase due to treatment failure. The withdrawals should

not reflect on efficacy assessments since all these subjects were counted as failures. More details are provided in section 7.3.3 Dropouts and discontinuations.

6.1.4 Analysis of Primary Endpoint(s)

The cure rates in mITT population were similar in the fidaxomicin and vancomycin treated subjects in trials 101.1.C.003 and 101.1.C.004, 88% vs. 84%, treatment difference 4.2 (-1.4, 9.7) and 86% vs. 85%, treatment difference 0.2 (-5.9, 6.4).

Medical Reviewer comments: The reviewers' analysis supports the applicant's analysis. In all analyses, the treatment difference favoring fidaxomicin had a 95% CI lower limit well above the non-inferiority margin of -10%, demonstrating the non-inferiority of fidaxomicin relative to vancomycin. The reviewers' and the applicant's analyses of clinical cure are slightly different due to some inconsistencies in the assessment of clinical and global cure identified during the review. There were 13 subjects who were identified as cures by the applicant but who died before day 10, or had taken disallowed medication active against CDAD during treatment period (Table 7).

Table 7 Clinical Cure Rates at End of Treatment Visit

Applicant's Results				
Study	101.1.C.003		101.1.C.004	
	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Fidaxomicin n/N (%)	Vancomycin n/N (%)
mITT population	255/289 (88.2)	263/307 (85.7)	222/253 (87.7)	222/256 (86.7)
Difference ¹ 95% CI	2.6 (-2.9, 8.0)		1.0 (-4.8, 6.8)	
PP population	247/268 (92.2)	251/280 (89.6)	199/217 (91.7)	212/234 (90.6)
Difference ¹ 95% CI	2.5 (-2.4, 7.3)		1.1 (-4.2, 6.4)	
FDA's Results				
Study	003		004	
Treatment (mITT)	Fidaxomicin (N= 289)	Vancomycin (N = 307)	Fidaxomicin (N = 253)	Vancomycin (N = 256)
Inconsistencies with Applicant's assessment of cure mITT population	0	5	5	3
Cure n/N (%)	255/289 (88.2)	258/307 (84)	217/253 (85.8)	219/256 (85.5)
Difference ¹ 95% CI	4.2 (-1.4, 9.7)		0.2 (-5.9, 6.4)	

¹ Difference = Cure Rate for Fidaxomicin – Cure Rate of Vancomycin

In addition, fidaxomicin demonstrated non-inferiority in sensitivity analyses using a modified endpoint based strictly on the resolution of diarrhea (i.e., ≤ 3 UBMs during treatment that was sustained to the EOT visit) (Table 8).

Table 8 Clinical Cure Rates at End of Treatment Visit – Sensitivity Analysis with Modified Cure Definition

	101.1.C.003		101.1.C.004	
	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Fidaxomicin n/N (%)	Vancomycin n/N (%)
PP population	226/268 (84.3)	241/280 (86.1)	187/217 (86.2)	197/234 (84.2)
Difference ¹ 95% CI	-1.7 (-7.7,4.2)		2.0 (-4.6,8.5)	
mITT population	228/289 (78.9)	247/307 (80.5)	201/253 (79.4)	203/256 (79.3)
Difference ¹ 95% CI	-1.6 (-8.0,4.9)		0.1 (-6.9,7.2)	

¹ Difference = Cure Rate Fidaxomicin treatment arm – Cure Rate of Vancomycin treatment arm
Adapted from Applicant's Table 3.3-2 ISE

6.1.5 Analysis of Secondary Endpoints(s)

Global Cure

Global cure was defined as achieving a cure response at the end of therapy and not having a recurrence at any time up to the post-study visit. In both studies, the global cure rate was higher in the fidaxomicin group versus the vancomycin group.

There were 85 patients declared as global cures despite death during the study, concomitant medication treating CDAD during treatment period or follow up, or recurrence assessment visit before study day 31. The breakdown by treatment, study and reason of inconsistency is shown in Table 9.

Table 9 Inconsistencies in Assessment of Global Cure

Study	003		004	
	Fidaxomicin (N= 215)	Vancomycin (N = 197)	Fidaxomicin (N = 194)	Vancomycin (N = 162)
Treatment (Applicant's global cure)				
Total Inconsistencies with Applicant's Assessment of Global Cure	18 (8%)	26 (13%)	18 (9%)	23 (14%)
Inconsistency due to death before study day 31	4	6	8	4
Inconsistency due to CDAD Concomitant Med during treatment or follow up	12	18	12	13

Inconsistency due to recurrence visit before day 31	10	13	6	9
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The Agency performed three sensitivity analyses to evaluate a possible impact of these inconsistencies on efficacy results. The results of these analyses, as well as the applicant results are presented in Table 10. The results of the analyses did not change applicant’s conclusions that the global cure rate in the fidaxomicin group was superior to vancomycin group. Sensitivity analysis number 1 treated all inconsistencies as failures. Results of this sensitivity analysis showed superiority of fidaxomicin to vancomycin for Global Cure assessed at day 31.

Two additional sensitivity analyses used multiple imputation method. In this method, missing outcomes are imputed using a logistic model predicting the probability of global cure with covariates of baseline characteristics, follow-up information for diarrhea and timing variables such as length of treatment. More specifically, the following variables were included in the logistic model: treatment assignment, study, study center, sex, race, age, weight, height, BMI, subject status, prior CDAD episodes, daily bowel movement at baseline or baseline disease severity, diarrhea alone or other symptoms, prior use of CDAD antibiotics, metronidazole failure, number of study days in treatment phase, diarrhea at follow up visits after cure, serum albumin concentration (below 2.5 mg/dl or not).

In sensitivity analysis for global cure number 2, the global cure outcome of subjects who died before study day 31 or who had suspected CDAD recurrence defined as diarrhea during follow up period prompting CDAD therapy regardless of toxin results, was changed to failure. All other inconsistencies were changed to missing. In addition, the outcome of global cure was changed to missing for all subjects who were cured at TOC and had a missing outcome for recurrence. The results of this analysis showed superiority of fidaxomicin. The difference between global cure rate for fidaxomicin treatment arm and global cure rate for vancomycin treatment arm were 13.1% (95% CI 5.0%, 21.2%) and 13.3% (95% CI 4.5%, 22.0%) in studies 101.1.C.003 and 101.1.C.004, respectively.

In Sensitivity analysis for global cure number 3, the global cure outcome of subjects who died before study day 31 was set to missing and imputed, whereas it was set to failure in Sensitivity analysis 2. The results of this analysis showed superiority of fidaxomicin. The difference between global cure rate for fidaxomicin treatment arm and global cure rate for vancomycin treatment arm were 13.1% (95% CI 5.0%, 21.2%) and 14.3% (95% CI 5.5%, 23.0%) in studies 101.1.C.003 and 101.1.C.004, respectively.

Table 10 Global Cure Rates – Applicant’s and FDA Analysis - All inconsistencies treated as failures.

	101.1.C.003		101.1.C.004	
Treatment mITT	Fidaxomicin (N=289) n/N (%)	Vancomycin (N=307) n/N (%)	Fidaxomicin (N=253) n/N (%)	Vancomycin (N=256) n/N (%)
Global Cure Applicant’s results	215/289 (74)	197/307 (64)	194/253 (77)	162/256 (63)
Difference ¹ 95% CI	10.2 (2.8, 17.5)		13.4 (5.4, 21.1)	
Inconsistencies Total	18/289 (6)	26/307 (8)	18/253 (7)	23/256 (9)
Sensitivity 1	197/289 (68)	171/307 (56)	176/253 (70)	139/256 (54)
Difference ¹ 95% CI	12.5 (4.7,20)		15.3 (6.8,23.4)	
Sensitivity 2	71 %	57%	72%	59%
Difference ¹ 95% CI	13.1(5.0, 21.2)		13.3 (4.5, 22.0)	
Sensitivity 3	71%	58%	73%	59%
Difference ¹ 95% CI	13.1 (5.0, 21.2)		14.3 (5.5, 23.0)	

¹ Difference = Cure Rate Fidaxomicin treatment arm – Cure Rate of Vancomycin treatment arm

Medical Reviewer Comments: The results of all Agency analyses demonstrate that the global cure rate in the fidaxomicin group was superior to that of vancomycin group, and thus, are in agreement with Applicant’s results.

Clinical recurrence

The recurrence rate was higher in the vancomycin groups in both studies (Table 11).

Table 11 CDAD Recurrence Rates

	101.1.C.003		101.1.C.004	
	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Fidaxomicin n/N (%)	Vancomycin n/N (%)
mITT population	40/255 (15.7)	66/263 (25.1)	28/222 (12.6)	60/222 (27.0)
Difference 95% CI P-value	-9.4 (-16.2, -2.5) p=0.008		-14.4 (-21.6, -7.0) p<0.001	
PP population	28/213 (13.1)	53/219 (24.2)	23/181 (12.7)	46/181 (25.4)
Difference 95% CI p-value	-11.1 (-18.2, - 3.7) p=0.003		-12.7 (-20.6, -4.6) p=0.002	

Adapted from ISE Table 3.2-3

Medical Reviewer comments: Based on the 95% CIs and corresponding p-values fidaxomicin demonstrated superiority over vancomycin in the rates of recurrence.

The evaluation of the time to CDAD recurrence, defined as the number of days from the date of cure at EOT to date of recurrence, showed that subjects treated with fidaxomicin experienced recurrence later than subjects treated with vancomycin (Table 12).

Table 12 Summary of Time-to-Recurrence of CDAD (days)

mITT population	101.1.C.003		101.1.C.004	
	Fidaxomicin N=255 n/N (%)	Vancomycin N=263 n/N (%)	Fidaxomicin N=222 n/N (%)	Vancomycin N=222 n/N (%)
N, Recurrence	40 (15.7)	66 (25.1)	28 (12.6)	60 (27.0)
N, Censored ^a	215 (84.3)	197 (74.9)	194 (87.4)	162 (73.0)
10 th Percentile Difference 95% CI P-value	21 (12.0, 25.0)	9.0 (8.0, 10.0)	18.0 (13.0, NE ^b)	8.0 (6.0, 10.0)

^a Subjects who did not experience recurrence during the follow-up period are censored at 40 days.

^b NE – not evaluated

Adapted from ISE Table 14.2.4.1

Medical Reviewer comments: Recurrences at a later point may more likely represent re-infections rather than relapses of the initial infection. Thus, a longer time-recurrence in fidaxomicin treated subjects argues in favor of the Applicant claim that fidaxomicin is superior to vancomycin in preventing CDAD recurrences.

6.1.6 Other Endpoints

The median time-to-resolution of diarrhea was 75 hours in the fidaxomicin and 81 hours in the vancomycin group. This difference was not statistically significant.

6.1.7 Subpopulations

The fidaxomicin arm did not demonstrate superiority in global cure when compared with vancomycin for patients CDAD caused by the BI strain of *C. difficile* due to higher recurrence rates among fidaxomicin patients infected with the BI strain.

There were a number of analyses that showed an association of different variables with cure rates. The analyzed variables were as follows:

- Age group (<65, 65-74 and ≥75)
- Sex

- Race
- Country
- Prior occurrence (no prior episodes, single prior episode)
- CDAD-prescribed antibiotic within 24 hours prior to study treatment (yes, no)
- Metronidazole failure prior to the study (yes, no)
- Concomitant systemic anti-infectives throughout the study:
 - medications taken during treatment period (cure, global cure)
 - medications taken during follow-up (recurrence, global cure)
 - medications taken during treatment or during follow-up (recurrence, global cure)
 - medications taken during treatment and during follow-up (recurrence, global cure)
- Baseline disease severity based on European Society of Clinical Microbiology and Infectious Disease (ESCMID) criteria to define baseline disease severity:
 - Mild CDI: 4 to 5 UBMs per day or WBC $\leq 12000/\text{mm}^3$
 - Moderate CDI: 6 to 9 UBMs per day or WBC 12001 - 15000/ mm^3
 - Severe CDI: ≥ 10 UBMs per day or WBC $\geq 15001/\text{mm}^3$
- Subject status (inpatient, outpatient)
- Initial strain of CDI (BI, non-BI)

BI strain

BI strain has been considered to be associated with more severe CDAD when compared with non-BI strains. In both treatment groups, cure rates and global cure rates were lower in subjects infected with BI strain in both Phase 3 trials (Table 13 and 14). Comparison between the fidaxomicin and vancomycin groups demonstrated similar cure rates for both CDAD strains in two Phase 3 trials with both drugs having lower cure rates among patients with CDAD caused by the BI strain.

However, for the BI strain, the fidaxomicin arm did not demonstrate superiority in global cure when compared with vancomycin. It appears that higher recurrence rates among fidaxomicin patients infected with the BI strain are responsible for this result. In study 101.1.C.003 recurrence rates in fidaxomicin group for BI and non-BI strains were 27.1% and 10.3%, respectively. Recurrence rates in the vancomycin group in study 101.1.C.003 for BI and non-BI strains were 20.9% and 28.1%, respectively.

In study 101.1.C.004 recurrence rates in fidaxomicin group for BI and non-BI strains were 22.2% and 9.2%, respectively. Recurrence rates in the vancomycin group for BI and non-BI strains were 29.7% and 18%, respectively.

Table 13 Cure Rates at EOT for Different Initial Strains of *C. difficile*

Study 003			
	Fidaxomicin	Vancomycin	Difference¹ (95% CI)²
Missing	77/87 (88%)	77/94 (82%)	6.6%

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			(-4.0%, 16.9%)
Virulent (BI)	60/76 (79%)	66/82 (80%)	-1.5% (-14.2%, 10.9%)
Non-virulent (non BI)	118/126 (94%)	120/131 (92%)	2.0% (-4.7%, 8.8%)
Study 004			
	Fidaxomicin	Vancomycin	Difference¹ (95% CI)²
Missing	48/57 (84%)	66/75 (88%)	-3.8% (-16.6%, 8.0%)
Virulent (BI)	54/65 (83%)	50/60 (83%)	-0.2% (-13.4%, 13.2%)
Non-virulent (non BI)	120/131 (92%)	106/121 (88%)	4.0% (-3.6%, 11.9%)
Pooled 003 and 004 studies			
	Fidaxomicin	Vancomycin	Difference¹ (95% CI)²
Missing	125/144 (87%)	143/169 (85%)	2.2% (-5.8%, 9.9%)
Virulent (BI)	114/141 (81%)	116/142 (82%)	-0.8% (-10.0%, 8.2%)
Non-virulent (non BI)	238/257 (93%)	226/252 (90%)	2.9% (-2.1%, 8.0%)

Difference = Cure Rate Fidaxomicin treatment arm – Cure Rate of Vancomycin treatment arm

Table 14 Global Cure Rates for Different Initial Strains of *C. difficile*

Study 003			
Initial Strain of CDI	Fidaxomicin	Vancomycin	Difference¹ (95% CI)²
Missing	66/87 (76%)	58/94 (61%)	14.1% (0.6%, 26.9%)
Virulent (BI)	44/76 (58%)	52/82 (63%)	-5.5% (-20.3%, 9.5%)
Non-virulent (non BI)	105/126 (83%)	87/131 (66%)	16.9% (6.3%, 27.0%)
Study 004			
Initial Strain of CDI	Fidaxomicin	Vancomycin	Difference¹ (95% CI)²
Missing	43/57 (75%)	54/75 (72%)	3.4% (-11.9%, 17.9%)
Virulent (BI)	42/65 (65%)	31/60 (52%)	12.9% (-4.2%, 29.2%)
Non-virulent (non BI)	109/131 (83%)	77/121 (64%)	19.6% (8.7%, 30.0%)
Pooled 003 and 004 studies			
Initial Strain of CDI	Fidaxomicin	Vancomycin	Difference¹ (95% CI)²
Missing	109/144 (76%)	112/169 (66%)	9.4% (-0.7%, 19.1%)
Virulent (BI)	86/141 (61%)	83/142 (58%)	2.5% (-8.8%, 13.8%)
Non-virulent (non BI)	214/257 (83%)	164/252 (65%)	18.2% (10.6%, 25.5%)

Difference = Cure Rate Fidaxomicin treatment arm – Cure Rate of Vancomycin treatment arm

Medical Reviewer comments: fidaxomicin did not demonstrate superiority when compared to vancomycin for global cure rates for the virulent strain. The main factor for this are higher recurrence rates in fidaxomicin subjects infected with BI strain. .

Other Subpopulation Analysis

Global cure rates were lower in subjects > 65 years, with prior CDI episode, administration of systemic antibiotics during treatment period, severe disease at baseline, and inpatient status in both treatment groups. The global cure rates were still higher in fidaxomicin compared to vancomycin subjects. Table 15 provides the results of analyses in the selected subgroups.

Table 15 Summary of Global Cure Rates at End of Therapy by Selected Subgroups by Applicant (mITT Population)

	101.1.C.003			101.1.C.004		
	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95% CI	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95% CI
Global Cure	215/289 (74)	197/307 (64)	10.2 (2.8,17.5)	194/253 (77)	162/256 (63)	13.4 (5.4,21.1)
Age < 65	132/166 (80)	106/156 (68)	11.6 (1.9,20.9)	89/111 (80)	84/125 (67)	13.0 (1.7,23.7)
Age ≥ 65	83/123 (67)	91/151 (60)	7.2 (-4.2,18.3)	105/142 (74)	78/131 (60)	14.4 (3.2,25.2)
Prior Single CDAD Episode						
No	182/241 (76)	164/253 (65)	10.7 (2.6,18.6)	164/213 (77)	141/220 (64)	12.9 (4.3,21.2)
Yes	33/48 (69)	33/54 (61)	7.6 (-10.7,25.3)	30/40 (75)	21/36 (58)	16.7 (-4.4,36.2)
Anti-Infectives for Systemic Use During Treatment or Follow-up Period						
YES	67/101 (66)	65/113 (58)	8.8 (-4.2,21.4)	71/101 (70)	61/100 (61)	9.3 (-3.8,22.0)
NO	148/188 (79)	132/194 (68)	10.7 (1.8,19.3)	123/152 (81)	101/156 (65)	16.2 (6.3,25.7)
Baseline Disease Severity						
Severe	45/74 (61)	45/81 (56)	5.3 (-10.1,20.3)	44/63 (70)	29/61 (48)	22.3 (5.1,38.2)
Non-Severe	170/215 (79)	152/226 (67)	11.8 (3.5,19.8)	150/190 (79)	133/195 (68)	10.7 (1.9,19.3)
Hospitalization						
Inpatient	112/168 (67)	106/186 (57)	9.7 (-0.4,19.6)	132/175 (75)	106/172 (62)	13.8 (4.0,23.3)
Outpatient	103/121 (85)	91/121 (75)	9.9 (-0.2,19.7)	62/78 (79)	56/84 (67)	12.8 (-0.9,25.8)

Adapted from ISE Table 6.3-1

Medical Reviewer comments: global cure rates were overall higher among fidaxomicin subjects in the analyzed subpopulations with the exception of subjects infected with BI strain.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The most favorable response for the treatment of CDAD in the Phase 2A study was observed in the 400 mg/day treatment group. There were 3 treatment groups in this study assigned to 100 mg/day, 200 mg/day, and 400 mg/day of fidaxomicin with 16 subjects per dose group. One subject in the 400 mg group did not meet inclusion criteria for CDAD resulting in 15 mITT subjects in this group. Clinical cure rate was achieved in 15/15 (100 %) of subjects in the 400 group, 13/16 (81.3%) of subjects in 200 mg group,

and in 12/16 (75%) of subjects in 100 mg group. There were 2 treatment failures in the 200 mg and 2 treatment failures in 100 mg. In addition 3 subjects in the 100 mg and 1 in the 200 mg group terminated the study earlier due to withdrawal of consent or other reason.

Another primary endpoint was CDAD symptoms relief which was observed in 86.7%, 50%, and 37.5% of subjects in the 400 mg, 200 mg, and 100 mg of subjects, respectively. The estimated median time to resolution of diarrhea was 5.5 days, 3.5 days and 3.0 days for the 100 mg, 200 mg and 400 mg treatment groups, respectively.

There was one recurrence in 100 mg group, one recurrence in 400 mg group, and no recurrences in the 200 mg group.

The plasma concentrations of fidaxomicin were higher in subjects who received 200 and 400 mg compared to those who received 100 mg (Table 16). Higher OP-1118 concentrations were observed with increasing fidaxomicin dose.

Table 16 Range of Fidaxomicin Plasma Concentrations in Study OPT-80 Phase 2A

Sample	Analyte	100 mg/day	200 mg/day	400 mg/day
Day 1 and Day 10, ng/mL	Fidaxomicin	9.45, 12.3	5.12, 93.7	5.32, 84.9
Day 1 and Day 10, ng/mL	OP-1118	5.23, 77.2	5.04, 154.3	5.92, 402.3

Source: Applicant's Summary of Clinical Pharmacology Studies Table 2.7.2-9

As a result of this study the 400 mg/day (200 mg q12h) daily dose was chosen for evaluation in the Phase 3 studies.

Medical Reviewer comments: the results of the Phase 2 study supported the choice of the dose of 400 mg/day. Adverse event rates in different dose groups are discussed in section 7.5.1 of this review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Overall, fidaxomicin has demonstrated good activity against *C. difficile* with fecal concentrations well above the MIC. The discussion of a potential for the development of resistance is provided in section 4.2 Clinical Microbiology. As mentioned in the section, there was a strain that developed an MIC of 16 mcg/mL in a subject with recurrent CDAD. The isolate developed a mutation in the β subunit of RNA polymerase which was similar to the mutation identified in a spontaneous laboratory-derived *C. difficile* mutant displaying decreased susceptibility to fidaxomicin. Thus, a potential for resistance development to fidaxomicin exists.

6.1.10 Additional Efficacy Issues/Analyses

An impact of P-glycoproteins (P-gp) inhibitors on efficacy and safety of fidaxomicin was examined because cyclosporine, a known P-gp inhibitor, was shown to increase fidaxomicin and OP-1118 plasma level exposure (AUC) to 1.9- and 4.1-fold, respectively (see section 7.5.5 Drug-Drug Interactions for details). A potential concern was whether P-glycoprotein inhibitors affect efficacy and safety of fidaxomicin by increasing its absorption and possibly, decreasing intestinal exposure to the drug.

In phase 3 trials P-glycoprotein inhibitors were identified as follows:

- omeprazole, esomeprazole
- azithromycin; cefuroxime
- clotrimazole; ketoconazole; posaconazole
- diltiazem; verapamil; atorvastatin; carvedilol
- cyclosporine, Taxol
- atazanavir, lopinavir
- quinidine
- cetirizine

The results of our analysis of the impact of P-glycoprotein inhibitors on efficacy of fidaxomicin are presented in tables 17 and 18.

Table 17 Impact of P- glycoprotein inhibitor use on Efficacy: Phase 3 trials

	Fidaxomicin		Vancomycin	
	P-gp Inhibitor Use		P-gp Inhibitor Use	
	No	Yes	No	Yes
Clinical Cure mITT population	280/311 90%	192/225 85%	290/332 87%	196/232 84%
Global Cure mITT population	249/311 80%	157/225 70%	221/332 67%	139/232 60%

Table 18 Impact of Selected P-glycoprotein inhibitors use on Efficacy: Phase 3 trials

	Fidaxomicin N=225		Vancomycin N=232	
	Cure N=157 n(%)	Failure N=68 n(%)	Cure N=139 n(%)	Failure N=93 n(%)
Atorvastatin	56 (35.7)	22 (32.4)	46 (33.1)	29 (31.2)
Azithromycin	9 (5.7)	9 (13.2)	19 (13.7)	14 (15.1)
Cefiroxime	9 (5.7)	1 (1.5)	5 (3.6)	7 (7.5)
Carvedilol	13 (8.3)	7 (10.3)	22 (15.8)	19 (20.4)
Diltiazem	20 (12.7)	13 (19.7)	12 (8.6)	18 (19.3)
Esomeprazole	27 (17.1)	8 (11.8)	23 (16.5)	12 (12.9)
Omeprazole	44 (28)	13 (19.1)	31 (22.3)	16 (17.2)

Medical Reviewer comments: Lower cure rates and even more significant decreases in global rates were observed in patients who received P-glycoprotein inhibitors in phase 3 trials. However, decreases in cure rates were observed in both treatment groups and the overall clinical response still favored the fidaxomicin group.

The evaluation for possible association of individual P-gp inhibitors or their groups, e.g. proton-pump inhibitors with clinical failures is difficult owing to small numbers of subjects. Nevertheless, it appears that the use of proton-pump inhibitors, an acknowledged risk factor for CDAD treatment failure, was not associated with increases in failure rates in both treatment groups. In contrast, diltiazem, a calcium channel blocker was associated with failure increases. This may suggest that patients' comorbidities requiring the administration of P-gp inhibitors rather than the P-gp inhibitors themselves were responsible for decreases in cure rates among P-gp users.

7 Review of Safety

Safety Summary

The NDA database includes two phase 3 trials, one phase 2 ranging dose study, and three phase 1 PK studies. There were 676 patients who received at least one dose of fidaxomicin in all trials including 564 subjects who received at least 1 dose of fidaxomicin in phase 3 trials. The mean duration of exposure to fidaxomicin in phase 3 trials was 10.2 days. There were 593 subjects who received comparators, including vancomycin (n=583) and placebo (n=10). In addition, there were three drug-drug interaction studies discussed in this review that were not part of the safety database.

There were 75 deaths including 74 deaths in the phase 3 trials and 1 death in the phase 2 trial. In the phase 3 trials, the incidence of death was similar for subjects in the fidaxomicin and vancomycin groups [36 (6.4%) and 38 (6.5%), respectively].

The incidence of treatment-emergent serious adverse events in phase 3 trials was 25.7% and in 23.2% in the fidaxomicin and vancomycin groups, respectively. Adverse events of interest that occurred at a higher rate in the fidaxomicin when compared to vancomycin group included gastrointestinal (GI) hemorrhage, megacolon and decreases in WBC counts.

There were 20 (3.5%) vs. 12 (1.7%) phase 3 trial subjects in the fidaxomicin and vancomycin groups with AEs related to GI hemorrhage. In addition, there was one fidaxomicin patient in the phase 2 trial who experienced GI hemorrhage. The number of GI-hemorrhage events defined as serious was similar in both fidaxomicin and vancomycin groups (6 vs. 5). Two fidaxomicin patients stopped study drug due to GI hemorrhage and one patient in the fidaxomicin group died from GI hemorrhage. The review of the death indicated that the hemorrhage was unlikely related to the study drug. There was also a case of duodenal perforation following the administration of two doses of fidaxomicin at once. Of note, neither GI hemorrhage nor any changes in the GI tract were reported in the preclinical studies. The provided data do not allow concluding a causal relationship between fidaxomicin and GI hemorrhage. However, postmarketing surveillance is warranted.

More subjects in the fidaxomicin than in vancomycin group discontinued the study due to treatment failure during the treatment phase in phase 3 trials [13 (2.3%) vs. 5 (0.9%)], and all three cases of megacolon were observed in fidaxomicin-treated patients with two cases possibly related to insufficient clinical response to study drug. Based on similar overall cure rates in the fidaxomicin and vancomycin groups and a small number of the cases of megacolon, no conclusions with regard to association of fidaxomicin and megacolon could be made.

There were more subjects in the fidaxomicin than in vancomycin group with adverse events related to decreases in WBC counts [23 (4.1%) vs. 10 (1.7%)]. All adverse events were reported in Phase 3 trials. No abnormal shifts in hematology values were reported for subjects in the fidaxomicin 100-200 mg group and no bone marrow toxicity was observed in the animal toxicology studies. There were 14 (2.5%) vs. 6 (1.0%) adverse events consistent with neutropenia in the fidaxomicin and vancomycin groups, respectively. There were 11 (1.9%) vs. 5 (0.9%) adverse events consistent with lymphopenia in the fidaxomicin and vancomycin groups, respectively. The majority of fidaxomicin-treated subjects (20 out of 23) had underlying comorbidities or received medications that may have contributed to the decrease in WBC counts.

In summary, the data submitted by the Application demonstrate the overall similar safety profile of fidaxomicin and the comparator, vancomycin. No causal relationship between fidaxomicin and a particular category of adverse events has been clearly demonstrated. However, postmarketing monitoring of adverse events especially those related to GI hemorrhage, decreases in WBC counts, and in subjects with severe CDAD may provide additional information on the safety profile of fidaxomicin.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data for this review included all studies completed under the IND prior to August 2010 (Table 19 and Table 20). The safety population included subjects who took at least one dose of study drug and had at least one post-baseline assessment of vital signs, AE, or laboratory data. Overall, 676 patients received at least 1 dose of fidaxomicin. Five subjects received study drug but did not have any post-baseline safety assessment. There were 52 fidaxomicin-treated subjects in 3 drug interaction studies with results available after August 2010; these subjects were not included in the safety database. This was done after an agreement between the applicant and the review division, so as not to delay preparation of the integrated summary of safety (ISS) and submission of the NDA. The safety data in these studies were reviewed and would not have changed the safety conclusions from the ISS.

All statistical summaries were based on the safety population, except for subject disposition, which was based on all randomized subjects.

Table 19 Studies Included in the Safety Database

Study ID	Study Description	Treatment groups	No of subjects /Location
OPT-80 1A-SD	Phase 1A, single dose, double-blinded, randomized placebo-controlled, dose escalation study.	<ul style="list-style-type: none"> • Fidaxomicin 100 mg x 1 • Fidaxomicin 200 mg x 1 • Fidaxomicin 300 mg x 1 • Fidaxomicin 450 mg x 1 • Placebo x 1 	16; fidaxomicin (n=12) Placebo (n=4) /US
OPT-80 1B-MD	Phase 1B, multiple dose escalating safety study of OPT-80 in healthy volunteers	<ul style="list-style-type: none"> • Fidaxomicin 150 mg x 10 days • Fidaxomicin 300 mg x 10 days • Fidaxomicin 450 mg x 10 days • Placebo x 10 days 	24;fidaxomicin (n=18; 6 per dose group) placebo (n=6) /US
OPT-80-005	A Single Center, Open-Label, Randomized, Two-Period, Cross Over Study to Determine the Pharmacokinetics and the Effect Of Food on the Bioavailability of OPT-80 in Healthy Subjects and the Pharmacokinetics of a Lead-in Single Arm of 200 mg OPT-80 in Healthy Subjects.	<ul style="list-style-type: none"> • Fidaxomicin 200 mg x 1 • Fidaxomicin 400 mg – 2 single doses 7 days apart with and without food 	34 /US
OPT-80 Phase 2A	An Open-Label, Dose Ranging, Randomized Clinical Evaluation of OPT-80 in Patients with <i>Clostridium difficile</i> -associated Diarrhea (CDAD)	<ul style="list-style-type: none"> • Fidaxomicin 50 mg Q12h x 10 days • Fidaxomicin 100 mg Q12h x 10 days • Fidaxomicin 200 mg Q12h x 10 days 	48/16 in each treatment group /US and Canada
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 125 mg Vancomycin Taken q6h for Ten Days in Subjects with <i>Clostridium difficile</i> -Associated Diarrhea	<ul style="list-style-type: none"> • Fidaxomicin 200 mg Q12h x 10 days • Vancomycin 125 mg Q6h x 10 days 	623; fidaxomicin (n=300); vancomycin, (n=323) /US and Canada
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 125 mg Vancomycin Taken q6h for Ten Days in Subjects with <i>Clostridium difficile</i> -Associated Diarrhea	<ul style="list-style-type: none"> • Fidaxomicin 200 mg Q12h x 10 days • Vancomycin 125 mg Q6h x 10 days 	524; fidaxomicin (n=264) vancomycin (n=260) /US, Canada Belgium France Germany Italy Spain Sweden the UK

Table 20 Enumeration of Subjects for Fidaxomicin Development Program Safety Population, Cutoff Date: August, 2010

Clinical Trial Groups	Treatment Groups		
	Fidaxomicin	Active Control (Vancomycin)	Placebo
Completed Phase 1 (Clinical Pharmacology)			
Single Dose OPT-80 1A-SD	12	NA*	4
Multiple Dose OPT-80 1B-MD	18	NA	6
Single Dose OPT-80-005 (effect of food and bioavailability)	34	NA	NA
Phase 1 Subtotal	64	NA	10
Completed Phase 2A Clinical Trial of Proposed Indication			
	48	NA	NA
Completed Phase 3 Clinical Trials of Proposed Indication			
Study No. 101.1.C.003	300	323	NA
Study No. 101.1.C.004	264	260	NA
Phase 3 Subtotal	564	583	NA

* NA – not applicable

7.1.2 Categorization of Adverse Events

An adverse event (AE) was defined as:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any occurrence that was new in onset or aggravated in severity or frequency from the baseline condition
- Any deterioration in measurements of a laboratory value or other clinical test (e.g., ECG or X-ray) associated with clinical signs or symptoms judged by the investigator to have had a significant clinical impact or to have required treatment or any other therapeutic intervention, resulted in discontinuation of the study drug, discontinuation of the subject from the study, or required additional diagnostic evaluation

A laboratory value that increased in severity compared with baseline by 2 grades of the modified National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) (version 3.0) was recorded as an AE, with the exception of the following laboratory values: albumin, cholesterol, glucose, phosphate (phosphorous), and lymphocytes unless deemed significant by the investigator. An increase in severity of less than 2 NCI CTCAE grades was reported as an AE at the discretion of the investigator.

Surgical procedures were not considered AEs, but therapeutic measures for conditions that required surgery. The condition for which a surgery was required was an AE if it occurred, or was detected, during the study. A planned surgical measure permitted by the clinical study protocol and the condition leading to this measure were not AEs if the condition was known before the start of study treatment. In the latter case, the condition was reported as medical history.

Events reflecting the underlying disease state (CDAD) and not considered clinically significant in the opinion of the investigator (e.g., an increase in the number of UBMs) were not considered AEs. However, events that were medically important in the opinion of the investigator, including events that required intervention (e.g., pharmacologic intervention) that reflected the underlying condition (e.g., the development of bloody diarrhea), were reported as AEs.

Serious Adverse Events

An SAE was any untoward medical occurrence that at any dose:

- Resulted in death
- Was life-threatening in that the subject was at immediate risk of death from the AE as it occurred, except for events that, had they occurred in a more severe form or were allowed to continue, might have caused death
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity (e.g., a substantial disruption of a person's ability to carry out normal life functions)
- Was a congenital anomaly/birth defect in the child of a subject who was exposed to the study drug
- Was an important medical event

The following events were considered important medical events and therefore were reported as SAEs:

- Laboratory values that were within normal limits at baseline and increased in severity to meet the modified NCI CTCAE version 3.0 criteria of Grade 3 or higher
- Laboratory values that were outside normal limits at baseline and met the modified NCI CTCAE criteria of Grade 1 or 2 and increased in severity to Grade 4
- A newly diagnosed cancer

Medical Events of Interest

Two medical events were of particular interest:

- Overdose: If a subject took a dose that was higher than the highest dose allowed for that subject at any time (as stated in the protocol), the overdose was reported on the SAE form.
- Pregnancy

The incidence of TEAEs was summarized based on Medical Dictionary for Regulatory

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Activities (MedDRA) (Version 10) coded terms at the System Organ Class (SOC) and preferred term levels.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

All studies completed under the US IND #64,435 prior to August 2010 were analyzed for safety, Phase 1 (n=3), phase 2 (n=1) and 3 (n=2).

The applicant pooled the studies into two pools and one sub-pool:

- Pool 1 – all Phase 1 (n=3), phase 2 (n=1) and 3 (n=2) studies (Table 7.1.1 – 1).
- Pool 2 – Phase 2 and 3 studies
- Pool 2A – Phase 3 studies

Medical reviewer comments: This review will mainly focus on the results of Phase 3 trials.

The following analyses were conducted on Pool 1:

- Subject Disposition
- Demographics and Baseline Characteristics
- Exposure to Study Drug
- Treatment-Emergent Serious Adverse Events (SAEs)
- Treatment-Emergent Deaths
- All Treatment-Emergent Adverse Events (TEAEs)
- Treatment-Emergent Adverse Events (AEs) Leading to Discontinuation of Study Drug
- Treatment-Emergent Adverse Events Leading to Dose Modification and Use of Concomitant Medication
- 12-Lead Electrocardiogram (ECG) Analysis
- All Adverse Events Resulting in Death
- All Serious Adverse Events
- All Adverse Events Leading to Discontinuation of Study Drug
- All Adverse Events Leading to Dose Modification and Use of Concomitant Medication

The following safety analyses were conducted on Pool 2 and Pool 2A:

- Subject Disposition
- Demographics and Baseline Characteristics
- Exposure to Study Drug
- Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by Severity
- Treatment-Emergent Adverse Events by Relationship to Study Drug
- Treatment-Emergent Serious Adverse Events
- Treatment-Emergent Deaths
- All Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug

- Treatment-Emergent Adverse Events Leading to Dose Modification and Use of Concomitant Medication
- Treatment-Emergent Adverse Events Occurring in $\geq 2\%$ of Fidaxomicin-Treated Subjects (Pool 2A only)
- Treatment-Emergent Adverse Events Occurring in $\geq 3\%$ of Fidaxomicin-Treated Subjects (Pool 2A only; end-of-text table only)
- Related Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of Fidaxomicin-Treated Subjects (Pool 2A only)
- Plasma Levels of Fidaxomicin and its Main Metabolite OP-1118 (Pool 2A only)
- Laboratory Findings
- Electrocardiogram Findings
- Vital Signs
- Concomitant Medications

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall summary of exposure to study drug in phase 1, 2 and 3 trials is presented in Table 21. There were 676 subjects who received any dose of fidaxomicin including 580 subjects in phase 2 and 3 trials who received the dose of 200 mg PO BID recommended for CDI treatment.

Table 21 Summary of Exposure to Study Drug

Subjects	Fidaxomicin n (%)					Vancomycin n (%)
	100 - 200 mg	300 mg	450 mg	400 mg	Any dose	
Received ≥ 1 Dose	56	12	11	608	676	583
Discontinued the Study	7 (12.5)	0 (0)	1 (8.3)	81 (13.1)	88 (12.8)	96 (16.2)

Source: Integrated Summary of Safety (ISS) Table 14.1.1 – Revised Subject Disposition, edited)

The duration of study drug exposure was defined 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. Subjects could take greater than 11 days of study drug if they missed doses. The most tablets that could have been received by any subject were 11 days' worth.

In phase 3 trials, the mean duration of exposure to fidaxomicin 400 mg and to vancomycin 500 mg was 10.2 days (Table 22). The majority of subjects in both the fidaxomicin 400 mg (82.1%) and vancomycin (80.4%) groups were exposed to study

drug for 10 to 11 days. In the phase 1 and 2 trials, subjects were exposed to study drug for a mean of 6.8, 5.5, and 5.9 in the fidaxomicin 100-200 mg, fidaxomicin 300 mg, and fidaxomicin 450 mg groups, respectively.

Table 22 Summary of Exposure to Study Drug (Phase 3 Studies)

Duration of exposure (days)	Fidaxomicin 400 mg N=564 n(%)	Vancomycin 500 mg N=583 n (%)
N	564	583
Mean	10.2	10.2
S.D.	2.2	2.4
Median	11.0	11.0
Min, Max	1, 14	1,22
< 3 days	16 (2.8)	18 (3.1)
3-9 days	59 (10.5)	53 (9.1)
10-11 days	463 (82.1)	469 (80.4)
≥ 12 days	26 (4.6)	43(7.4)

Source: Applicant, ISS, Table 3.2-3

Medical reviewer comments: The extent and duration of exposure appears to be adequate to assess the safety of fidaxomicin.

The incidence of adverse events was analyzed in subjects who received study drug for more than 3 days vs. subjects who received study drug for less than 3 days. This cut-off was selected because it was specified in the Phase 3 protocols as the minimum required dosing duration for evaluation of treatment failures. There were 16 (2.8%) and 18 (3.1%) subjects in the fidaxomicin and vancomycin group who received study drug for less than 3 days. There were 548 (97.2%) and 565 (96.9%) subjects in the fidaxomicin and vancomycin group who received study drug for 3 or more days. Because no more than 20 doses of fidaxomicin were given and the majority of patients received the intended treatment course, no significant relationship was seen between adverse reactions and duration of exposure.

Medical reviewer comments: The low number of subjects exposed to < 3 days of study drug makes the interpretation of the exposure data in this group less informative.

7.2.2 Explorations for Dose Response

A more favorable response to the dose of 400 mg/day when compared with lower doses was observed in a Phase 2 study titled “An Open-Label, Dose Ranging, Randomized Clinical Evaluation of OPT-80 in Patients with Clostridium difficile-Associated Diarrhea (CDAD).” In this study subjects were randomized to receive either 100 (50 mg q12h), 200 (100 mg q12h), or 400 (200 mg q12h) mg/day for 10 days. There was an increase

in the rate of relief of symptoms of CDAD and increase in time to resolution of diarrhea at each higher dose level.

A total of 49 subjects were enrolled. There were 47 subjects in the modified intent-to-treat (mITT) population: 16 subjects in the 100 mg treatment group, 16 subjects in the 200 mg treatment group, and 15 subjects in the 400 mg treatment group. 45 subjects were evaluable for clinical cure at end of therapy. No treatment failures occurred in the 400 mg/day treatment group. Four treatment failures were observed in this study, 2 in each of the 200 mg/day and 100 mg/day treatment groups.

A dose response was observed for the relief of CDAD, with the most favorable response seen in the 400 mg/day treatment group, where a large majority of subjects experienced total relief of symptoms (13/15; 86.7% subjects) compared to those who did not experience relief (2/15; 13.3% subjects). In the 200 mg/day treatment group, more subjects had total relief (8/16; 50.0% subjects) than did not experience relief (6/16; 37.5% subjects). More subjects in the 100 mg/day treatment group did not have relief of symptoms of CDAD than those who had their symptoms relieved (9/16; 56.3% subjects vs. 6/16; 37.5% subjects, respectively). Across the treatment groups, time to relief of diarrhea appeared to decrease with increasing dose. The estimated median time to relief was 5.5 days, 3.5 days, and 3.0 days for the PAR-101 100 mg/day, 200 mg/day and 400 mg/day treatment groups, respectively. Two subjects (1 subject in the 100 mg/day treatment group and 1 subject in the 400 mg/day treatment group) experienced clinical recurrence.

In general, considering all parameters, clinical cure, relief of symptoms of CDAD, recurrence rates, time to resolution of diarrhea, and persistence of toxin positive diarrhea at end of therapy, a dose response was suggested. No adverse impact on safety was noted with increasing dose.

7.2.3 Special Animal and/or In Vitro Testing

The safety of fidaxomicin has been evaluated in genotoxicity, safety pharmacology, reproductive toxicity, and general toxicology (up to 3 months repeated dosing in the dog) studies. Overall, fidaxomicin at plasma or fecal exposure levels considerably higher than plasma concentrations in humans at the therapeutic dose showed no fidaxomicin-related toxicity or adverse pharmacological activity in preclinical studies.

No observed adverse effect levels (NOAEL) were achieved in the definitive toxicology studies at fidaxomicin exposure levels which were at least 100-fold (dog 3-month toxicity, NOAEL) or 30-fold (rat and rabbit reproductive toxicity, no observed effect level [NOEL]) above the human plasma concentrations at the therapeutic dose, based on both the maximum plasma concentration (C_{max}) and area under the curve (AUC). Body weights, food consumption, clinical pathology parameters, electrocardiography parameters and organ weights were unaffected by test article administration when

fidaxomicin was administered to Beagle dogs for a minimum of 91 days at dosage levels of 48 tablets a day (9.6 g/animal/day).

Carcinogenicity studies were not conducted for fidaxomicin. Although fidaxomicin tested positive in the in vitro Chinese hamster ovary (CHO) chromosomal aberration assay, it was negative in the in vitro bacterial reverse mutation assay and the in vivo micronucleus study, and the weight of evidence of the overall data support that fidaxomicin is not expected to be genotoxic in humans.

The effects of fidaxomicin on embryo-fetal development were studied in rats and rabbits. No maternal and developmental toxicity was observed for any of the doses of fidaxomicin used in these studies.

No specific studies on the hematopoietic effects of fidaxomicin have been conducted, although hematology was assessed as part of all definitive general toxicity studies and no impact on hematology was observed.

Medical Reviewer comments: The non-clinical program appears adequate to explore potential adverse reactions. Overall, no specific safety concerns were demonstrated in the animal toxicology studies.

7.2.4 Routine Clinical Testing

The schedule of assessments in phase 3 trials is presented in Appendix 1.

Medical reviewer comments: the clinical testing, including physical examination and laboratory parameters appear adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Fidaxomicin is poorly absorbed and is metabolized primarily by esterase dependent metabolism to OP-1118. The majority of the fidaxomicin dose is excreted in the feces as unchanged fidaxomicin or unmetabolized OP-1118. Following a single dose of 200 mg fidaxomicin in humans, more than 92% of the dose was recovered in the stool as fidaxomicin or its metabolite OP-1118. In dogs less than 1% of the administered fidaxomicin dose was excreted in bile. No human bile excretion studies were performed. In humans, 0.59% of the fidaxomicin dose was recovered in urine.

Plasma concentrations of fidaxomicin and its main metabolite OP-1118 are in the ng/mL range in humans at the therapeutic dose. In healthy adults, maximum concentration (C_{max}) was approximately 9.88 ng/mL with the peak concentration occurring 3.25 hours after dosing and a half life of 11.8 hours. In CDAD patients, average peak plasma concentrations of fidaxomicin and OP-1118 tend to be 2- to 6-fold higher than in healthy adults. Fidaxomicin and OP-1118 plasma concentrations were similar at Day 1 and following administration of the drug 200 mg every 12 hours for 10 days.

Fidaxomicin is a substrate for efflux transporters (e.g. P-glycoprotein) as well as an inhibitor of efflux of the P-glycoprotein (P-gp) substrate, digoxin. It has been demonstrated that co-administration of fidaxomicin and cyclosporine increased absorption of fidaxomicin.

Metabolism of fidaxomicin is not dependent on CYP enzymes. However, fidaxomicin and its primary metabolite, OP-1118, have the ability to inhibit cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4/5 *in vitro*. Clinical studies in which CYP 175 substrates warfarin, midazolam, and omeprazole were co-administered with fidaxomicin showed no significant effect of fidaxomicin on the pharmacokinetics of these drugs. Based on these results, no dose adjustment of either drug is recommended when fidaxomicin is co-administered with CYP substrate compounds.

Medical Reviewer Comments: more detailed discussions of drug-drug interaction studies and analysis of safety and efficacy of fidaxomicin are provided in Section 7.5.5 Drug- Drug Interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Fidaxomicin structure classifies it as a macrolide. Due to its minimal absorption fidaxomicin may not exhibit the expected spectrum of adverse events associated with macrolides. However, the following macrolides-related adverse events should be kept in mind when reviewing the safety of fidaxomicin:

- Gastrointestinal effects: nausea, vomiting, diarrhea, dyspepsia, and melena
- Liver toxicity: cholestatic hepatitis
- Drug interactions through cytochrome P 450 enzymes inhibition

7.3 Major Safety Results

Tables 23 and 24 present overall summaries of TEAEs in all studies and in phase 3 studies only, respectively.

Table 23 Summary of Treatment-Emergent Adverse Events in Phase 1, 2 and 3 studies

Subjects with ≥1 TEAE	Fidaxomicin						Vancomycin
	Placebo (N=10) n (%)	100-200 mg (N=56) n (%)	300 mg (N=12) n (%)	400 mg (N=608) n (%)	450 mg (N=11) n (%)	Any dose (N=676) n (%)	(N=583) n (%)
All TEAEs	3 (30)	19 (34)	0	395 (65)	2 (18)	416 (61.5)	382 (65.5)
Deaths	0	1 (1.8)	0	36 (5.9)	0	37 (5.5)	38 (6.5)

Adapted from ISS, Table 5.3-4, edited.

Table 24 Summary of Treatment-Emergent Adverse Events: Phase 3 Studies

Subjects with ≥1 TEAE	Fidaxomicin (N=564) n (%)	Vancomycin (N=583) n (%)
All Treatment-Emergent Adverse Events	385 (68.3%)	382 (65.5%)
Mild	160 (28.4)	171 (29.3)
Moderate	117 (20.7)	113 (19.4)
Severe	108 (19.1)	98 (16.8)
TEAE Related to Study Drug	60 (10.6)	65 (11.1)
TEAE Not Related to Study Drug	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)

Applicant ISS Table 5.3-3

In phase 3 trials the incidence of related and not related TEAEs was similar for the fidaxomicin and vancomycin groups. The incidences of related and not-related TEAEs were 10.6% vs. 11.1% and 57.6% vs. 54.4% for the fidaxomicin and vancomycin groups, respectively.

The related TEAEs reported at the highest incidences in the fidaxomicin group were nausea in 15 (2.7%) subjects; constipation and vomiting in 7 (1.2%) subjects; dizziness in 5 (0.9%) subjects; alanine aminotransferase increased and anorexia in 4 (0.7%) subjects; dysgeusia and headache in 3 (0.5%) subjects; and abdominal distension, dry mouth, and flatulence in 2 (0.3%) subjects.

Treatment-related TEAEs reported at the highest incidences in the vancomycin group were nausea in 20 (3.4%) subjects; pruritis in 5 (0.9%) subjects; vomiting in 8 (1.4%) subjects; hypokalemia and headache in 4 (0.7%) subjects; constipation and dysgeusia in 3 (0.5%) subjects; and upper abdominal pain, AST increased, pyrexia, and peripheral edema in 2 (0.3%) subjects

Medical Reviewer comments: The overall incidence of adverse events in the fidaxomicin and vancomycin patients appears to be similar.

7.3.1 Deaths

The incidence of TEAEs resulting in death in phase 3 trials was similar for subjects in the fidaxomicin and vancomycin groups, [36 (6.4%) and 38 (6.5%)]. There was one death in a Phase 2A trial.

The SOCs with the highest incidence of TEAEs resulting in death reported in the fidaxomicin and vancomycin groups, respectively, were infections and infestations

(2.0% and 1.9%); respiratory, thoracic, and mediastinal disorders (1.6% and 0.5%); and neoplasms benign, malignant and unspecified (0.9% and 0.5%).

The TEAEs resulting in death reported at the highest incidences in the fidaxomicin 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 vancomycin group were sepsis in 4 (0.7%) subjects; and multi-organ failure in 3 (0.5%) subjects.

All of the TEAEs leading to deaths were assessed by the investigator as not related or unlikely related to study drug. The reviewer deemed that nine deaths in Phase 3 trials could possibly be related to study drug; five deaths occurred in the fidaxomicin group (subjects 003-016005, 004-025008, 004-057022, 004-088026, 004-154002, and 004-172019) and four deaths in the vancomycin group (patients 003-010029, 003-011033, 004-049002, and 004-178004). Deaths in both groups were attributed to possible lack of efficacy of study drug.

Thirteen deaths, seven in the fidaxomicin and six in vancomycin groups, were deemed unlikely related to study drug. The other deaths were considered not related to study drug but to the underlying medical conditions. The death in Phase 2 trial was considered not related to study drug.

The majority of deaths in phase 3 trials occurred during first 30 study days. There were 26 and 29 deaths in the fidaxomicin and vancomycin groups, respectively, which occurred within 30 study days.

Fifty two patients with an outcome of death had information on their baseline strain of *C. difficile* (BI vs. non-BI), 27 in the fidaxomicin and 25 in the vancomycin groups. Among these patients, there were 17/27 (63%) and 11/25 (44%) fidaxomicin and vancomycin patients with BI-strains by REA analysis.

A listing of deaths is presented in Table 25. Selected narratives of the deaths are provided as well.

Table 25 By Subject Listing of Deaths Reported at Any Time in Phase 2 and 3 Fidaxomicin trials: Safety Population

Subject ID	Age Sex	Days on Study Drug	Study Day of Death	Cause of death Event preferred term	Relationship to Study Drug		
					Applicant-Defined	Reviewer - Defined	Suggested Relationship
Study 101.1.C.003 Fidaxomicin							
005004	92M	11	19	Pneumonia	Not related	Not related	
009024	79F	6	19	Acute myeloid leukemia	Not related	Not related	
011052	81M	6	8	Multi-organ failure	Not related	Not related	
016005*	79F	11	55	Sepsis syndrome / Pseudomembranous colitis	Not related	Possibly related	Lack of efficacy
016008	36F	11	36	Adrenal gland cancer metastatic	Not related	Not related	
017004	83M	11	26	Chronic obstructive pulmonary disease	Not related	Not related	
017008	49F	11	19	Renal cell carcinoma stage unspecified	Not related	Not related	
020002*	86M	9	29	Gastrointestinal hemorrhage	Not related	Unlikely related	
028001	68M	7	36	Bacteremia	Not related	Not related	
081002	62M	11	44	Vascular graft occlusion	Not related	Not related	
132004	94F	4	10	Cardiac failure congestive	Not related	Not related	
136004	58F	9	28	Respiratory failure	Not related	Not related	
137014	76F	4	7	Sepsis / Pneumonia	Not related	Not related	
140003	59F	3	28	Pneumonia aspiration	Not related	Unlikely related	
160013	90F	1	2	Pneumonia	Unlikely related	Unlikely related	
177008*	84F	11	27	Renal failure acute	Not related	Unlikely related	
Study 101.1.C.003 Vancomycin							
001016	82M	11	23	Sepsis / Pneumonia	Not related	Not related	
002021	61M	7	8	Lung cancer metastatic	Not related	Not related	
002029	87F	5	7	Respiratory failure	Not related	Not related	
006009	63M	4	4	Escherichia sepsis	Not related	Not related	
007001*	92F	11	23	Myocardial infarction and Colitis ischaemic	Unlikely related	Unlikely related	

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009001	53FF	11	25	Cardiac arrest	Not related	Not related	
009056	78F	7	36	Cardiogenic shock	Not related	Not related	
010029*	74F	8	10	Septic shock	Not related	Possibly related	Lack of efficacy
011033*	76M	4	11	Sepsis	Unlikely related	Possibly related	Lack of efficacy
011050	68F	11	46	Urosepsis	Not related	Not related	
011055*	41M	8	24	Large intestine perforation	Not related	Unlikely related	
013030	87M	11	22	Manutrition	Not related	Not related	
017002	90F	11	39	Failure to thrive	Not related	Not related	
030002	55F	2	3	Cardiogenic shock	Not related	Not related	
045002	28F	3	7	Endometrial cancer	Not related	Not related	
048001	65M	7	9	Peritonitis	Not related	Not related	
100003	71F	8	9	Respiratory failure	Not related	Not related	
136003	93F	4	12	Dehydration	Not related	Not related	
137022	79M	3	4	Myocardial infarction	Not related	Not related	
160004	82F	2	2	Sepsis	Unlikely related	Unlikely related	
160011	82M	11	19	Ascites / Colon cancer metastatic	Unlikely related	Unlikely related	
Study 101.1.C.004 Fidaxomicin							
025008*	81F	6	16	Respiratory failure / Megacolon	Not related	Possibly related	Lack of efficacy
049004	94M	11	33	Renal Failure /Drug withdrawal therapies	Not related	Not related	
055004	63M	10	44	Peritonitis / Colon cancer	Not related	Not related	
057016	66F	7	7	Gallbladder cancer	Not related	Not related	
057022*	89M	5	12	Gastrointestinal perforation	Unlikely related	Possibly related	Lack of efficacy
057035	89M	10	54	Peripheral ischemia / Drug withdrawal therapies	Unlikely related	Unlikely related	
064001	89M	11	29	Colon cancer	Not related	Not related	
069009	83M	11	67	Sepsis	Not related	Not related	
070026	74M	11	22	Respiratory failure	Not related	Not related	
088026	58M	5	20	Neutropenic sepsis	Not related	Unlikely related	
088028	74F	11	35	Bronchopulmonary aspergillosis	Not related	Not related	
093003*	78M	11	50	Septic shock	Unlikely related	Not related	
098001	69M	2	2	Myocardial infarction	Unlikely related	Unlikely related	
154002*	72M	4	23	Renal Failure / Pseudomembranous colitis	Not related	Possibly related	Lack of efficacy
169014	87F	11	15	Respiratory arrest	Not related	Not related	

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172007	77F	11	25	Chronic obstructive pulmonary disease	Not related	Not related	
172019*	83M	11	31	Sepsis / Clostridium difficile sepsis	Not related	Possibly related	Lack of efficacy
172023	88F	11	25	Pneumonia	Not related	Not related	
173003	90F	3	26	Respiratory failure	Not related	Not related	
181004	76F	11	15	Respiratory distress / Myocardial infarction	Not related	Not related	
Study 101.1.C.004 Vancomycin							
003007	82M	1	9	Urosepsis	Not related	Not related	
030001	77F	11	17	Cerebral infarction	Unlikely related	Unlikely related	
049002*	85F	7	8	Pneumonia	Not related	Possibly related	Lack of efficacy
055002	74M	3	9	Euthanasia	Not related	Not related	
064003	63F	11	26	Small intestinal obstruction / Ovarian cancer	Not related	Not related	
070025	59M	11	38	Sepsis / Pneumonia fungal	Not related	Not related	
086003	77F	8	35	Multi-organ failure	Unlikely related	Unlikely related	
088011	75F	1	31	Multi-organ failure	Not related	Not related	
088020	71F	11	38	Multi-organ failure / Infective endocarditis	Not related	Not related	
092002	76F	10	20	Cardio-respiratory arrest / Pneumonia	Not related	Not related	
172006	65M	3	21	Small intestinal obstruction / Colo-rectal cancer	Not related	Not related	
172014	82F	11	18	Lung neoplasm malignant	Not related	Not related	
175002	82M	11	11	Cardiopulmonary arrest	Not related	Not related	
178004*	50M	5	33	Septic shock	Not related	Possibly related	Lack of efficacy
178015	67F	11	37	Tachypnea	Not related	Not related	
180003	76M	9	9	Intestinal obstruction	Not related	Not related	
180011	92F	11	35	Pneumonia	Not related	Not related	
Phase 2 Study OPT-80 P2A Fidaxomicin							
006200	85F	8	16	Cerebral hemorrhage	Not related	Not related	

Adapted from ISS Table 5.4-1, Listing 16.2.7.1.2, CRFs and case narratives

* Case narrative is provided

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Selected Narratives of Deaths

Subject 003-016005
Study drug: Fidaxomicin

This 79-year-old female was declared a clinical failure after receiving 11 days of study therapy due to persistent diarrhea and pseudomembranous colitis found on sigmoidoscopy. The patient received repeated courses of intravenous metronidazole and oral vancomycin but continued to have diarrhea and colonoscopic signs of pseudomembranous colitis. She subsequently developed acute renal failure, septic shock and died on study day 55.

Medical reviewer comments: in this case of refractory C. difficile infection, the lack of efficacy of the study drug could possibly be related to the outcome of death since the patient failed initial therapy of CDAD and finally died from complications of C. difficile infection.

Subject 003-020002
Study drug: Fidaxomicin

This 85-year-old male with diverticulosis, an episode of GI hemorrhage two weeks prior to enrollment and continuous black stools at the time of enrollment was declared a clinical failure after 9 days of study therapy. Colonoscopy on study day 10 was consistent with pseudomembranous colitis. The patient was treated with vancomycin and nitazoxanide for CDAD. He subsequently developed more episodes of GI hemorrhage. Upper endoscopy and colonoscopy on study day 21 showed diverticulosis, internal hemorrhoids, and no active bleeding. The patient continued to decline with poor oral intake and worsening respiratory status thought to be related to aspirations. The patient was changed to hospice care and died on day 29 reportedly from another episode of GI hemorrhage. The event was reported as severe and serious.

Medical reviewer comments: The death of this patient and the event of GI hemorrhage, were unlikely related to study drug but rather to underlying comorbidities.

Subject 003-177008
Study drug: Fidaxomicin

This 84-year-old female with a history of diabetes mellitus and chronic renal insufficiency was declared a cure after an 11-day course of study medication. Her creatinine was 1.4 mg/dL (approximate normal range 0.5-1.1) and 0.7 mg/dL on the first and the last day of therapy, respectively. Thirteen days after completion of therapy (study day 23) the patient was diagnosed with recurrence of CDAD and started oral vancomycin and rifaximin. The same day she was noted to have creatinine of 2 mg/dL and estimated GFR of 24 (Normal range >60 mL/min). The subject's renal failure continued to worsen with creatinine of 2.8 on study day 26 when according to her wish

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the patient was started on comfort care. The patient died on study day 28 from renal failure.

Medical reviewer comments: The study drug was unlikely related to the death of this patient. However, the recurrence of CDAD could have triggered acute renal failure.

Subject 003-007001
Study drug: Vancomycin

This 92-year-old white female received oral vancomycin for *Clostridium difficile* infection for 11 days with resolution of CDAD. On study day 20, ten days after the completion of CDAD therapy, she was found unresponsive and hypotensive. In addition, she started having bloody bowel movements. The patient was determined to have ischemic colitis. The patient received comfort care and subsequently died on study day 23. No *C. difficile* stool toxin assays were obtained after the onset of bloody bowel movements and no autopsy results were reported.

Medical reviewer comments: the study drug was unlikely related to this patient death. The clinical presentation is not consistent with recurrence of CDAD but more compatible with ischemic colitis or possibly diverticular bleeding.

Subject 003-010029
Study drug: Vancomycin

This 74-year-old white female was admitted to the hospital with vomiting, diarrhea and hypotension and she was considered to be in septic shock. She subsequently tested positive for CDAD and was started on study drug the next day. Her condition continued to deteriorate. The patient required vasopressors and was intubated on study day 6. The study medication was stopped on study day 8 due to treatment failure. The patient's condition continued to worsen. She expired from septic shock on study day 10.

Medical reviewer comments: the study drug may possibly be related to the death due to lack of efficacy.

Subject 003-011033
Study drug: Vancomycin

This 76-year-old male was declared a clinical failure on study day 4 when he developed hypotension, respiratory failure, and required intubation. The subject continued to have diarrhea at that time. CDAD therapy was changed to vancomycin via nasogastric tube and intravenous metronidazole. The patient's conditions continued to worsen and he died on study day 11 from septic shock.

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Medical reviewer comments: the study drug could possibly be related to the outcome of death due to lack of efficacy. The patient failed initial CDAD therapy which may have contributed to progression of sepsis resulting in septic shock and death.

Subject 003-011055
Study drug: Vancomycin

This 41-year-old patient with a history of progressive T-cell lymphoma was declared a clinical failure due to continuous diarrhea after 8 days of treatment with study medication. The patient was initiated on oral metronidazole in addition to piperacillin/tazobactam and intravenous vancomycin. On study day 18 the patient was diagnosed with a transverse colon perforation and underwent emergency colectomy. The biopsy of the colon demonstrated T-cell lymphoma. The patient's condition continued to deteriorate, the treatment eventually was limited to comfort measures only and the patient expired on study day 24.

Medical reviewer comments: the study drug is unlikely related to this patient's bowel perforation and death which was primarily related to the underlying disease, specifically to T-cell lymphoma involving the colon.

Subject 004-025008
Study drug: Fidaxomicin

This 81-year-old woman was switched to intravenous metronidazole and oral vancomycin due to treatment failure and progression of CDAD on study day 6. On study day 9 the patient underwent subtotal colectomy for toxic megacolon. The patient's condition continued to worsen and she expired on study day 16.

Medical reviewer comments: This subject failed initial therapy of CDAD which eventually resulted in toxic megacolon and death. The study drug could be possibly related to the outcome of death due to lack of efficacy.

Subject 004-057022
Study drug: Fidaxomicin

This 89-year-old male was declared a clinical failure after a 5-day course of study drug due to persistent diarrhea. The patient was started on oral vancomycin and intravenous metronidazole. On study day 9 the patient was diagnosed with bowel perforation. It was concluded that the patient was not fit for surgery. The patient deemed to be a poor surgical candidate. Her condition continued to deteriorate and the patient expired on study day 12. Autopsy was not performed.

Medical reviewer comments: This patient died from complications of C. difficile infection after he had failed therapy with study drug. The study drug may possibly be related to the outcome of death due to lack of efficacy.

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Subject 004-093003
Study drug: Fidaxomicin

This 78-year-old male with multiple myeloma and chronic renal insufficiency was declared cured from CDAD after receiving an 11-day course of study medication. Seven days after completing the study drug (study day 18) the patient became febrile and started on ceftriaxone and ofloxacin for possible urinary tract infection. These medications were continued for 10 days. No recurrence of CDAD was documented and no additional therapy for CDAD was administered. On study day 45 the patient was diagnosed with *Staphylococcus aureus* skin ulcers, his condition continued to worsen and on study day 51 he died from septic shock.

Medical reviewer comment: this patient with a cure and non-recurrence of CDAD died from septic shock on study day 50. It is the opinion of the medical officer, that the death was not related to the study drug.

Subject 004-154002
Study drug: Fidaxomicin

This 72-year-old male with a history of end-stage renal disease requiring hemodialysis was declared a clinical failure after four days of therapy with the study drug. The patient continued to have diarrhea and on study day 4 developed hypotension requiring vasopressors. CT scan of the abdomen demonstrated significant colitis of ascending and transverse colon. CDAD therapy was changed to oral vancomycin and intravenous metronidazole. The subsequent course was complicated by myocardial infarction and pulmonary edema that occurred on study day 15. On study day 22 the patient decided to discontinue hemodialysis and subsequently died.

Medical reviewer comment: the initial failure to control CDAD may have complicated clinical course of this patient and contributed to the outcome of death. Thus, the study drug may possibly be related to this patient's death due to lack of efficacy.

Subject 004-172019
Study drug: Fidaxomicin

This 83-year-old male was initially successfully treated with an 11-day course of study drug. She had a recurrence of CDAD on study day 26 confirmed by positive toxin assay. The patient was hospitalized in a non-affiliated facility with severe *C. difficile* colitis, hypotension and coma. The investigators were later informed by the treating hospital that the patient had sepsis and died on study day 31. Autopsy was not performed.

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Medical reviewer comments: This patient died from sepsis seemingly related to severe recurrent C. difficile infection. The study drug may be possibly related to the outcome of death due to lack of efficacy.

Subject 004-049002
Study drug: Vancomycin

This 85-year-old female had continuous diarrhea and developed hypotension, respiratory failure, oliguria, and metabolic acidosis on study day 6. On study day 7 the patient was withdrawn from the study, changed to palliative care and then died on study day 8.

Medical reviewer comments: This patient continued to have persistent symptoms of C. difficile infection which likely contributed to the deterioration of her condition. Thus, the study drug may possibly be related to this patient's death due to lack of efficacy.

Subject 004-178004
Study drug: Vancomycin

This 50-year-old male with hepatitis C, cirrhosis, portal hypertension and hepatic encephalopathy had a recurrence of CDAD by study day 27, associated with worsening liver insufficiency and acute renal failure. The patient developed septic shock and died on study day 33.

Medical reviewer comments: The death of this patient appears could possibly be related to lack of efficacy of vancomycin resulting in recurrence of CDAD and subsequent death.

Overall, no differences in outcomes of death were found in a comparison of the two treatment groups. Due to small numbers, the significance of an increased number of deaths among fidaxomicin patients with BI strain of C. difficile at baseline is difficult to interpret.

7.3.2 Nonfatal Serious Adverse Events

The incidence of treatment-emergent serious adverse events in phase 3 trials was 25.7% and 23.2% in the fidaxomicin and vancomycin group, respectively. In phase 1 and 2 trials 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. The incidence of selected adverse events by MedDRA system organ class (SOC) and preferred terms is presented in Table 26.

Table 26 Incidence of Selected Serious Adverse Events: Phase 3 trials

System Organ Class Preferred Term	Fidaxomicin N=564 n (%)	Vancomycin N=583 n (%)
No of subjects with ≥ 1 SAE	145 (25.7)	135 (23.2)
Blood and lymphatic system disorders	13 (2.3)	8 (1.4)
Anemia	4 (0.7)	2 (0.3)
Granulocytopenia	0	1 (0.2)
Leukocytosis	0	1 (0.2)
Leukopenia	4 (0.7)	1 (0.2)
Lymphopenia	3 (0.5)	2 (0.3)
Febrile neutropenia	1 (0.2)	0
Neutropenia	4 (0.7)	0
Thrombocytopenia	3 (0.5)	2 (0.3)
Gastrointestinal disorders	26 (4.6)	24 (4.1)
Megacolon	3 (0.5)	0
Colitis	2 (0.4)	0
Gastrointestinal perforation	1 (0.2)	0
Large intestine perforation	0	2 (0.3)
Diarrhea hemorrhagic	2 (0.4)	0
Gastrointestinal hemorrhage	4 (0.7)	1 (0.2)
Upper gastrointestinal hemorrhage	0	1 (0.2)
Esophageal varices hemorrhage	0	1 (0.2)
Colitis ischemic	0	1 (0.2)
Crohn's Disease	1 (0.2)	0
Ileus / Ileus paralytic	0	2 (0.3)
Vomiting	2 (0.4)	3 (0.5)
Nausea	1 (0.2)	0
Infections and infestations	45 (8)	50 (8.6)
Clostridium difficile colitis	8 (1.4)	9 (1.5)
Clostridial infection	1 (0.2)	2 (0.3)
Clostridium difficile sepsis	0	1 (0.2)
Sepsis	7 (1.2)	5 (0.9)
Sepsis Syndrome	1 (0.2)	0
Septic shock	1 (0.2)	2 (0.3)
Neutropenic sepsis	1 (0.2)	0
Abdominal sepsis	1 (0.2)	0
Abdominal abscess	1 (0.2)	0
Investigations	24 (4.3)	11 (1.9)
Lymphocyte count decreased	4 (0.7)	1 (0.2)
Lymphocyte count abnormal	0	1 (0.2)
Neutrophil count decreased	2 (0.4)	0
White blood count decreased	2 (0.4)	0
Alanine aminotransferase increased	2 (0.4)	2 (0.4)
Aspartate aminotransferase increased	1 (0.2)	1 (0.2)
Liver function test abnormal	2 (0.4)	1 (0.2)
Hepatic enzyme increased	1 (0.2)	1 (0.2)
Blood alkaline phosphatase increased	1 (0.2)	0
Blood bicarbonate decreased	1 (0.2)	0
Electrocardiogram QT prolonged	0	1 (0.2)
Congenital, familial and genetic disorders	1 (0.2)	0
Cleft palate	1 (0.2)	0

Anaphylactic reaction	1 (0.2)	0
Metabolism and nutrition disorders	27 (4.8)	28 (4.8)
Hypokalemia	2 (0.4)	6 (1)
Dehydration	2 (0.4)	4 (0.7)
Metabolic acidosis	1 (0.2)	1 (0.2)
Hypophosphatemia	5 (0.9)	1 (0.2)
Pregnancy, peripartum and perinatal conditions**	1 (0.2)	0
Intra-uterine death	1 (0.2)	0
Pregnancy	1 (0.2)	0

Adapted from ISS Tabke 5.3-22.

For subjects in the fidaxomicin and vancomycin groups, respectively, the highest incidence of treatment-emergent SAEs occurred in the following SOCs: infections and infestations (8.0% and 8.6%); metabolism and nutrition disorders (4.8% and 4.8%); gastrointestinal disorders (4.6% and 4.1%); and investigations (4.3% and 1.9%).

Serious TEAEs related to gastrointestinal bleeding were reported more often in the fidaxomicin group (6) than in the vancomycin group (3). Further analysis of these events is provided in section 7.3.4 - Significant Adverse Events).

More serious adverse events related to decrease in WBC indices were found in the fidaxomicin group than in the vancomycin group. The total number of serious adverse events reported with preferred terms of febrile neutropenia, granulocytopenia, leukopenia, lymphopenia, neutropenia, neutropenic sepsis, lymphocyte count abnormal, lymphocyte count decreased, neutrophil count decreased, and white blood cell count decreased were 21 (3.7%) and 11 (1.9%) in the fidaxomicin and vancomycin groups, respectively. No abnormal shifts in hematology values were reported for subjects in the fidaxomicin 100-200 mg group. Further analysis of adverse events related to decrease in WBC counts is provided in section 7.4.2 Laboratory findings.

Overdose / Duodenal Perforation

Patient ID: 003-137011
Study drug: Fidaxomicin

This 64-year-old male without reported history of peptic ulcer disease received all four doses of study drug at once on day 3 of study drug therapy without any immediate adverse reactions. The same day the patient was withdrawn from the study and started on vancomycin 125 mg PO QID. Past medical history included renal cell cancer with spinal metastases, coronary artery disease, hyperlipidemia and hypertension. Concomitant medications included enteric coated aspirin, atorvastatin, metoprolol, and intravenous potassium chloride.

On the next day after overdose the patient developed hypotension, anuria and required intubation. On study day 5 his condition remained critical; the patient was taken to the

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operating room and diagnosed with perforated duodenal ulcer. Subsequently, his conditions slowly improved.

Subject's day 1 postdose fidaxomicin and OP-1118 plasma concentrations were 17.7 mg/dL and 89.1 ng/mL, respectively. Study day 3 post-therapy fidaxomicin and OP-1118 plasma concentrations were 69.5 mg/dL and 125 ng/mL, respectively. Fecal concentrations of fidaxomicin and its metabolite were not obtained.

Medical reviewer comments: Perforation of duodenal ulcer coincided with study drug overdose. The study drug could possibly be related to duodenal perforation in this patient. According to the applicant's definitions, the subject had high plasma concentrations of fidaxomicin and its metabolite (fidaxomicin plus OP-1118 plasma concentrations \geq 150 ng/mL). However, association of the plasma levels of study drug and its metabolite to duodenal perforation is unclear.

Pregnancy

Patient ID: 003-009021
Study drug: Fidaxomicin

This 19-year-old female with precursor B cell acute lymphocytic lymphoma had a negative serum pregnancy test on study day 1 (b) (6). Three weeks prior to enrollment the patient received vincristine and methotrexate for lymphoma treatment. Two weeks prior to enrollment she received ceftazidime and intravenous clindamycin for neutropenic fever and a skin infection. Her last menstrual period occurred two weeks prior to study entry.

The patient completed the course of study drug through study day 11 (b) (6) with resolution of CDAD. Other medications during the treatment period included nystatin, chlorhexidine orally for esophagitis, sucralfate, famotidine, and diphenhydramine. During a follow-up visit on study day 25 (b) (6) a serum pregnancy test was positive. The patient decided to stop treatment for lymphoma and continue with pregnancy.

The subject's first trimester ultrasound on (b) (6) showed 5 live intrauterine fetuses and the growth of each fetus was within normal limits. An ultrasound on (b) (6) revealed four fetuses with positive cardiac pulsations and one without cardiac pulsation, consistent with fetal demise. On (b) (6), at 18 weeks of pregnancy, the patient spontaneously delivered one fetus. An ultrasound showed that 1 of the remaining 4 fetuses had no heartbeat. On (b) (6) the patient delivered 3 live and 1 deceased fetuses. One female fetus was found to have a cleft palate and extensive autolysis of organs.

Medical reviewer comments: The relationship of fetal death and congenital anomalies and the study drug in this patient are uncertain. The patient was exposed to

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methotrexate and vincristine which are known to cause fetal harm. The patient completed these medications prior to enrollment but adverse effects of methotrexate and vincristine on fetuses are still possible.

Anaphylactic reaction

Patient ID: 003-002-007
Study drug: Fidaxomicin

This 66-year-old male with a history of aortic valve replacement, on warfarin, was given subcutaneous injection of vitamin K and fresh frozen plasma for elevated normalization ratio on study day 2. In 20-30 minutes after initiation of treatment the patient developed nausea, vomiting, and hypotension requiring vasopressors. The symptoms resolved in 3.5 hours and vasopressors were stopped. The patient continued to receive the study drug and completed an 11-day course of study treatment with an outcome of cure. The investigator deemed that anaphylactic reaction was not related to study drug.

Medical reviewer comments: Anaphylactic reaction was most likely not related to study drug but rather to fresh frozen plasma or vitamin K. Moreover, subsequent uneventful administration of fidaxomicin argues against its relationship to anaphylactic reaction.

Megacolon

Three subjects in the fidaxomicin group and none in the vancomycin group were reported to develop megacolon. All cases of megacolon were caused by BI strains of *C. difficile* and occurred in subjects with severe baseline disease. The severity of CDI was defined according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) severity categorization{Bauer, 2009 #552}, 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.

Two cases of megacolon in the fidaxomicin group were considered possibly related to study drug by the medical reviewer (subject ID 003-048003 and 004-025008). The study drug in these subjects was discontinued due to treatment failure after 3 and 6 days of therapy, respectively. Both subjects then underwent colectomy. The subject 003-048003 recovered and the subject 004-025008 died on study day 16. The third case of megacolon in the fidaxomicin group, subject 003-010002, was deemed unlikely related to study drug. This subject had received only two doses of fidaxomicin before his conditions worsened and urgent colectomy was performed the next day.

Further review of the adverse event dataset and case narratives by the medical reviewer revealed a patient in the vancomycin group (subject ID 004-177002) whose presentation may represent a case of megacolon. This patient entered the study with WBC of $46.6 \times 10^9/L$ and signs of pancolitis on CT scan. She developed abdominal distention and acute renal failure the same day. Her condition continued to worsen and

she was withdrawn from the study on day 2 and underwent colectomy on the same day with subsequent recovery. The case narrative of this patient is provided in Section 7.3.3.

7.3.3 Dropouts and/or Discontinuations

In phase 3 trials the incidence of TEAEs leading to study drug discontinuation was 5.9% in the fidaxomicin and 6.9% in the vancomycin group as per the applicant. According to the reviewer’s analysis of case narratives and CRFs, the incidence of discontinuations due to adverse events was 44 (7.8%) and 53 (9.1%) in the fidaxomicin and vancomycin groups, respectively. For subjects in both the fidaxomicin and vancomycin groups, the SOCs with the highest incidence of TEAEs leading to study drug discontinuation were gastrointestinal disorders (2.3% and 1.4%, respectively) and infections and infestations (1.2% and 1.5%, respectively). Vomiting was the primary TEAE leading to study drug discontinuation; this occurred at an incidence of 0.5% in both treatment groups. No TEAEs leading to study drug discontinuation were reported in the fidaxomicin 300 mg or 450 mg groups. Two out of 54 subjects stopped study drug in the fidaxomicin 100-200 mg group, one subject due to chronic pancreatitis and the other due to pneumonia.

According to the reviewer’s analysis, 57 (10.1%) and 58 (9.9%) subjects were withdrawn from phase 3 trials due to treatment failure or adverse events in the fidaxomicin and vancomycin groups, respectively (Table 27). There were 22 (3.9%) and 36 (6.2%) subjects who discontinued study drug due to adverse event during the treatment phase in the fidaxomicin and vancomycin groups, respectively. There were 22 (3.9%) and 17 (2.9%) subjects who discontinued the study due to adverse events during the follow-up phase in the fidaxomicin and vancomycin groups, respectively. In addition to adverse events, 13 (2.3%) and 5 (0.9%) subjects stopped study drug prematurely due to treatment failure in the fidaxomicin and vancomycin groups, respectively. The treatment failure was concluded when a subject received study drug for at least 3 days.

Table 27 Withdrawals in Phase 3 trials (Reviewer-Defined)

	101.1.C.003		101.1.C.004	
	Fidaxomicin n (%)	Vancomycin n (%)	Fidaxomicin N (%)	Vancomycin n (%)
No. of subjects who were enrolled and randomized	302	327	270	265
Received study medication	300	323	264	260
Completing the study	265 (87.7)	275 (84.1)	212 (78.5)	214 (80.8)
Withdrawn during the treatment phase	22 (7.3)	32 (9.9)	45 (17.0)	34 (13.1)
Adverse event	10	22	12	14
Clinical failure	8	3	5	2
Withdrawn in follow-up phase	15 (5)	20 (6.2)	13 (4.9)	17 (6.5)
Adverse event	9	8	13	9

Clinical Review
Dmitri Iarikov, MD, PhD
NDA 201699, Dificid (fidaxomicin)

The selected case narratives describe treatment discontinuations where AEs or treatment failure may be related to study drug.

Patient ID: 003-009040
Study drug: Fidaxomicin

For this 77-year-old male, study drug was stopped after 9 days of treatment when the patient was readmitted to the hospital with acute on chronic renal failure and pneumonia. The patient continued to have diarrhea and despite negative toxin assays was treated with oral vancomycin and metronidazole for possible CDAD. On study day 24 the patient underwent colonoscopy which demonstrated lymphocytic colitis on pathology studies. Of note, a colonoscopy earlier that year was reported as “negative.” The investigators deemed that lymphocytic colitis was not related to the study drug.

Medical reviewer comments: While continuous diarrhea may have contributed to dehydration and worsening of renal failure, the diarrhea was apparently related to lymphocytic colitis, not CDAD. Even though the association between fidaxomicin and lymphocytic colitis can not be completely ruled out, this is unlikely.

Patient ID: 003-010002
Study drug: Fidaxomicin

This 43-year-old female with acute myelogenous leukemia and status post stem cell transplantation received two doses of study drug before undergoing urgent subtotal colectomy for megacolon. The surgical specimen was consistent with pseudomembranous colitis. The study drug was discontinued after the surgery and intravenous metronidazole was initiated. The patient was eventually discharged to a rehabilitation facility.

Medical reviewer comments: The event of toxic megacolon was unlikely related to lack of efficacy of the study drug but rather to the severity of the disease.

Patient ID: 003-048003
Study drug: Fidaxomicin

This 64-year-old male was initially discharged home on the second day of CDAD treatment with fidaxomicin. Of note, patient’s had baseline WBC of $24.2 \times 10^9/L$, albumin of 1.5 g/dL and creatinine of 3 mg/dL. On study day 3 the patient was readmitted with worsening abdominal pain and distention, continuous diarrhea and oliguria. The study drug was discontinued and oral vancomycin 125 mg QID, vancomycin retention enemas QID and oral nitazoxanide 500 mg BID were initiated. The patient underwent colectomy on day 8. Surgical pathology demonstrated pseudomembranous colitis. On study day 19 the patient was discharged to a skilled nursing facility. No further information is available.

Clinical Review
Dmitri Iarikov, MD, PhD
NDA 201699, Dificid (fidaxomicin)

Medical reviewer comments: the development of megacolon could possibly be related to lack of efficacy of the study drug. It has to be noted that this patient had severe CDI and received less than three days of study medication.

Patient ID: 003-105005
Study drug: Fidaxomicin

This 84-year-old female with chronic renal insufficiency and creatinine at enrollment of 1.7 mg/dL failed after 3 days of CDAD therapy with fidaxomicin and was switched to intravenous metronidazole and oral vancomycin. By that time the creatinine level was 4 mg/dL. Diarrhea finally improved and renal functions returned to baseline levels. The patient required hemodialysis in the interim.

Medical reviewer comments: The event of acute renal failure could possibly be related to lack of efficacy in controlling CDAD, which resulted in dehydration and sepsis.

Patient ID: 003-131001
Study drug: Fidaxomicin

This 55-year-old female with a history of primary central lymphoma and kidney transplantation failed CDAD therapy with study drug and was switched to oral metronidazole on study day 7 because of continuing diarrhea. At the time of enrollment the patient was found to have pancytopenia with WBC of $1.79 \times 10^9/L$ and platelet count of $46 \times 10^9/L$. The pancytopenia had worsened by study day 9 but subsequently improved and the patient was discharged on study day 24. Bone marrow aspiration at the time of worsening of pancytopenia was suspicious for hemophagocytic syndrome.

Medical reviewer comments: The development of pancytopenia coincided with worsening of Clostridium difficile infection and might be related to sepsis and thus, to the lack of efficacy of study drug. Direct bone marrow toxicity of study drug appears less likely.

Patient ID: 003-137005
Study drug: Fidaxomicin

This 50-year-old male apparently failed CDAD treatment with study drug when he presented on study day 7 having 5 unformed bowel movements, fever and WBC count of $16 \times 10^9/L$ (baseline $9.4 \times 10^9/L$) and a sodium level of 126 mEq/L (baseline 135 mEq/L). The patient was switched to oral vancomycin. Low sodium level was reported as the reason to discontinue the study drug.

Medical reviewer comments: This patient experienced progression of CDAD resulting in Clostridium difficile related sepsis, dehydration and hyponatremia. These adverse events may possibly be related to the lack of efficacy of the study drug.

Clinical Review
Dmitri Iarikov, MD, PhD
NDA 201699, Difucid (fidaxomicin)

Patient ID: 003-137011
Study drug: Fidaxomicin

The case narrative of this patient is presented in section 7.3.2 – Nonfatal Serious Adverse Events, Overdose / Duodenal Perforation.

Patient ID: 003-138006
Study drug: Fidaxomicin

This 62-year-old male failed CDAD therapy with fidaxomicin was initiated on intravenous metronidazole, oral vancomycin and rifampin on study day 6. The patient's condition continued to worsen and on study day 17 he underwent total colectomy. The patient's condition subsequently improved and he was discharged on study day 29. The investigators deemed that the worsening of CDAD was not related to study drug.

Medical reviewer comments: worsening of CDAD may possibly be related to lack of efficacy of the study drug.

Patient ID: 003-167003
Study drug: Fidaxomicin

This 44-year-old HIV-infected male was declared a clinical failure after 6 days of study drug therapy. At that time, the patient continued to have up to 9 loose daily bowel movements associated with abdominal pain. Therapy with oral vancomycin and metronidazole resulted in resolution of diarrhea by study day 11. The investigators deemed that diarrhea was not related to study drug.

Medical reviewer comments: continued CDAD may be related to lack of efficacy of study drug.

Patient ID: 003-017003
Study drug: Vancomycin

This 88-year-old male with ongoing urinary tract infection was diagnosed with CDAD and started the study medication on the third day of his hospital admission. On study day 2 the patient became delirious. The cause of the delirium was attributed to urinary tract infection, CDAD, and hypoglycemia, but the investigators felt that the delirium could possibly be related to the study drug. The study drug was discontinued on study day 3 after seven doses. The subject's diarrhea resolved and his mental status improved by study day 6. The patient was discharged on oral vancomycin.

Medical reviewer comments: The delirium in this elderly patient was unlikely related to study drug but rather resulted from multiple infections, other medications and inpatient care.

Clinical Review
Dmitri Iarikov, MD, PhD
NDA 201699, Dificid (fidaxomicin)

Patient ID: 004-045007
Study drug: Fidaxomicin

This 76-year-old female was withdrawn from the study on day 4 due to dehydration. By the time of withdrawal the patient continued to have diarrhea with up to 9 loose bowel movements a day.

Medical reviewer comments: This patient failed to respond to CDAD therapy with fidaxomicin and continued to have diarrhea. Thus, the adverse event of dehydration could possibly be related to lack of efficacy of study drug.

Patient ID: 004-057010
Study drug: Fidaxomicin

This 70-year-old male was withdrawn from the study on day 9 due to abnormal liver function tests. The patient's significant medical history included gastrointestinal stromal tumor with omental and liver metastases. The patient received amoxicillin/clavulanic acid 600 mg twice daily for four days prior to enrollment for sepsis of unknown source.

Concomitant medications included furosemide, dalteparin, ramipril, metoclopramide, ondansetron, bumetanide, imatinib, ferrous sulphate, temazepam, dalteparin, ensure, aspirin, digoxin, omeprazole, dipyridamole, paracetamol, and midazolam.

Patient's baseline ALT was 15 U/L (normal ranges 6-35 U/L), AST 27 U/L (normal ranges 11-36 U/L), direct bilirubin 0.1 mg/dL (normal ranges 0-0.4 mg/dL), and alkaline phosphatase 53 U/L (normal ranges 35-130 U/L). The case report form does not include liver function tests at the time of study drug discontinuation. The case narrative states that on "on day 8 of study drug therapy, investigations revealed abnormal liver function tests including grade 4 variation in ALP and grade 3 variation in ALT." The subject was asymptomatic. Abdominal ultrasound showed no focal liver lesions or evidence of cholestasis.

The study drug was discontinued as well as spironolactone and bumetanide on study day 9. The patient's diarrhea resolved and the patient was discharged on study day 14. On the day of discharge ALT was 288 U/L, AST was 91 U/L, direct bilirubin was 0.2 mg/dL, and alkaline phosphatase was 212 U/L. The investigators deemed that this severe mixed liver function test abnormality was unlikely related to the study drug. The investigators thought that the time course of improvement did coincide with study drug withdrawal, but was also consistent with amoxicillin/clavulanic acid hepatotoxicity.

Medical reviewer comments: the development mixed liver function abnormalities in this patient coincided with study drug administration and may possibly be related to the study drug. The medical reviewer agrees, however, that liver function abnormalities may be related to other medications as well, especially to amoxicillin/clavulanic acid.

Clinical Review
Dmitri Iarikov, MD, PhD
NDA 201699, Dificid (fidaxomicin)

Patient ID: 004-057012
Study drug: Fidaxomicin

This 66-year-old male was declared a treatment failure after 6 days of therapy due to worsening diarrhea associated with fever of 38.5°C and increased abdominal pain. The patient was started on intravenous metronidazole and oral vancomycin with subsequent improvement of diarrhea and resolution of fever. The investigators deemed that the worsening of *C. difficile* colitis was not related to the study drug.

Medical reviewer comments: worsening of C. difficile colitis was possibly related to lack of efficacy of the study drug.

Subject 004-088026
Study drug: Fidaxomicin

This 58-year-old male with acute myeloid leukemia and white blood cell count on enrollment of $0.06 \times 10^9/L$ was declared a clinical failure and withdrawn from the study on day 5 due to continuous diarrhea. The patient had an episode of bloody diarrhea on day 5 of study medication. In addition, at the time of withdrawal the patient developed respiratory failure due to aspiration pneumonia, was placed on mechanical ventilation and started on systemic antibiotics and vasopressors. The patient's condition continued to deteriorate and over the following days he became unresponsive. Due to poor prognosis therapy was discontinued and the patient expired on study day 20.

Medical reviewer comments: The reason for withdrawal from the study for this patient was clinical failure and, thus, lack of efficacy of study drug could possibly be related to discontinuation from the study.

Patient ID: 004-136003
Study drug: Fidaxomicin

This 80-year-old female who underwent sinus surgery five days prior to study enrollment presented with hallucinations on study day 2 after receiving five doses of fidaxomicin. She developed hallucinations at night and they resolved in the morning. Past medical history was significant for mild forgetfulness. Concomitant medications included acetylsalicylic acid, atenolol, enalapril, omeprazole, paracetamol, and simvastatin. The hallucinations reoccurred the next night and the study drug was stopped. By that time, the patient's diarrhea improved but she still continued to have five loose bowel movements a day and her temperature was 38° C. The study drug was stopped on study day 3. The patient was started on metronidazole with resolution of diarrhea and hallucinations. The investigators deemed that hallucinations were possibly related to the study drug.

Clinical Review
Dmitri Iarikov, MD, PhD
NDA 201699, Difucid (fidaxomicin)

Medical reviewer comments: the clinical presentation in this elderly patient with baseline forgetfulness is compatible with sundown syndrome that may have been exacerbated by acute illness. The association between fidaxomicin and hallucinations seems to be less likely.

Patient ID: 004-171006
Study drug: Fidaxomicin

This 81-year-old male was withdrawn from the study drug on day 2 due to increasing abdominal pain and leukocytosis. By that time, the patient received 5 doses of the study drug. His WBC at study entry was $32.8 \times 10^9/L$ and the next day it was $50.8 \times 10^9/L$. The patient was started on intravenous metronidazole and oral vancomycin which were continued for the next 15 days. The events of increased abdominal pain and leukocytosis were deemed not related to the study drug.

Medical reviewer comments: This patient's CDAD continued to worsen despite treatment with the study drug. However, the patient received only five doses of the drug and it is unlikely that the worsening of CDAD was related to lack of efficacy of the study drug.

Patient ID: 004-201004
Study drug: Fidaxomicin

This 23-year-old female withdrew her consent and was withdrawn from the study on day 9 after she had developed vomiting the same day. The patient had resolved diarrhea by that time. The vomiting resolved after the medication was stopped. The event of vomiting was deemed not related to the study drug by the investigators.

Medical reviewer comments: This patient's vomiting could possibly be related to the study drug, because no other cause of vomiting has been provided and the symptoms resolved after the study drug was stopped.

Patient ID: 004-003002
Study drug: Vancomycin

This 86-year-old female was withdrawn from the study on day 2 after receiving 4 doses of the study drug due to QT prolongation. Her past medical history included atrial fibrillation for which she was receiving amiodarone and digoxin and myocardial infarction that she sustained four weeks prior to study entry. Baseline ECG on study day 1 showed QTc interval of 419 ms. On study day 2 ECG showed a QTc of 671msec. Serum electrolytes were checked and were normal. Serum digoxin level was within the therapeutic range. Digoxin, amiodarone and the study medication were discontinued. Repeat ECG on the next day after the study drug discontinuation showed QTc of 414 msec. The investigators deemed that the study drug was possibly related to QT prolongation.

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Dmitri Iarikov, MD, PhD
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Medical reviewer comments: The medical officer thinks that the study drug was unlikely related to QT-prolongation which was probably related to amiodarone rather than to the study drug.

Patient ID: 004-048003
Study drug: Vancomycin

This 76-year-old male with a history of ventricular tachycardia, on sotalol and amiodarone, was withdrawn from the study on day 2 after he developed Torsades de Pointes. His serum potassium at the time of event was 2.8 mEq/L (normal 3.6 – 5.0). The baseline QTcB was 457 msec. The patient had received four doses of study medication. The event of Torsades de Pointes was deemed possibly related to the study drug.

Medical reviewer comments: Torsades de Pointes in this patient was probably related to sotalol, which is one of the most common medications causing this type of arrhythmia. Treatment with amiodarone and hypokalemia are other contributing factors. The study drug was unlikely related to Torsades de Pointes.

Patient ID: 004-177002
Study drug: Vancomycin

This 76-year-old female was withdrawn from the study on day 2 after receiving 5 doses of study drug. The patient entered the study with WBC of $46.6 \times 10^9/L$ and signs of pancolitis on CT scan. On study day 1 she developed abdominal distention and acute renal failure. Her conditions continued to worsen and she was withdrawn from the study on day 2 and underwent colectomy the same day. The patient was started on intravenous metronidazole and eventually was discharged from the hospital on day 22 after enrollment. The event of *Clostridium difficile* sepsis was deemed unrelated to the study drug.

Medical reviewer comments: This subject had severe and rapidly progressing C. difficile infection. The exposure to the study drug was short and the study drug was unlikely related to the progression of C. difficile sepsis. Overall, the incidence of discontinuations of the study drug was similar in the fidaxomicin and vancomycin groups. Discontinuations due to early treatment failures were reported somewhat more frequently in the fidaxomicin group. However, the significance of this observation is uncertain because the efficacy data demonstrated that cure rates were similar in both groups.

7.3.4 Significant Adverse Events

Gastrointestinal hemorrhage

There were 21 fidaxomicin patients that experienced an adverse event of gastrointestinal hemorrhage. Twenty patients in the fidaxomicin group were seen in phase 3 trials and one patient participated in the phase 2 trial (Table 28, 29 and 30). There were 12 vancomycin patients that were reported to experience GI hemorrhage.

Table 28 Treatment-Emergent Adverse Events Related to GI Hemorrhage (Preferred terms)

Preferred terms	Fidaxomicin (N=564) n (%)	Vancomycin (N=583) n (%)
Total in Phase 3 trials	20 (3.5%)	12 (2.1%)
Hematochezia	7	1
Gastrointestinal Hemorrhage	5	1
Diarrhea Hemorrhagic	5	0
Rectal / Hemorrhoidal Hemorrhage	3	4
Occult Blood Positive	0	1
Hematemesis / Upper GI Hemorrhage / Esophageal Varices Hemorrhage	0	3
Colitis ischaemic	0	1
Large intestine perforation	0	1
Phase 2 trial (N=48)		
Gastrointestinal Hemorrhage	1 (2.1%)	NA

Two fidaxomicin-treated patients stopped study drug due to GI hemorrhage and one patient in the fidaxomicin group died from GI hemorrhage. Two episodes of GI hemorrhage in the fidaxomicin group were judged as severe, four as moderate and 14 as mild. Seven events of GI hemorrhage were considered to be serious, 6 in phase 3 and 1 in phase 2 trials.

Nine episodes of GI hemorrhage in the fidaxomicin group occurred during administration of the study drug and 12 occurred after the study drug was completed. All but one serious episode of GI hemorrhage occurred off the study drug. Fourteen episodes of GI hemorrhage represented lower GI hemorrhages, two episodes were likely to be upper GI hemorrhages, and the source of hemorrhage was difficult to infer in 5 subjects. The reviewer deemed that nine episodes of GI hemorrhage in the fidaxomicin group could be possibly related to study drug.

Five GI hemorrhages in the vancomycin group were considered to be serious, three were judged to be severe, five moderate, and four mild. There were no reports of death or study withdrawals related to GI hemorrhage. Eight episodes occurred off study drug. The location of GI hemorrhage was suggested to be in the lower GI tract in six subjects, upper GI tract in four subjects, and was difficult to infer in two subjects (Table 30). Four episodes of GI hemorrhage were deemed to be possibly related to study drug by the reviewer.

Our analysis did not demonstrate obvious association between GI hemorrhage and the severity of CDAD at baseline (Table 29). Fidaxomicin-treated subjects with severe and non-severe baseline disease developed TEAEs related to GI hemorrhage in 4.1% and 3.1%, respectively. In the vancomycin group, subjects with severe and non-severe CDAD at baseline developed TEAEs related to GI-hemorrhage in 1.3% and 2.3%, respectively. Two thirds of GI hemorrhage episodes in both groups occurred after study drug was stopped. All but one serious episode of GI hemorrhage in the fidaxomicin group and all serious episodes in the vancomycin group occurred after study drug was discontinued.

Table 29 TEAEs related to Gastrointestinal Hemorrhage in Phase 3 trials

	Fidaxomicin N=20	Vancomycin N=12
Severe CDAD at baseline	7 /142 (4.9%)	2 /150 (1.3%)
Non-Severe CDAD at baseline	13 / 422 (3.1%)	10 /433 (2.3%)
Occurred After Study Drug Stopped	12	8

Table 30 Patients with GI hemorrhage

Patient ID / Study Drug	Days on Study Drug	Study Day of event	Event Description	Serious Event	Outcome	Relationship to study / Source of GI hemorrhage*
003-009049 Fidaxomicin	11	26	This 23-year-old female with a history of recurrent urinary tract infections and no history of GI diseases, not on anticoagulants or NSAIDs, had a single loose stool with blood 16 days after completing study drug. <i>C. difficile</i> toxin assay the next day was negative. The event was reported as mild.	Not Serious	Recovered	Possibly related/ Lower GI hemorrhage
003-009005 Fidaxomicin	11	35	This 64-year-old female with endometrial cancer complicated by small bowel obstruction and radiation enteritis underwent small bowel resection for obstruction on study day 35 and had hem-positive stools shortly after surgery. The event was reported as mild.	Not Serious	Recovered	Not related/ Lower GI hemorrhage
003-011027 Fidaxomicin	11	9	This 80-year-old male with a history of hemorrhoids, not on anticoagulants, had blood in stool on study day 9. The study drug continued. No recurrent blood in stool had been reported. The event was considered mild.	Not Serious	Recovered	Unlikely related/ Lower GI hemorrhage
003-011056 Fidaxomicin	11	25	This 65-year-old female with cervical cancer, rectal obstruction by cervical mass, status post radiation, not on anticoagulants, was reported to have hematochezia from day 14 until day 18 after completing study drug. The event was considered mild in severity.	Not Serious	Recovered	Unlikely related/ Lower GI hemorrhage
003-020002 Fidaxomicin	9	29	This 86-year-old male with diverticulosis, an episode of GI hemorrhage two weeks prior to enrollment and continuous black stools at the time of enrollment was declared a clinical failure after 9 days of study therapy. Colonoscopy on study day 10 was consistent with pseudomembranous colitis. Patient was treated with vancomycin and nitazoxanide for CDAD. He subsequently developed more episodes of GI hemorrhage. Upper endoscopy and colonoscopy on study day 21 revealed diverticulosis, internal hemorrhoids and no active bleeding. The patient continued to decline with poor oral intake and worsening respiratory status thought to be related to aspirations. The patient was changed to hospice care and died on day 29 reportedly from another episode of GI hemorrhage. The event was reported as severe and serious.	Serious	Death**	Unlikely related/ Lower GI hemorrhage

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003-058004 Fidaxomicin	11	6	This 23-year-old female with a history of recurrent urinary tract infections had “small amount of bloody stool” on day 6 of study drug administration. The event was considered mild.	Not Serious	Recovered	Unlikely related/ Lower GI hemorrhage
003-076006 Fidaxomicin	11	23	This 66-year-old male with Barrett’s esophagus, not on NSAIDs or anticoagulants, presented with hematemesis 12 days after completing study therapy. The event was considered mild in severity but serious. EGD demonstrated Barrett’s esophagus and a “small vascular abnormality” in the pylorus.	Serious	Recovered	Unlikely related/ Upper GI hemorrhage
003-105004 Fidaxomicin	2	11	This 61-year-old female with prior colonic resection for ischemic colitis and colostomy withdrew consent for an unspecified reason after taking 3 doses of the study drug. On study day 11 there was bleeding from her colostomy for 2 days. The event was considerate moderate in severity. Colonoscopy on study day 15 was unrevealing.	Serious	Recovered	Unlikely Related/ Lower GI hemorrhage
003-140003 Fidaxomicin	3	3	This 59-year-old female with a history of bowel ischemia, on aspirin and clopidrogel but no NSAIDs, developed hematochezia on study day 3. <u>The study drug was discontinued</u> . The event was considered severe and serious. The GI bleeding resolved by study day 15. Endoscopy on study day 15 revealed multiple erosions and healing ulcers in the stomach, mild esophagitis and duodenitis. No prior history of stomach ulcers and no previous endoscopy results had been reported. The patient eventually died on study day 28 from aspiration pneumonia.	Serious	Recovered	Possibly related/ Upper GI hemorrhage
003-160001 Fidaxomicin	9	9	This 79-year-old male with a history of upper GI bleeding one year prior to enrollment took 9 days of study medication when blood in stool was reported once. The study medication <u>was stopped</u> and the patient was started on vancomycin. The event was considered moderate in severity.	Not Serious	Recovered	Possibly related/ Location is uncertain
004-057006 Fidaxomicin	11	36	This 88-year-old female completed 11 days of study drug and was declared a cure. On study day 36 the patient developed rectal bleeding. The event was considered mild in severity. The patient “was referred for further investigation and no pathology was found.” Concomitant medications included warfarin and paracetamol.	Not Serious	Recovered	Possibly related/ Lower GI hemorrhage
004-057028 Fidaxomicin	10	2	This 85-year-old female with no history of GI-bleeding, not on anticoagulants, had rectal bleeding on day 2 of study drug. The study drug continued with subsequent cure of CDAD. The event was considered mild and not serious.	Not Serious	Recovered	Unlikely related/ Lower GI hemorrhage

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004-088026 Fidaxomicin	5	5	This 58-year-old male with acute myeloid leukemia and neutropenia developed bloody diarrhea which was considered mild in severity on day 5 of study drug administration. The patient continued to have diarrhea and was withdrawn from the study due to sepsis and neutropenic enterocolitis. The patient eventually died on study day 20.	Not Serious	Recovered	Possibly related/ Location is uncertain
004-088027 Fidaxomicin	10	20	This 38-year-old male with a history of CNS Non-Hodgkin lymphoma, on chemotherapy, developed hemorrhoidal bleeding of mild severity on study day 20. The hemorrhage resolved the same day. The patient was not thrombocytopenic and was not on anticoagulants at the time of event.	Not Serious	Recovered	Not related/ Lower GI Hemorrhage
004-105001 Fidaxomicin	11	23	This 80-year-old female presented with CDAD recurrence associated with hemorrhagic diarrhea on study day 23, twelve days after completing the study medication. The event deemed to be moderate in severity. The patient was started on oral vancomycin and metronidazole with subsequent resolution of hemorrhagic diarrhea.	Serious	Recovered	Unlikely related/ Location is uncertain
004-125002 Fidaxomicin	11	31	This 38-year-old female presented 20 days after completing CDAD treatment with a 1-day history of multiple episodes of diarrhea with red blood in stool and vomiting. The event was considered to be moderate in severity. <i>C. difficile</i> toxin assay had been negative times three. Diarrhea resolved after 7 days. The episode was attributed to viral gastroenteritis.	Serious	Recovered	Possibly related/ Lower GI hemorrhage
004-184001 Fidaxomicin	11	7	This 90-year-old female with a history of angiodysplasia of the colon was noted to have blood in stool on study day 7 with no recurrent episodes. The event was considered mild in severity. The patient completed study therapy with an outcome of cure.	Not Serious	Recovered	Unlikely related/ Lower GI hemorrhage
004-189004 Fidaxomicin	11	31	This 76-year-old male with a history of stomach ulcer had one liquid stool with blood 21 days after completing the study drug. No recurrent episodes of blood in stool were reported. Patient was not receiving anticoagulants or NSAIDs.	Not Serious	Recovered	Unlikely related/ Location is uncertain
004-189008 Fidaxomicin	11	5	This 29-year-old female with psoriatic arthritis, on methotrexate, etanercept, and pantoprazole, had stools with blood starting on day 5 of study drug administration over approximately three days. The study medication was continued, no specific actions were taken, and the event resolved spontaneously.	Not Serious	Recovered	Possibly related/ Location is uncertain

Clinical Review
Dmitri Iarikov, MD, PhD
NDA 201699, Dificid (fidaxomicin)

004-201017 Fidaxomicin	10	9	This 18-year-old female had bleeding with bowel movement on day 9 of study drug administration. Her past medical history was significant for <i>Yersinia</i> (the species is not specified, likely <i>Yersenia enterocolitica</i> - Medical Reviewer) approximately one month prior to study enrollment. No concomitant medications except for study drug were given at the time of event. The study treatment was completed with an outcome of cure and no recurrent bleeding was reported.	Not Serious	Recovered	Possibly related/ Lower GI hemorrhage
2A-002-208 Fidaxomicin	10	15	This 71-year-old female completed 10 days of CDAD therapy with fidaxomicin with resolution of diarrhea. Five days after completing study drug the patient developed lower GI hemorrhage requiring blood and fresh frozen plasma transfusions. The endoscopy was normal and colonoscopy revealed polyps. A subsequent sigmoidoscopy revealed "anorectal clots and no bleeding." The bleeding was reported to resolve by study day 28.	Serious	Recovered	Possibly related/ Lower GI hemorrhage
003-007001 Vancomycin	11	21	This 92 year-old female became unresponsive and started having bloody bowel movements on study day 21, ten days after the completion of successful CDAD therapy. The patient was diagnosed with ischemic colitis, received comfort care and died on study day 23. The event of ischemic colitis was considered severe and serious. <i>This subject was added to the list of patients with adverse events of GI hemorrhage by the reviewer.</i>	Serious	Death	Possibly related/ Lower GI hemorrhage
003-009001 Vancomycin	11	22	This 53-year-old female developed methicillin-resistant <i>Staphylococcus aureus</i> bacteremia and septic shock and had an episode of coffee ground aspirate from nasogastric tube on study day 22, eleven days after successful CDAD therapy. The event was reported as moderate severity.	Not Serious	Recovered	Unlikely related/ Upper GI hemorrhage
003-011055 Vancomycin	8	17	This 41-year-old male had progressive T-cell lymphoma, involving the esophagus and colon with esophageal and stomach ulcers, and thrombocytopenia. The patient was receiving prednisone and naproxen. He was declared a clinical failure on study day 8. On study day 17, he started having bright red blood per rectum, and underwent colectomy for colon perforation the next day. The transverse colon pathology demonstrated T-cell lymphoma. Gastrointestinal bleeding continued postoperatively. The patient died on study day 24. <i>This subject was added to the list of patients with adverse events of GI hemorrhage by the Reviewer.</i>	Serious	Death	Unlikely related/ Upper & Lower GI hemorrhage
003-081004 Vancomycin	11	7	This 82-year-old male with continuous diarrhea despite study drug treatment, eventually declared a clinical failure, had a positive hemocult on study day 7. The study drug was continued at that time. The event was deemed mild and not serious.	Not Serious	Not recovered	Unlikely related/ Location is uncertain

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003-137006 Vancomycin	11	23	This 65-year-old female underwent endoscopic retrograde cholangiopancreatography, sphincterotomy and gallstone removal from the common bile duct on study day 22 and had blood from the rectum the next day. The event was reported as mild.	Not Serious	Recovered	Unlikely related/ Upper GI hemorrhage
003-140007 Vancomycin	11	15	This 62-year-old male with no history of peptic ulcer disease completed 11 days of study drug and was declared cured from CDAD. Four days after completing the study drug, the patient had an episode of coffee ground vomiting. The event was reported as moderate. Endoscopy on study day 24 was unrevealing. The patient was receiving aspirin, heparin and clopidogrel at the time of event.	Serious	Recovered	Possibly related/ Upper GI hemorrhage
004-057030 Vancomycin	11	2	This 61-year-old female with a history of diverticulosis and an episode of fresh blood per rectum approximately one month prior to enrollment in the study, had four episodes of small amounts of fresh blood per rectum starting on day 2 of study drug administration. The patient completed the study with an outcome of cure. Her medication did not include anticoagulants or NSAIDs at the time of event which was reported as moderate.	Not Serious	Recovered	Unlikely related/ Lower GI hemorrhage
004-057031 Vancomycin	11	28	This 49-year old male with a history of liver cirrhosis and esophageal varices had hematemesis and melena secondary to variceal bleeding over three days that he developed 18 days after completing study drug therapy. The event was considered moderate in severity.	Serious	Recovered	Not related/ Upper GI hemorrhage
004-070012 Vancomycin	12	5	This 82-year-old male had hematochezia on study day 5 and 6 which resolved spontaneously. The event was reported as moderate. The patient was eventually declared a failure and required repeated treatment with oral vancomycin.	Not Serious	Recovered	Possibly related/ Lower GI hemorrhage
004-088020 Vancomycin	11	7	This 71-year-old female developed mild hemorrhoid bleeding on study day 7 that resolved the next day. The study drug continued. The patient was on enoxaparin at the time of event which was reported as mild.	Not Serious	Recovered	Unlikely related/ Lower GI hemorrhage
004-180011 Vancomycin	11	32	This 92-year-old female with a history of angiodysplasia of the colon and duodenitis had 2 large black stools positive for occult blood 20 days after completing study therapy (study day 32). The patient was given a blood transfusion and melena resolved. The event was considered severe. At the same time the patient was diagnosed with pneumonia and started on systemic antibiotics. On study day 35 the patient was found pulseless and died later that day. No repeated episodes of GI hemorrhage were reported. The death was attributed to cardio-respiratory arrest due to pneumonia.	Serious	Recovered	Possibly related/ Lower GI hemorrhage

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004-189023 Vancomycin	11	24	This 45-year-old female noticed blood on toilet paper after stool 14 days after completing successful CDAD therapy with the study drug. The patient was noted to have "perianal irritation" at the time of CDAD treatment. The event was reported as mild.	Not Serious	Recovered	Not related/ Lower GI hemorrhage
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* As suggested by the reviewer

** More detailed narrative can be found in 7.3.1 subsection of the review

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Medical reviewer comments: There is a numerical imbalance in the number of GI hemorrhages between the fidaxomicin and vancomycin groups. The overall severity of GI hemorrhages in both groups appears to be similar. The significance of these differences is uncertain at this point. No GI hemorrhage was reported in animal studies nor were there any changes in the GI tract described in animal studies, including a 3-month exposure study in dogs. Accumulation of additional clinical data may elucidate whether the difference between fidaxomicin and vancomycin in terms of the incidence of GI-hemorrhage was observed by chance or there is an association between fidaxomicin and gastrointestinal bleeding.

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The incidence of TEAEs in phase 3 trials was 68.3% in the fidaxomicin and 65.5% in the vancomycin group (Table 31). The most common TEAEs in both fidaxomicin and vancomycin groups were nausea (11.0% and 11.3%), vomiting (7.3% and 6.3%), hypokalemia (7.3% and 6.5%), headache (6.6% and 4.6%), abdominal pain (5.9% and 3.9%), diarrhea (5.0% and 6.7%), constipation (4.4% and 2.1%), and pyrexia (4.3% and 5.3%). The incidence of abdominal pain and constipation was somewhat higher in fidaxomicin-treated patients. Neutropenia (2.5% vs. 1.0%) and gastrointestinal hemorrhage (3.5% vs. 2.1%) were also more frequent in the fidaxomicin group than in the vancomycin group.

Table 31 Treatment-Emergent Adverse Events with a $\geq 2\%$ Incidence in Fidaxomicin-Treated Subjects: Phase 3 Studies (Safety Population)

System organ Class Preferred Term	Fidaxomicin (N=564) n (%)	Vancomycin (N=583) n (%)
Number Of Subjects With ≥ 1 TEAE	385 (68.3)	382 (65.5)
Blood And Lymphatic System Disorders	37 (6.6)	25 (4.3)
Anemia	14 (2.5)	12 (2.1)
Neutropenia	14 (2.5)	6 (1.0)
Cardiac Disorders	28 (5.0%)	36 (6.2)
Eye Disorders	12 (2.1)	8 (1.4)
Gastrointestinal Disorders	177 (31.4)	170 (29.2)
Abdominal pain	33 (5.9)	23 (3.9)
Constipation	25 (4.4)	12 (2.1)
Diarrhea	28 (5.0)	39 (6.7)
Gastrointestinal hemorrhage	20 (3.5)	12 (2.1)
Nausea	62 (11.0)	66 (11.3)
Vomiting	41 (7.3)	37 (6.3)
General Disorders and Administration Site Condition	90 (16.0)	113 (19.4)
Fatigue	17 (3.0)	20 (3.4)
Edema peripheral	20 (3.5)	27 (4.6)
Pyrexia	24 (4.3)	31 (5.3)
Infections and Infestations	129 (22.9)	121 (20.8)
Pneumonia	13 (2.3)	18 (3.1)
Urinary Tract Infections	20 (3.5)	24 (4.1)
Injury, Poisoning and Procedural Complications	26 (4.6)	31 (5.3)
Investigations	73 (12.9)	58 (9.9)
Metabolism And Nutrition Disorders	104 (18.4)	87 (14.9)
Hyperkalemia	16 (2.8)	10 (1.7)
Hypokalemia	47 (8.3)	38 (6.5)
Nervous System Disorders	71 (12.6)	64 (11.0)
Dizziness	16 (2.8)	12 (2.1)
Headache	37 (6.6)	27 (4.6)
Psychiatric Disorders	41 (7.3)	44 (7.5)
Insomnia	13 (2.3)	14 (2.4)
Renal and Urinary Disorders	30 (5.3)	27 (4.6)
Reproductive System and Breast Disorders	14 (2.5)	7 (1.2)
Respiratory, Thoracic And Mediastinal Disorders	63 (11.2)	76 (13.0)
Dyspnea	14 (2.5)	13 (2.2)
Vascular Disorders	36 (6.4)	31 (5.3)
Hypotension	11 (2.0)	12 (2.1)

Adapted from ISS Table 5.3-7, Edited

Medical Reviewer Comments: The incidence of common adverse events was overall similar in fidaxomicin and vancomycin treated subjects with some increase in gastrointestinal hemorrhage and leukopenia. These adverse events discussed in more details in sections 7.3.4 and 7.4.2 of the review.

7.4.2 Laboratory Findings

Hematology

Decrease in WBC Counts

There were more subjects in the fidaxomicin than in the vancomycin group with adverse events related to decrease in WBC counts [23 (4.1%) vs. 10 (1.7%)]. Several subjects had more than one adverse event and some events were reported with overlapping preferred terms.

For 23 fidaxomicin subjects the events included leukopenia (10), lymphocyte count decreased (5), lymphopenia (4), febrile neutropenia (2), neutropenia (5), neutropenic sepsis (1), neutrophil count decreased (7), pancytopenia (1), and white blood cell count decreased (2). For 10 vancomycin patients with a decrease in WBC counts the preferred terms included granulocytopenia (1), leukopenia (5), white blood cell count decreased (2), lymphocyte count decreased (2), lymphopenia (2), and lymphocyte count abnormal (1). All adverse events were reported in Phase 3 trials. No abnormal shifts in hematology values were reported for subjects in the fidaxomicin 100-200 mg group.

For the purpose of analysis, overlapping reports were excluded and the events were divided into two categories of neutropenia and lymphopenia (Table 32).

Table 32 TEAES related to Decreases in WBC Counts

	Fidaxomicin N=564 n (%)	Vancomycin N=583 n (%)
Total Subjects	23 (4.1)	10 (1.7)
Neutropenia	14 (2.5)	6 (1.0)
Lymphopenia	11 (1.9)	5 (0.9)
Baseline WBC < 4.0 x 10 ⁹ /L	10 / 23	5 / 10

* both neutropenia and leukopenia may be included for a subject but the event was included only once; events reported with overlapping terms are excluded

In the fidaxomicin groups, neutropenia and lymphopenia were reported in 14 and 11 subjects, respectively. A total of 19 out of 23 decreases in WBC count in the fidaxomicin and 9 out of 10 decreases in WBC counts in vancomycin groups occurred during study drug treatment. A low WBC count at baseline, defined as WBC < 4.0 x 10⁹/L, was observed in approximately half of the patients in both groups. Further analysis of case

report forms and adverse event datasets demonstrated that 20 out of 23 subjects had underlying comorbidities that may have contributed to the decrease in WBC counts. These conditions included lymphoma, leukemia, multiple myeloma, systemic lupus erythematosus, M-component hyperglobulinemia, and severe sepsis. In addition, several patients were receiving chemotherapy or glucocorticoids. In the other three subjects, a reason for neutropenia was not evident and could possibly be related to study drug or underlying infection.

In the vancomycin group, neutropenia and lymphopenia were reported in 6 and 5 subjects, respectively. There were 7 subjects with underlying immunosuppressive states that may have contributed to the decrease in WBC count. Three subjects did not have an obvious explanation for neutropenia (2) or lymphopenia (1).

The applicant indicates that the fidaxomicin arm had a higher incidence of pre-existing blood and lymphatic disorders compared to vancomycin (38.7% vs. 32.6%), and that more fidaxomicin than vancomycin subjects received concomitant anti-neoplastic or immunomodulatory agents (11.9% vs. 8.2%, respectively).

However, shifts in WBC from normal to low were reported 2-times more frequently in the fidaxomicin compared to vancomycin groups (Table 33).

Table 33 Shift from Baseline in Hematology Laboratory Measurements: Phase 3 Trials

	Fidaxomicin 400mg N=564 n(%)	Vancomycin 500mg N=583 n(%)
Neutrophils Normal to Low	11 (2.5)	5 (1.2)
Lymphocytes Normal to Low	20 (4.6)	10 (2.3)
Leukocytes Normal to Low	14 (3.1)	8 (1.8)

Adapted from ISS Table 6.1-2

Medical reviewer comments: An increase in the number of subjects with leukopenia in the fidaxomicin compared to vancomycin groups are probably mostly related to underlying comorbidities, immunosuppressants and/or sepsis. On the other hand, fidaxomicin toxicity as a cause of the decrease in WBC counts can not be rule out.

In an analysis of all low WBC values regardless of whether or not they were reported as adverse events, low WBC baseline values of any significance were slightly more frequent in fidaxomicin-treated patients (Table 34). Low baseline WBC counts defined as clinically significant were equally distributed in fidaxomicin and vancomycin groups, 2.0% and 1.7%, respectively. At the end of therapy there were more subjects in the fidaxomicin compared to vancomycin groups whose low WBC counts were judged to be clinically significant, 4.4% vs. 2.7%, respectively.

Additional analysis of a group with low neutrophil counts at the end of treatment demonstrated that 7 out of 23 fidaxomicin-treated subjects had low neutrophil counts at baseline, meaning that in 16 subjects neutrophil counts decreased during study treatment. In contrast, 10 out of 15 subjects in the vancomycin group had low neutrophil counts at baseline; thus only 5 subjects decreased neutrophil counts during study treatment.

Table 34 Baseline and End of Treatment WBC Values Reported as Below Normal Ranges: Phase 3 trials

All subjects with WBC Results	Day 1 N=1017		End of Treatment N=993	
	Fidaxomicin	Vancomycin	Fidaxomicin	Vancomycin
	502	515	505	488
Subjects with any WBC below normal ranges ¹	112 (22.3)	99 (19.2)	83 (16.4)	71 (14.5)
Lymphocyte below normal ranges	97 (19.3)	82 (15.9)	67 (13.3)	55 (11.3)
Neutrophil below normal ranges	17 (3.4)	18 (3.5)	23 (4.6)	15 (3.1)
WBC below normal ranges	28 (5.6)	23 (4.5)	31 (6.1)	29 (5.9)
Subjects with significant WBC abnormalities ²	10 (2.0)	9 (1.7)	22 (4.4)	14 (2.9)

¹ Includes both clinically significant and non-significant decreases in WBC, lymphocytes, and neutrophils

² Includes decreases in WBC, lymphocytes, and neutrophils defined as clinically significant

Overall, the significance of these findings is not certain. Postmarketing experience may provide more information with regard to the incidence of neutropenia and leukopenia in fidaxomicin patients.

Clinical Chemistry

Overall, no clinically significant difference in clinical chemistry parameters was observed between fidaxomicin and vancomycin groups. Additional discussion of clinical chemistry abnormalities in glucose, ALT, and bicarbonate values in subjects ≥ 65 years of age presented in section 7.5.3 Drug-Demographic Interactions.

7.4.3 Vital Signs

Mean demographic measurements were reported at baseline for height (cm), weight (kg), and BMI (kg/m²). Mean vital sign measurements were reported at baseline and EOT. Changes were reported from baseline to EOT results for systolic BP (mm Hg), diastolic BP (mm Hg), pulse rate (beats per minute [bpm]), and oral body temperature (°C).

No meaningful differences were reported in either mean baseline or mean change from baseline values between any treatment groups in phase 2 or phase 3 trials.

7.4.4 Electrocardiograms (ECGs)

Fidaxomicin does not appear to have adverse effects on ECG parameters. In phase 3 trials shifts from normal to abnormal ECG interpretation were reported for 5.8% and 9.6% of subjects in the fidaxomicin and vancomycin groups, respectively.

Fidaxomicin does not appear to have an adverse effect on QTc measurements. A specific corrected QT interval (QTc) study could not be conducted since very low plasma levels seen after oral fidaxomicin dosing in healthy subjects makes the necessary supra-therapeutic exposure not achievable. Of note, preclinical in vivo and in vitro studies failed to show an effect of fidaxomicin on ECG parameters or hERG channels. No clinically relevant differences between the fidaxomicin 400 mg and vancomycin 500 mg groups were noted with respect to changes in QTcB or QTcF intervals or other ECG parameters (Table 35 and 36).

Table 35 Summary of Mean and Mean Changes from Baseline – ECG QTc Prolongation Parameters: Safety population

ECG parameter	Vancomycin (N=583) n (%)	Fidaxomicin (N=564) n (%)
Patients with ECG measurements	503	501
Changes in QTcB Interval From Baseline		
> 30 msec	32 (6.4)	42 (8.4)
> 60 msec	6 (1.2)	6 (1.2)
QTcB Interval Post-baseline		
> 450 msec	109 (21.7)	96 (19.2)
> 480 msec	34 (6.8)	26 (5.2)
> 500 msec	14 (2.8)	12 (2.4)
Changes in QTcF Interval From Baseline		
> 30 msec	35 (7)	37 (7.4)
> 60 msec	5 (1)	6 (1.2)
QTcF Interval Post-baseline		
> 450 msec	54 (10.7)	43 (8.6)
> 480 msec	16 (3.2)	13 (2.6)
> 500 msec	11 (2.2)	7 (1.4)

Adapted from ISS table 6.4-8

Table 36 Summary of Mean and Mean Changes in ECG Parameters from Baseline in Phase 3 trials – Safety population

ECG parameter	Vancomycin (N=323) Study 003	Fidaxomicin (N=300) Study 003	Vancomycin (N=260) Study 004	Fidaxomicin (N=264) Study 004
Heart Rate per minute				
N	264	253	220	230
Baseline Mean (SD)	77.2 (16)	79.2 (16)	78.6 (16)	79.5 (15)
End of Therapy Mean (SD)	76.5 (15.4)	76.6 (16.5)	76.6 (16)	76.6 (14)
Change form Baseline				
Mean (SD)	-0.7 (13)	-2.6(15.1)	-2.1 (13)	-2.8 (13)
Min, Max	-71,75	-68,41	-48,36	-47,47
PR Interval (msec)				
N	243	233	202	204
Baseline Mean (SD)	158.9 (28.2)	153.9 (25.1)	158.1 (28.6)	156.5 (30.5)
End of Therapy Mean (SD)	159.3 (28.5)	157 (26.6)	161.9 (32.4)	159.4 (29.2)
Change form Baseline				
Mean (SD)	0.4 (18.94)	3.1 (19.4)	3.85 (17.9)	2.88 (17.3)
Min, Max	-61,94	-60,95	-53, 86	-69,53
QRS Interval (msec)				
N	264	253	220	230
Baseline Mean (SD)	96.9 (22.1)	94.3 (19.1)	97 (19.4)	95.4 (16.6)
End of Therapy Mean (SD)	95.2 (21.5)	92.4 (17.8)	95.5 (20.6)	94.6 (16.5)
Change form Baseline				
Mean (SD)	-1.7 (13.4)	-1.9 (12.3)	-1.4 (9.9)	-0.7 (11.8)
Min, Max	-73,88	-50,32	-25,54	-85,66

Adapted from Table 54 - Clinical Study Report: Study No. 101.1.C.003 and Table 52 - Clinical Study Report: Study No. 101.1.C.004

Medical reviewer comments: fidaxomicin does not appear to have an adverse effect on ECG parameters.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

No specific immunogenicity studies for fidaxomicin have been conducted. The search of AEs dataset for potential allergic events with the preferred terms of pruritus, pruritus generalized, rash, rash pruritic, rash macular, and dermatitis allergic identified 25 (4.4%) and 23 (3.9%) events in the fidaxomicin and vancomycin groups, respectively. All events were mild or moderate in severity. A case of anaphylactic reaction in the fidaxomicin group was discussed earlier and deemed not related to study drug.

Medical Reviewer comments: No significant differences in the rates of adverse events possibly related to allergic reactions were observed between fidaxomicin and vancomycin treated patients.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the phase 2 dose ranging study the incidence of adverse events were 4/16 (25%) subjects in the 100 mg/day treatment group, 4/16 (25%) in the 200 mg/day treatment group, and 1/16 (6.3%) in the 400 mg/day treatment group. The incidence of TEAEs in fidaxomicin subjects receiving different doses in all trials were 3/10 (30%) in the placebo group, 19/54 (35.2%) in the 100-200 mg group, 0/12 in the 300 mg group, 395/608 (65.0%) in the 400 mg group, and 2/11 (18.2%) in the 450 mg group.

The relationships of the rates of TEAEs and fidaxomicin plasma concentrations were explored. The cut-off of ≥ 150 ng/mL for fidaxomicin and its main metabolite, OP-1118, was selected as the high plasma concentration as it represents approximately double the average values measured in subjects in the 101.1.C.003 study. Subjects with concentrations < 150 ng/mL for the combination of fidaxomicin and OP-1118 were defined as those with low plasma concentrations.

There were 41 subjects with the plasma concentrations ≥ 150 ng/mL and 200 subjects with a plasma concentrations < 150 ng/mL. Plasma concentrations of fidaxomicin and OP-1118 were higher in subjects with CDAD in Phase 3 trials than in healthy volunteers. No healthy volunteers receiving fidaxomicin alone had fidaxomicin or OP-1118 plasma concentrations above 50 ng/mL while CDAD patients had concentrations of fidaxomicin and OP-1118 up to 237 ng/mL and 871 ng/mL, respectively. Plasma concentrations of fidaxomicin remained relatively stable throughout the duration of the study while OP-1118 plasma concentrations increased through the EOT in Phase 3 studies (Table 37).

Table 37 Fidaxomicin and OP-1118 Plasma Concentrations in Phase 3 Studies

Study days and Hours Post Dose	Fidaxomicin Mean (Minimal, Maximal) ng/mL	OP-1118 Mean (Minimal, Maximal) ng/mL
Day 1 at 3-5 hours	22.8 (0.364, 197.0)	44.5 (0.283, 363.0)
Day 1 at 0-12 hours	22.1 (0.262, 237.0)	43.6 (0.243, 406.0)
EOT at 3-5 hours	28.5 (0.305, 191.0)	85.6 (1.1, 871.0)
EOT at 0-12 hours	24.0 (0.305, 191.0)	72.6 (1.1, 871.0)

Adapted from ISS Table 9.1-1

For almost all SOCs, TEAEs in subjects with high plasma concentrations occurred at a higher incidence when compared with subjects with low plasma concentrations (Table 7.5.1-2). The SOCs with the highest incidence of TEAEs were gastrointestinal disorders (53.7%), infections and infestations (53.7%), and metabolism and nutrition disorders (51.2%). In addition, blood and lymphatic system disorders, cardiac disorders, psychiatric disorders, as well as several laboratory abnormalities, including hepatic enzyme elevations, occurred more frequently in subjects with high fidaxomicin plasma concentrations (Table 38). Increasing concentrations of fidaxomicin or OP-1118 were not associated with an increase in QTc. However, the number of patients with high plasma concentrations is small, so differences in AE rates between subgroups with high or low concentrations should be interpreted with caution.

Subjects with higher plasma concentrations vs. lower plasma concentrations were older (mean age of 74.6 vs. 60.6), were more frequently inpatients (92.7% vs. 62.5%), more frequently had severe CDAD (46.3% vs. 21.5%), more frequently had lower baseline albumin [<2.5 mg/dL] (43.2% vs. 17.0%), and more frequently had higher baseline creatinine [≥ 1.5 mg/dL] (29.7% vs. 11.3%). Plasma fidaxomicin and OP-1118 were approximately 2 times higher in older (≥ 65 years) than younger (<65 years) subjects at each measured time point on Day 1 and EOT. It has been suggested that more severe CDAD may be associated with poor intestinal integrity and thus higher systemic absorption of fidaxomicin and OP-1118.

Plasma concentrations of fidaxomicin or OP-1118 were not significantly affected by renal status when compared in patients with estimated creatinine clearance of 51-79 mL/min, 31-50 mL/min, and less than 30 mL/min.

Table 38 Summary of Selected Treatment-Emergent Adverse Events by Plasma Concentrations at End of Treatment (Safety Population)

System Organ Class Preferred Term*	Plasma Concentration ≥150 ng/mL (N=41) n (%)	Plasma Concentration <150 ng/mL (N=200) n (%)
Number Of Subjects With ≥1 TEAE	38 (92.7)	129 (64.5)
Blood And Lymphatic System Disorders	8 (19.5)	11 (5.5)
Anemia	3 (7.3)	5 (2.5)
Lymphopenia	2 (4.9)	1 (0.5)
Neutropenia / Leukopenia	2 (4.9)	3 (1.5)
Cardiac Disorders	6 (14.6)	1 (0.5)
Bradycardia	2 (4.9)	0 (0)
Gastrointestinal Disorders	22 (53.7)	50 (25)
Constipation	7 (17)	10 (5)
Nausea	7 (17)	21 (10.5)
Vomiting	9 (22)	14 (7)
Infections and Infestations	22 (53.7)	42 (21)
Pneumonia	4 (9.8)	4 (2)
Sepsis / Sepsis Syndrome	3 (7.3)	2 (1)
Investigations	14 (34.1)	17 (8.5)
Alanine Aminotransferase Increased	2 (4.9)	4 (2)
Hepatic enzyme increased	2 (4.9)	0 (0)
Metabolism And Nutrition Disorders	21 (51.2)	22 (11)
Hyperkalemia	6 (14.6)	3 (1.5)
Hypokalemia	7 (17.1)	9 (4.5)
Hyponatremia	4 (9.8)	2 (1)
Psychiatric Disorders	7 (17.1)	14 (7.0)

Adapted from ISS Table 9.1-8 and 14.3.1.9

Medical reviewer comments: Comments on the association between the dose and adverse events in fidaxomicin patients are limited by low numbers of subjects exposed to doses other than suggested therapeutic dose of 400 mg daily. Explorations of the association between fidaxomicin exposure and adverse events based on fidaxomicin plasma concentrations are also limited because the concentrations in phase 3 subjects were quite variable. It is plausible that the observed increase in TEAEs in patients with higher fidaxomicin plasma concentrations was due to more severe disease. High plasma concentrations may be a reflection of the severity of CDAD rather than a cause of adverse events.

On the other hand, an association between the degree of fidaxomicin exposure and TEAEs can not be completely dismissed. Overall, no evident association between fidaxomicin dose and adverse event rates can be concluded based on the results of submitted clinical trials.

7.5.2 Time Dependency for Adverse Events

The time of occurrence of GI hemorrhage with regard to study drug administration is discussed in section 7.3.4. Otherwise, no specific analyses of time dependency of adverse events have been conducted.

7.5.3 Drug-Demographic Interactions

Clinical safety results in subgroups of subjects were analyzed for drug-demographic interactions by age (< 65 years and ≥ 65 years), gender (male and female), race (White and non-White), and country (Belgium, Canada, France, Germany, Italy, Spain, Sweden, United Kingdom, and US) Overall, no clinically significant differences with regard to drug-demographic interactions were observed in Phase 3 trials.

The incidence of adverse events was higher in subjects ≥ 65 years of age in both treatment groups. The incidence of TEAEs in subjects ≥ 65 years versus subjects < 65 years of age was 72.4% vs. 64.4% in the fidaxomicin group and 69.8% vs. 61.1% in the vancomycin group, respectively (Table 39).

The incidence of TEAEs reported under SOC of gastrointestinal disorders was similar in both age groups and treatment groups. The events related to GI hemorrhage were more prevalent in the fidaxomicin group, but were observed at the same rate in patients < 65 years and ≥ 65 years, 3.4% and 2.9%, respectively.

The incidence of leukopenia and neutropenia when reported as TEAEs was higher in the fidaxomicin group, but was not more prevalent in older subjects. On the other hand, when low lymphocytes were reported as markedly abnormal hematology measurements, a more pronounced decrease in lymphocytes was reported in fidaxomicin- when compared to vancomycin-treated subjects ≥ 65 years of age. Abnormally low lymphocyte values were reported in 5.3% vs. 2.4% of subjects ≥65 years of age and in 2.7% vs. 1.7% of subjects <65 years of age in the fidaxomicin and vancomycin groups, respectively.

The incidence of SAEs in subjects ≥65 years of age was similar in the fidaxomicin (30.9%) and vancomycin (28.8%) groups. In subjects <65 years of age, the overall incidence of SAEs was lower, but also similar in the fidaxomicin (20.9%) and vancomycin (17.4%) groups.

The clinical chemistry parameters reported at the highest incidence in the fidaxomicin and vancomycin groups, respectively, were abnormally high glucose values in subjects ≥65 years of age (8.1% vs. 4.8%). In comparison, high glucose values were reported in 3.1% vs. 4.8 %, respectively, of subjects <65 years of age.

Table 39 Incidence of TEAEs and Markedly Abnormal Laboratory Measurements by Age

	Fidaxomicin		Vancomycin	
	< 65 Years N=292	≥ 65 Years N=272	< 65 Years N=288	≥ 65 Years N=295
Subjects with ≥ 1TEAE	188 (64.4%)	197 (72.4%)	176 (61.1%)	206 (69.8%)
Gastrointestinal Disorders	87 (29.8%)	90 (33.1%)	86 (29.9%)	84 (28.5%)
Constipation	8 (2.7%)	17 (6.2%)	3 (1%)	9 (3%)
Gastrointestinal hemorrhage ¹	10 (3.4%)	8 (2.9%)	3 (1%)	2 (0.7%)
Megacolon	2 (0.7%)	1 (0.4%)	0 (0%)	0 (0%)
Neutropenia ²	18 (6.2%)	6 (2.2%)	6 (2.1%)	0 (0%)
Lymphopenia ³	5 (1.7%)	4 (1.5%)	2 (0.7%)	4 (1.4%)
Alanine Aminotransferase High	2 (0.7%)	5 (1.8%)	1 (0.3%)	2 (0.7%)
Bicarbonate Low	1 (0.3%)	8 (2.9%)	0 (0%)	3 (1%)
Glucose High	9 (3.1%)	22 (8.1%)	14 (4.9%)	14 (4.7%)
Lymphocyte Low	7 (2.4%)	12 (4.4%)	4 (1.4%)	6 (2%)

Adapted from ISS, Tables 11.1-1, 7, -8, -9, and -10, 14.3.1.1.2A_Age; Edited

¹ Includes preferred terms of diarrhea hemorrhagic, gastrointestinal hemorrhage, hematemesis hematochezia, hemorrhoidal hemorrhage, esophageal varices hemorrhage

² Includes preferred terms of febrile neutropenia, granulocytopenia, leukopenia, neutropenia, neutrophil count decreases, pancytopenia, white blood cell count decreased, and neutropenic sepsis

³ Includes preferred terms of lymphopenia, lymphocyte count decreased, lymphocyte count abnormal

There were 5 (1.8%) and 2 (0.7%) subjects ≥ 65 years with markedly abnormal alanine aminotransferase elevations in the fidaxomicin and vancomycin groups, respectively. In subjects < 65 years, alanine aminotransferase elevations were reported in 2 (0.7%) and 1 (0.4%) subjects in fidaxomicin and vancomycin groups, respectively. Abnormally low bicarbonate values was reported in 8 (3.4%) and 3 (1.2%) of subjects ≥ 65 years of age in the fidaxomicin and vancomycin groups, respectively. In comparison, in subjects <65 years of age, low bicarbonate values were reported in 0.3% vs. 0%, in the fidaxomicin and vancomycin groups, respectively.

Medical reviewer comments: More adverse events occurred in the elderly subjects in both treatment groups, which is expected. There is no clear association between the age and adverse events in fidaxomicin-treated subjects. The reported differences in WBC counts, glucose, ALT, and bicarbonate between age and treatment groups are of uncertain clinical significance at this point. However, post-marketing monitoring of these events may be warranted.

7.5.4 Drug-Disease Interactions

The overall incidence of TEAEs and serious TEAEs in explored drug disease categories was similar between the fidaxomicin and vancomycin groups. The incidence of serious adverse events is presented in Table 40 and 41. The explored drug-disease categories were as follows:

- No prior CDAD episode versus single prior CDAD episode

- Inpatient versus outpatient
- Baseline Strain Type (BI versus non-BI)
- Baseline UBM (< median [6] versus ≥ median [6])
- Renal insufficiency (Estimated Creatinine Clearance (eCCL): mild [51-79 mL/min], moderate [31-50], and severe [≤30])
- Baseline CDAD Disease Severity (ESCMID: non-severe versus severe)
- Hepatic Insufficiency (at least 1 toxicity Grade ≥2 for ALT, AST, or bilirubin at baseline vs. no toxicity Grade ≥2 for ALT, AST, or bilirubin)

The baseline disease severity categories were defined in both study 101.1.C.003 and 101.1.C.004 as follows:

- Mild CDAD: 4 to 5 UBMs per day or WBC ≤12000/mm³
- Moderate CDAD: 6 to 9 UBMs per day or WBC 12001 - 15000/mm³
- Severe CDAD: ≥10 UBMs per day or WBC ≥15001/mm³

Any 1 of the 2 defining characteristics could have assigned a subject to a category, with a default to the more severe category when signs/symptoms overlapped.

Table 40 Serious AEs by Disease Characteristics

	Number of Subjects		Subjects With ≥ 1 Serious TEAEs n (%)	
	Fidaxomicin	VANC	Fidaxomicin	Vancomycin
No prior CDAD episode	471	491	123 (26.1)	115 (23.4)
Single Prior CDAD Episode	93	92	22 (23.7)	20 (21.7)
Inpatient	358	372	130 (36.3)	118 (31.7)
Outpatient	206	211	15 (7.3)	17 (8.1)
BI Strain	143	148	47 (32.9)	42 (28.4)
Non-BI Strain	266	255	63 (23.7)	47 (18.4)
≥ 6 UBM at Baseline	349	343	77 (22.1)	75 (21.9)
< 6 UBM at Baseline	213	240	68 (31.9)	60 (25.0)
Severe Renal insufficiency (eCCL* ≤ 30 mL/min)	74	82	33 (44.6)	28 (34.1)
Mild Renal insufficiency (eCCL 51-79 mL/min)	129	131	33 (25.6)	29 (22.1)
Hepatic Toxicity at Baseline	17	21	7 (41.2)	11 (52.4)
No Hepatic Toxicity at Baseline	547	562	138 (25.2)	124 (22.1)

eCCL* - estimated creatinine clearance

Adapted from ISS Tables 11.2-3, -4, -13, -14, -23, 24, -33, -34, -44, 46, -58, -59, -68, and -69

The incidence of adverse events did not depend on the history of prior CDAD. In subjects with no prior episode of CDAD, the overall incidence of TEAEs was similar for

the fidaxomicin (69.4%) and vancomycin (66.8%) groups. In subjects with a single prior episode of CDAD, the overall incidence of TEAEs was similar for subjects in the fidaxomicin (62.4%) and vancomycin (58.7%) groups.

There were somewhat more SAEs reported under the SOC of GI disorders in the fidaxomicin BI strain population than in the vancomycin BI strain population, [8 (5.6%) vs. 4 (2.7%)] (Table 41). All three cases of megacolon occurred in subjects infected with the BI strain. In contrast, the incidence of serious TEAEs reported under the SOC of gastrointestinal disorders in non-BI subjects was 10 (3.8%) vs. 13 (5.1%), respectively.

Table 41 Selected SAEs by Baseline Strain Type

	Fidaxomicin		Vancomycin	
	BI strain N=143 n (%)	non-BI strain N=266 n (%)	BI strain N=148 n (%)	non-BI strain N=255 n (%)
Subjects with ≥ 1 TEAE	104 (72.7)	171 (64.3)	104 (70.3)	156 (61.2)
Subjects with ≥ 1 SAE	47 (32.9)	63 (23.7)	42 (28.4)	47 (18.4)
Gastrointestinal Disorders	8 (5.6)	10 (3.8)	4 (2.7%)	13 (5.1)
Abdominal Rebound Tenderness / Pain	0 (0)	3 (1.1)	1 (0.7)	1 (0.4)
Colitis	1 (0.7)	-	0 (0)	
Diarrhea	1 (0.7)	1 (0.4)	0 (0)	1 (0.4)
Diarrhea hemorrhagic	-	1 (0.4)	-	0 (0)
Gastrointestinal Hemorrhage	1 (0.7)	2 (0.8)	1 (0.7)	0 (0)
Gastrointestinal Perforation	1 (0.7)	0 (0)	0 (0)	1 (0.4)
Megacolon	3 (2.1)	-	0 (0)	-
Intestinal Obstruction	0 (0)	2 (0.8)	1 (0.7)	1 (0.4)
Upper Gastrointestinal Hemorrhage	0 (0)	0 (0)	1 (0.7)	1 (0.4)
Ileus	-	0 (0)	-	2 (0.8)
Lymphopenia ¹	1 (0.7)	4 (1.5)	2 (1.4)	0 (0)
Neutropenia ²	0 (0)	6 (2.3)	1 (0.7)	0 (0)

Adapted from ISS Table 11.2-23, -24

¹ Includes preferred terms lymphopenia, lymphocyte count decreased

² Febrile neutropenia, neutropenia, neutropenic sepsis, neutrophil count decreased, granulocytopenia

Some differences in the incidence of SAEs were observed between the fidaxomicin and vancomycin groups in subjects with severe renal insufficiency, defined as eCCL ≤ 30 mL/min, 44.6% vs. 34.1%, respectively. In contrast, in subjects with mild renal insufficiency, (eCCL 51-79 mL/min), the overall incidence of SAEs was similar between fidaxomicin and vancomycin patients, 25.6% vs. 22.1%, respectively.

There were no differences in SAEs between fidaxomicin and vancomycin subjects with baseline liver toxicity defined as at least one toxicity Grade ≥ 2 for ALT, AST, or bilirubin, 64.7% vs. 66.7% respectively. The low number of patients makes the interpretation of these data limited.

There were somewhat more SAEs in fidaxomicin-treated subjects with severe CDAD at baseline when compared to vancomycin-treated subjects, 64 (42.3%) vs. 51 (34.0%) (Table 42). The rates of SAEs related to GI disorders were 14 (9.9%) vs. 9 (6.0%) in the fidaxomicin and vancomycin groups, respectively. There were no obvious correlations between the severity of CDAD and such SAEs as decrease in WBC counts or gastrointestinal hemorrhages.

Table 42 Incidence of Selected Treatment Emergent Serious AEs by Baseline CDAD Severity

System Organ Class Preferred Term	Fidaxomicin		Vancomycin	
	Severe N=142	Non Severe N=422	Severe N=150	Non Severe N=433
Total Subjects with ≥ 1 SAE	60 (42.3%)	85 (20.1%)	51 (34.0%)	84 (19.4%)
Leukopenia	1 (0.7%)	3 (0.7%)	1 (0.7%)	0 (0%)
Lymphopenia	2 (1.4%)	1 (0.2%)	0 (0%)	2 (0.5%)
Neutropenia	Not reported	4 (0.9%)	Not reported	0(0%)
Gastrointestinal Disorders	14 (9.9%)	12 (2.8%)	9 (6.0%)	15 (3.5%)
Gastrointestinal Hemorrhage	3 (2.1%)	1 (0.2%)	1 (0.7%)	0 (0%)
Diarrhea Hemorrhagic	1 (0.7%)	1 (0.2%)	0 (0%)	0 (0%)
Megacolon	3 (2.1%)	0 (0%)	0 (0%)	0 (0%)

Adapted from Integrated Summary of Safety, Tables 11.2-58, -59

Medical reviewer comments: No clinically meaningful differences between fidaxomicin and vancomycin in the incidence of SAEs by disease characteristics were observed. There were some numerical imbalances observed in different subgroups, but overall the safety profile of fidaxomicin and the comparator appear to be similar. The difference in SAEs between fidaxomicin and vancomycin treated subjects with severe renal insufficiency is probably related to more severe disease in these subjects. Urine excretion represents < 1% of total fidaxomicin dose and plasma concentrations of fidaxomicin were not affected by renal impairment in phase 3 trials.

7.5.5 Drug-Drug Interactions

Fidaxomicin is poorly absorbed and metabolized primarily by esterase to OP-1118. The majority of the fidaxomicin dose is excreted in the feces as unchanged fidaxomicin or unmetabolized OP-1118. There are no known drugs in the market that cause clinically relevant drug interactions by inhibiting esterases and the inhibition of metabolism of fidaxomicin is not anticipated.

However, *in vitro* studies have shown that fidaxomicin is a substrate for efflux transporters (e.g. p-glycoprotein) as well as an inhibitor of efflux of the P-glycoprotein (P-gp) substrate, digoxin. In addition, fidaxomicin and its primary metabolite, OP-1118, have the ability to inhibit cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4/5 *in vitro*.

Three clinical studies (OPT-80-007, OPT-80-008, and OPT-80-009) were conducted to evaluate the drug-drug interaction effects of fidaxomicin.

Study OPT-80-008 suggested that fidaxomicin has little effect on digoxin PK. Co-administration of digoxin with steady state fidaxomicin in healthy subjects resulted in a 14% increase in digoxin C_{max} values, and no significant change in digoxin AUC.

Study OPT-80-009 concluded that fidaxomicin did not alter the drug metabolizing capacity of CYP enzymes to metabolize warfarin, omeprazole, or midazolam.

Study OPT-80-007 demonstrated a statistically significant increase in fidaxomicin and OP-1118 exposure in the presence of 200 mg cyclosporine, a P-gp inhibitor. (Figure 2)

Fidaxomicin mean C_{max} and AUC values were 4.15- and 1.92-fold greater, respectively, when co-administered with cyclosporine compared to fidaxomicin treatment alone. Fidaxomicin metabolite OP-1118 C_{max} and AUC values were 9.51- and 4.11-fold greater, respectively, when fidaxomicin was co-administered with cyclosporine compared to fidaxomicin administered alone. There were no clinically significant changes or findings in clinical laboratory evaluations, vital sign measurements, physical examinations, or 12-lead ECGs for this study.

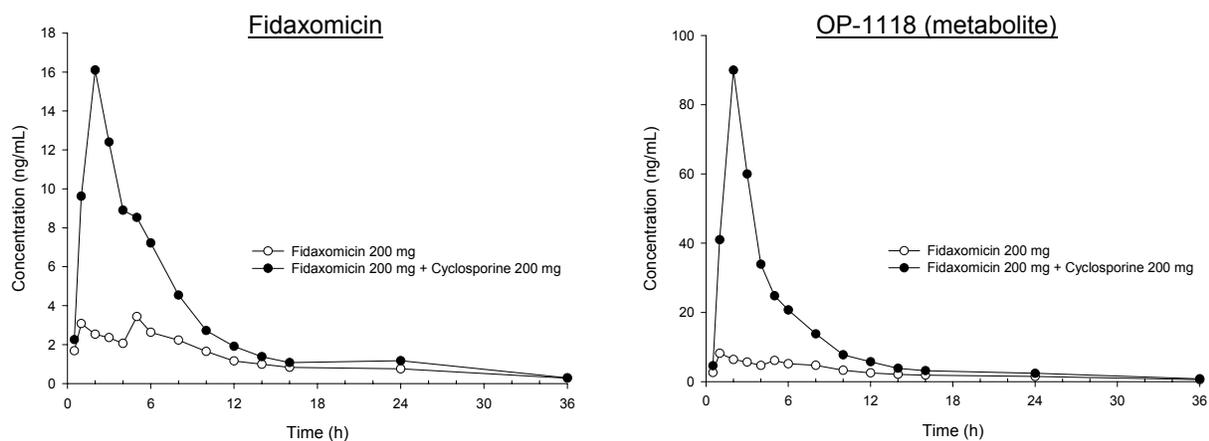


Figure 2 Increase in fidaxomicin and its metabolite in the presence of cyclosporine

In phase 3 studies, there were 240 subjects in the fidaxomicin group and 242 subjects in the vancomycin group who used P-gp inhibitors. P- gp inhibitors were identified as: omeprazole, esomeprazole, atorvastatin, carvedilol, azithromycin, cefuroxime, diltiazem and diltiazem HCl, verapamil and verapamil HCl, quinidine and quinidine gluconate, cetirizine, clotrimazole, ketoconazole, posaconazole, cyclosporine, atazanavir and atazanavir sulfate, lopinavir, and taxol. The mean duration of exposure to fidaxomicin and vancomycin was 10.0 and 10.1 days, respectively, for subjects who used P- gp inhibitors.

A higher incidence of TEAEs was reported in subjects who used P-gp inhibitors than in subjects who did not for both fidaxomicin and vancomycin subjects. The incidence of TEAEs was similar for P-gp inhibitor recipients in the fidaxomicin and vancomycin groups (73.8% vs. 72.3%), (Table 43). In subjects who did not use P-gp inhibitors, the overall incidence of TEAEs was also similar for subjects in the fidaxomicin (64.2%) and vancomycin (60.7%) groups.

Previously noted higher rates of decreases in WBC counts and GI-hemorrhages in fidaxomicin-treated subjects compared with vancomycin treated subjects were again observed. However, no meaningful differences in TEAEs were observed between P-gp inhibitor users and non-users within the fidaxomicin and vancomycin groups.

Table 43 Selected Treatment-Emergent Adverse Events by Use of P-Glycoprotein Inhibitors: Phase 3 trials

System Organ Class Preferred Term	Fidaxomicin		Vancomycin	
	Yes N=240 n (%)	No N=324 n (%)	Yes N=242 n (%)	No N=341 n (%)
Subjects with ≥ 1 TEAE	177 (73.8)	208 (64.2)	175 (72.3)	207 (60.7)
Blood And Lymphatic System Disorders	20 (8.3)	17 (5.2)	13 (5.4)	12 (3.5)
Neutropenia ¹	11 (4.6)	13 (4.0)	3 (1.2)	3 (0.9)
Lymphopenia ²	6 (2.5)	3 (0.9)	2 (0.8)	3 (0.9)
Thrombocytopenia	3 (1.3)	3 (0.9)	3 (1.2)	2 (0.6)
Gastrointestinal Disorders	70 (29.2)	107 (33.0)	76 (31.4)	94 (27.6)
Diarrhea Hemorrhagic	2 (0.8)	-	0 (0)	-
Gastrointestinal Hemorrhage	1 (0.4)	4 (1.2)	1 (0.4)	0 (0)
Haematochezia	3 (1.3)	4 (1.2)	1 (0.4)	0 (0)
Vomiting	20 (8.3)	21 (6.5)	15 (6.2)	22 (6.5)
Alanine Aminotransferase Increased	6 (2.5)	3 (0.9)	2 (0.8)	4 (1.2)
Hyperglycemia	4 (1.7)	3 (0.9)	3 (1.2)	4 (1.2)

Adapted from ISS Table 14.3.1.1.2A_CI

¹ includes preferred terms of Febrile Neutropenia, Granulocytopenia, Leukopenia, Neutropenia, Pancytopenia, Neutrophil count decreased, White Blood Cell Count Decreased, and Neutropenic sepsis.

² includes preferred terms of Lymphopenia, Lymphocyte count abnormal, and Lymphocyte count decreased

The incidence of serious adverse was also higher in P-gp inhibitor users for both fidaxomicin and vancomycin groups, 30.4% and 34.3%, respectively (Table 44). The

incidence of serious adverse in fidaxomicin and vancomycin subjects who did not take P-gp inhibitors was 22.2% and 15.2%, respectively. No differences in SAEs were observed between P-gp inhibitor users and non-users within the fidaxomicin and vancomycin groups.

Table 44 Selected Treatment-Emergent Serious Adverse Events by Use of P-Glycoprotein Inhibitors: Phase 3 trials

	Fidaxomicin		Vancomycin	
	Yes N=240 n (%)	No N=324 n (%)	Yes N=242 n (%)	No N=341 n (%)
Subjects with ≥ 1 SAE	73 (30.4%)	72 (22.2%)	83 (34.3%)	52 (15.2%)
Leukopenia	1 (0.4)	3 (0.9)	0 (0)	1 (0.3)
Lymphopenia	1 (0.4)	2 (0.6)	1 (0.4)	1 (0.3)
Lymphocyte Count Decreased / Abnormal	3 (1.3)	1 (0.3)	1 (0.4)	1 (0.3)
Neutropenia	1 (0.4)	3 (0.9)	0 (0)	0 (0)
Hyperglycemia	1 (0.4)	1 (0.3)	3 (1.2)	0 (0)
Diarrhea Hemorrhagic	Not reported	2 (0.6)	Not reported	0 (0)
Gastrointestinal Hemorrhage	1 (0.4)	3 (0.9)	1 (0.4)	0 (0)

Adapted from ISS Table 10.1-17, 18.

With regard to efficacy, P-gp recipients in both fidaxomicin and vancomycin group demonstrated higher recurrence rates. However, the global cure rate was still higher in fidaxomicin-treated subjects relative to vancomycin.

Table 45 Impact of P-gp inhibitor use on Phase 3 efficacy (pooled)

	Fidaxomicin		Vancomycin	
	P-gp Inhibitor Use		P-gp Inhibitor Use	
	No	Yes	No	Yes
Clinical Cure				
mITT	281/312 (90.1%)	196/230 (85.2%)	289/331 (87.3%)	196/232 (84.5%)
PP	265/285 (93.0%)	181/200 (90.5%)	276/299 (92.3%)	187/215 (87.0%)
Recurrence				
mITT	31/281 (11.0%)	37/196 (18.9%)	69/289 (23.9%)	57/196 (29.1%)
PP	23/238 (9.7%)	28/156 (17.9%)	53/242 (21.9%)	46/158 (29.1%)
Global Cure				
mITT	250/312 (80.1%)	159/230 (69.1%)	220/331 (66.5%)	139/232 (59.9%)
PP	235/285 (82.5%)	146/200 (73.0%)	209/299 (69.9%)	132/215 (61.4%)

Medical reviewer comments: concomitant administration of P-glycoprotein inhibitors did not appear to increase the incidence of adverse events in fidaxomicin treated patients.

Use of Systemic Anti-infective Therapy during Treatment Period

The variations between fidaxomicin and vancomycin treated subjects in the overall incidence of treatment emergent SAEs did not depend on the concomitant use of systemic anti-infectives.

There were 160 subjects in the fidaxomicin and 166 in vancomycin groups in phase 3 trials that received systemic anti-infectives other than those used for the treatment of CDAD. In these subjects, the mean duration of exposure to study drug was 9.7 and 9.8 days and the overall incidence of treatment emergent SAEs was 36.9% and 38.6% in the fidaxomicin and vancomycin groups, respectively. There were 404 and 417 subjects in the fidaxomicin and vancomycin groups who did not receive concomitant anti-infectives. In these subjects the overall incidence of treatment-emergent SAEs was 21.3% in the fidaxomicin and 17.0% in vancomycin groups.

Adverse events related to GI hemorrhage and decrease in WBC counts occurred more frequently among fidaxomicin-treated patients regardless of the use of other antimicrobials. The difference in abnormally low lymphocyte values was more pronounced in the fidaxomicin subjects who used systemic antimicrobial therapy when compared to vancomycin subjects, (7.6% vs. 3.0%), respectively.

Medical Reviewer comments: The increase of adverse events in subjects treated with systemic antimicrobials is likely related to underlying comorbidities and to adverse events associated with their use.

Interaction with Other Antibacterials

The interaction of fidaxomicin and its metabolite (OP-1118) with ampicillin, azithromycin, ciprofloxacin, clindamycin, metronidazole, rifampin, telithromycin, and vancomycin was studied in vitro against *C. difficile* American Type Culture Collection (ATCC) 43255, using the checkerboard technique (Study BIO021109A).

The interaction of fidaxomicin with OP-1118 was neither synergistic nor antagonistic. Neither fidaxomicin nor its main metabolite OP-1118 demonstrated antagonistic interactions with the other classes of antibiotics. Synergy was observed with the rifamycins. Weak synergy was observed with metronidazole and ampicillin. The interactions of macrolides/ketolides with fidaxomicin and OP-1118 could not be determined by the method used.

Medical reviewer comments: Clinical significance of these results has not been established.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies were not conducted for fidaxomicin. Fidaxomicin tested positive in the in vitro Chinese hamster ovary (CHO) chromosomal aberration assay, but was negative in the in vitro bacterial reverse mutation assay and the in vivo micronucleus study. Given the short expected duration of treatment in humans (10 days), the likelihood of a carcinogenic risk is considered to be minimal.

7.6.2 Human Reproduction and Pregnancy Data

No adequate and well-controlled studies with fidaxomicin have been conducted in pregnant women. Studies in rats did not reveal changes in reproductive or fertility parameters and no maternal and development toxicity was observed. There was a case of pregnancy in the fidaxomicin group in phase 3 trials (subject 003-009021) described in section 7.3.2 of this review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Fidaxomicin has not been evaluated to date in children below 18 years of age and is not proposed for use in the pediatric population in this application.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please, refer to Subsection 7.3.2 for the description of an overdose case. Given the relatively short treatment period, no withdrawal or rebound effects have been observed; no such effects are anticipated.

7.7 Additional Submissions / Safety Issues

Following NDA submission, fidaxomicin was not actively being studied in clinical trials or marketed anywhere in the world. No additional safety issues have been identified.

8 Postmarket Experience

None

9 Appendices

Appendix 1. Time and Events Schedule (Source: Applicant's CSR 101.1.C.004)

Assessments	Pre-Randomization/ Randomization Day 1 ^a	Treatment Period ^a Days 2-9	End-of- Therapy Visit Day 10-11	Contact ^b Days 12-31	Unscheduled Visit for Recurrence ^c	Early Termination	Post-study Visit ^{b,c} Days 36-40
Informed Consent	X						
Inclusion/Exclusion	X						
Medical history	X						
Physical examination	X		X		X	X	X
ECG ^{k,l}	X	X ^k	X ^l			X ^k	
Vital signs ^d	X		X		X	X	X
Clinical laboratory tests	X		X			X	
PK blood samples ^{e,i}	X ^e	X ^e	X ^{e,i}			X ^{e,k}	
Stool sample ^{f,g,h}	X ^f		X ^h		X ^{f,g}	X ^{f,g,h}	
Adverse events	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X
Pregnancy test ⁱ	X						
Investigator evaluation of signs & symptoms of CDI ^j	X	X	X	X ⁿ	X	X	X
Determine clinical response			X	X		X	
Assess outcome regarding recurrence					X		X
Study medication administration	X ^m	X	X				
Subject interview (CDI status) ^b	X	X	X	X	X	X	X

^a Subjects could be treated on a combined inpatient/outpatient basis at the discretion of the Investigator. All assessments occurred daily on Days 2-13. Day 1 = Treatment Period (Day 1).

^b Subject interviews daily up to End-of-Therapy visit (± 2 days). These interviews could be conducted by telephone. Subjects were contacted 2-4 days after the last dose of study drug to determine clinical response and then weekly thereafter (Day 17 ± 1 day, Day 24 ± 1 day, Day 31 ± 1 day) until recurrence or Post-study Visit.

^c Subjects considered a primary cure but who subsequently discontinued from the study for any reason (e.g., recurrence) before the Post-study Visit had all Post-study Visit procedures performed.

^d Included blood pressure, pulse, and body temperature. Height and weight were collected at Day 1 visit only.

^e PK samples were obtained on Day 1 before dosing and between 3 and 5 hours after dosing. A PK sample was collected if subject experienced an SAE during Days 1-13.

^f Stool sample was split in 2 aliquots, 1 for toxin assay at study site and 1 for reference laboratory (for microbiological testing).

^g Performed in subjects meeting criteria for diarrhea.

^h Stool sample collected for PK analysis.

ⁱ Urine pregnancy tests were used to qualify the subject for randomization. For the duration of the study, if there was a suspicion of pregnancy, a confirmatory serum test was performed.

^j PK samples were obtained before dosing and 3 to 5 hours after dosing providing the first or third dose of the last pack was administered in the clinic. If this dose was not administered in the clinic, a single PK sample was collected and the date and time of sample collection were recorded.

^k An ECG was performed for any subject who experienced a cardiovascular-related significant medical event (e.g., tachyarrhythmia).

^l ECG was collected immediately before the PK sample.

^m Study drug was administered after all other baseline Day 1 procedures were completed.

ⁿ For hospitalized subjects only.

KEY: ECG = Electrocardiogram; PK = Pharmacokinetic(s); CDI = *C. difficile*-infection.

Clinical Review
Dmitri Iarikov, MD, PhD
NDA 201699, Difucid (fidaxomicin)

9.1 Literature Review/References

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2. Clabots CR, Johnson S, Bettin KM, et al. Development of a rapid and efficient restriction endonuclease analysis typing system for *Clostridium difficile* and correlation with other typing systems. *J Clin Microbiol.* Jul 1993;31(7):1870-1875.

9.2 Labeling Recommendations

At the time of the review preparation the reviewer had no specific comments on labeling.

9.3 Advisory Committee Meeting

The Anti-Infective Drugs Advisory Committee met on April 5, 2011 in Hilton Washington DC/Silver Spring, MD to discuss NDA 201699 for fidaxomicin for the treatment of CDAD in adults submitted by Optimer Pharmaceuticals Inc. All thirteen members of Advisory committee voted yes on the question whether the Applicant demonstrated the safety and effectiveness if fidaxomicin for the treatment of CDAD.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DMITRI IARIKOV
04/25/2011

JOHN J ALEXANDER
04/25/2011

CLINICAL FILING CHECKLIST FOR NDA 201699

Drug Name: Difcid (fidaxomicin) Applicant: Optimer Pharmaceuticals, Inc.

NDA/BLA Number: 201699

**Applicant: Optimer
Pharmaceuticals, Inc.**

Stamp Date: 11/30/2010

Drug Name: Difcid (fidaxomicin) NDA/BLA Type: 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? <u>Study Number:</u> Protocol # OPT-80 Phase 2A <u>Study Title:</u> An Open-Label, Dose Ranging, Randomized Clinical Evaluation of OPT-80 in Patients with <i>Clostridium difficile</i> -associated Diarrhea (CDAD) <u>Sample Size:</u> 48 subjects: 16 subjects each in the 100 mg/day, 200 mg/day, and 400 mg/day treatment groups. <u>Arms:</u> Subjects were randomized to receive either 100 (50 mg q12h), 200 (100 mg q12h), or 400 (200 mg q12h) mg/day for 10 days <u>Location in submission:</u> Module 5.3.5.1	X			
EFFICACY					

CLINICAL FILING CHECKLIST FOR NDA 201699

Drug Name: Difcid (fidaxomicin) Applicant: Optimer Pharmaceuticals, Inc.

	Content Parameter	Yes	No	NA	Comment
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1 101.1.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 Q12 h with 125mg Vancomycin Taken Q 6h for Ten Days in Subjects with <i>Clostridium difficile</i>-Associated Diarrhea</p> <p style="text-align: center;">Indication: <i>Clostridium difficile</i>-Associated Diarrhea</p> <p>Pivotal Study #2 101.1.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 Q12 h with 125mg Vancomycin Taken Q 6h for Ten Days in Subjects with <i>Clostridium difficile</i>-Associated Diarrhea</p> <p style="text-align: center;">Indication: <i>Clostridium difficile</i>-Associated Diarrhea</p>	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA 201699

Drug Name: Difcid (fidaxomicin) Applicant: Optimer Pharmaceuticals, Inc.

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 201699
Drug Name: Difcid (fidaxomicin) Applicant: Optimer Pharmaceuticals, Inc.

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Dmitri Iarikov, MD, PhD Date

Clinical Team Leader John Alexander, MD, MPH Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DMITRI IARIKOV
01/12/2011

JOHN J ALEXANDER
01/12/2011