

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201699Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 201-699	<b>Reviewer:</b> Elsbeth Chikhale, PhD	
<b>Submission Date:</b>	November 29, 2010		
<b>Division:</b>	Division of Anti-Infective & Ophthalmology Products	<b>Team Lead:</b> Angelica Dorantes, PhD	
<b>Applicant:</b>	Optimer Pharmaceuticals. Inc.	<b>Supervisor:</b> Patrick Marroum, PhD	
<b>Trade Name:</b>	Dificid (fidaxomicin) Tablets	<b>Date Assigned:</b>	November 26, 2010
<b>Generic Name:</b>	Fidaxomicin	<b>Date of Review:</b>	April 13, 2011
<b>Indication:</b>	Treatment of <i>Clostridium difficile</i> infection (CDI) and prevention of recurrences.	<b>Type of Submission:</b> Original New Drug Application	
<b>Dosage form/ Strengths:</b>	Tablet/ 200 mg		
<b>Route of Administration</b>	Oral		
<b><u>SUBMISSION:</u></b>			
<p>In accordance with Section 505(b)(1) of the FD&amp;C Act and 21 CFR 341.50, the applicant has submitted a rolling NDA for Dificid (fidaxomicin) tablets for the treatment of <i>Clostridium difficile</i> infection (CDI) and prevention of recurrences. This NDA has priority review status. The active pharmaceutical ingredient in Dificid drug product is fidaxomicin, a member of a class of antibiotics called macrocycles, with a narrow spectrum antibacterial profile, potent bactericidal activity against <i>C. difficile</i>, and very low systemic availability. Fidaxomicin is a BCS class 4 (low solubility &amp; low permeability) compound. Low or no systemic availability is preferred because the infection/site of action is in the GI tract.</p>			
<b><u>BIOPHARMACEUTIC INFORMATION:</u></b>			
<p>The drug product, Dificid, is an immediate release, solid oral dosage form (tablet) containing 200 mg of fidaxomicin. Four drug product formulations (liquid-filled capsules for phase 1, powder-filled capsules for phase 2, uncoated tablets for the first phase 3 trial, and coated tablets for first and second phase 3 trial) were investigated during the drug product development. <span style="float: right;">(b) (4)</span></p> <div style="background-color: gray; width: 100%; height: 100px; margin-top: 10px;"></div>			

CMC information for the phase 3 clinical batches:

Clinical Study Number	Dosage Strength and Form	Drug Substance Lot(s)	Drug Product Lot	Site of Manufacture
101.1.C.003	200 mg uncoated tablet (b) (4)	B-0560065	181338	(b) (4)
		B-0660017	183194	
101.1.C.003 101.1.C.004	200 mg film coated tablet (b) (4)	B-0660051	184732	
		B-0660064	R0240001	
		B-0660051 B-0660072	R0242001	
		B-0660051 B-0660064	R0242002	

The composition of the two phase 3 trial formulations:

Dosage Form	Uncoated tablet		Film-coated tablet	
Dosage Strength	200 mg		200 mg	
Composition	Function	Amount Per Unit Dose	Function	Amount Per Unit Dose
<b>Drug Substance</b>				
Fidaxomicin	Active Ingredient	200 mg	Active Ingredient	200 mg
<b>Excipients</b>				
Microcrystalline Cellulose	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Pregelatinised Starch	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hydroxypropyl Cellulose	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Starch Glycolate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Butylated Hydroxytoluene	-	-	(b) (4)	(b) (4)
Magnesium Stearate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	-	-	(b) (4)	(b) (4)
(b) (4)	-	-	(b) (4)	*
<b>Total Tablet Weight</b>		<b>350 mg</b>		<b>360.0 mg</b>
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

The film-coated tablets are proposed for the commercial to-be-marketed formulation of the drug product.

**RECOMMENDATION:**

- The dissolution specification (method and revised acceptance criterion of  $Q = \frac{(b)}{(4)}$  at 45 minutes) is acceptable.
- Despite the fact that the old and new formulations, used during the phase 3 clinical trials, could not be linked by comparative dissolution data, it is still acceptable to include the ~ 100 patients who used the old formulation in the analysis of the clinical data.
- Over-encapsulation of the drug (Dificid) and the comparator drug (Vancocin), in the phase 3 clinical trial is acceptable for blinding purpose.

**Signature**

Elsbeth G. Chikhale, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Signature**

Patrick Marroum, Ph.D.  
Biopharmaceutics Supervisor  
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cc: Angelica Dorantes, Ph.D.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELSBETH G CHIKHALE  
04/13/2011

PATRICK J MARROUM  
04/14/2011

## CLINICAL PHARMACOLOGY REVIEW

<b>NDA: 201-699</b>	Submission Date(s): <ul style="list-style-type: none"> <li>• 29 Nov 2010 (SDN 003)</li> <li>• 28 Jan 2011 (SDN 009)</li> <li>• 01 Apr 2011 (SDN 011)</li> </ul>
<b>Drug</b>	Fidaxomicin
<b>Trade Name</b>	Dificid™ (proposed)
<b>OCP Reviewers</b>	Aryun Kim, Pharm.D.
<b>OCP Team Leader</b>	Kimberly Bergman, Pharm.D.
<b>OCP Division</b>	DCP4
<b>OND division</b>	DAIOP (520)
<b>Sponsor</b>	Optimer Pharmaceuticals, Inc., San Diego, CA
<b>Relevant IND(s)</b>	IND 64,435
<b>Submission Type; Code</b>	Original New Drug Application (New Molecular Entity), 1P
<b>Formulation; Strength(s)</b>	200 mg immediate-release tablet
<b>Indication</b>	Treatment of <i>Clostridium difficile</i> infection (CDI), also known as <i>Clostridium difficile</i> -associated diarrhea (CDAD), and for reducing the risk of recurrence when used for treatment of initial CDI (proposed)
<b>Dosage and Administration</b>	One 200 mg tablet twice daily for 10 days for adults (≥18 years of age)

<b>1. EXECUTIVE SUMMARY</b>	
<b>1.1 Recommendations</b>	4
<b>1.2 Phase 4 Commitments</b>	4
<b>1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings</b>	4
<b>2. QUESTION-BASED REVIEW</b>	8
<b>2.1 General Attributes of the Drug</b>	8
<b>2.2 General Clinical Pharmacology</b>	9
<b>2.3 Intrinsic Factors</b>	23
<b>2.4 Extrinsic Factors</b>	27
<b>2.5 General Biopharmaceutics</b>	35
<b>2.6 Analytical Section</b>	37
<b>3. DETAILED LABELING RECOMMENDATIONS</b>	40
<b>4. APPENDICES</b>	61
<b>4.1 Individual Study Reviews</b>	61
<b>4.1.1 In Vitro Studies</b>	61
<b>4.1.2 General Pharmacokinetics</b>	76
Study OPT-80 1A-SD	77
Study OPT-80 1B-MD	82
Study OPT-80-005	86
Study 101.1.C.003	96

	Study 101.1.C.004.....	98
<b>4.1.3</b>	<b>Extrinsic Factors</b> .....	<b>100</b>
	Study OPT-80-007.....	101
	Study OPT-80-008.....	110
	Study OPT-80-009.....	117

ATCC, American Type Culture Collection  
AUC<sub>0-3</sub>, area under the concentration-time curve over 0-3 hours  
AUC<sub>0-inf</sub>, area under the concentration-time curve from time 0 to infinity  
AUC<sub>0-t<sub>l</sub></sub>, area under the concentration-time curve from time 0 to last measured concentration  
BI, epidemic hyper-virulent strain of *Clostridium difficile*  
C<sub>max</sub>, maximum observed plasma concentration  
CDAD, *Clostridium difficile*-associated diarrhea  
CI, confidence interval  
CrCL, creatinine clearance  
CV, coefficient of variation  
CYP, cytochrome P450  
DDI, drug-drug interaction  
ECG, electrocardiogram  
EOT, end-of-therapy visit  
FDX, fidaxomicin  
FIC, fractional inhibitory concentration  
GI, gastrointestinal  
[I]<sub>2</sub>, intestinal concentration estimated as dose divided by 250 mL  
IC<sub>50</sub>, half maximal inhibitory concentration  
LC-MS/MS, liquid chromatography tandem mass spectrometry  
LLOQ, lower limit of quantification  
mITT, modified intent-to-treat population  
MIC, minimum inhibitory concentration  
MIC<sub>50</sub>, minimum inhibitory concentration for 50% of the bacterial population  
MIC<sub>90</sub>, minimum inhibitory concentration for 90% of the bacterial population  
NDA, new drug application  
ONDQA, Office of New Drugs Quality Assessment  
OP-1118, major metabolite of fidaxomicin  
OPT-80, fidaxomicin  
P-gp, P-glycoprotein  
PAE, post-antibiotic effect  
PAR-101, fidaxomicin  
PO, oral  
PP, per-protocol population  
Q6h or Q12h, every 6 hours or every 12 hours  
QTcF, corrected QT interval by the Fridericia method  
RNA, ribonucleic acid  
SAE, serious adverse event  
SD, standard deviation  
t<sub>1/2</sub>, apparent elimination half-life  
T<sub>max</sub>, time to maximum observed plasma concentration  
TEAE, treatment-emergent adverse event  
UBM, unformed bowel movement  
ULOQ, upper limit of quantification  
VAN, vancomycin  
WBC, white blood cell

## 1. EXECUTIVE SUMMARY

Optimer Pharmaceuticals Inc., submitted a New Drug Application (NDA) for fidaxomicin for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). Fidaxomicin is a locally-acting product that is mainly confined to the gastrointestinal (GI) tract (site of action/infection), with a narrow spectrum of activity, specifically against *C. difficile*. The proposed clinical dosing regimen is fidaxomicin 200 mg orally (PO) twice daily (i.e., every 12 hours, Q12h) for 10 days in adults  $\geq 18$  years of age.

Clinical components of the fidaxomicin NDA are summarized as follows:

- Ten *in vitro* studies using human biomaterials were submitted, evaluating metabolism by human intestinal/liver microsomes and hepatocytes, inhibition/induction of cytochrome P450 (CYP) isoenzymes, and efflux/inhibition of P-glycoprotein (P-gp).
- Six Phase 1 studies assessing the pharmacokinetics of fidaxomicin and its major active metabolite were submitted. Studies included single and multiple ascending dose pharmacokinetics, effect of food, and drug-drug interactions (DDI) via intestinal P-gp or CYP enzymes (CYP3A4, CYP2C9, and CYP2C19).
- One supportive Phase 2 trial evaluating the safety/efficacy of various fidaxomicin doses in the treatment of CDAD was submitted. Fidaxomicin regimens of 50, 100, and 200 mg twice daily were assessed for 10 days.
- Two pivotal Phase 3 trials evaluating the safety/efficacy of fidaxomicin versus PO vancomycin in the treatment of CDAD were submitted. Fidaxomicin 200 mg twice daily was compared to PO vancomycin 125 mg four times daily for 10 days in both trials.

### 1.1 Recommendations

The Office of Clinical Pharmacology, Division 4 has reviewed NDA 201-699, and it is acceptable from a clinical pharmacology perspective.

### 1.2 Phase 4 Commitments

None.

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

#### 1.3.1 Dose-Response

In a dose-ranging Phase 2 trial of fidaxomicin 50, 100, and 200 mg Q12h for 10 days (n=48), a clear dose-response relationship was evident, as efficacy was greatest and nearly maximized with the 200 mg Q12h regimen in clinical cure, symptom relief, and time to resolution of diarrhea. Contrastingly, there was no discernible dose-dependent trend in treatment-emergent adverse events, serious adverse events, death, or any parameter from laboratory tests, vital signs, physical exam, and electrocardiogram.

### 1.3.2 Pharmacokinetics

Pharmacokinetic parameters of fidaxomicin and its major active metabolite, OP-1118, following a single 200 mg dose in healthy adult males are summarized in **Table 1.3.2-1**. Systemic absorption is minimal following PO administration, with plasma concentrations of fidaxomicin and OP-1118 in the ng/mL range.

**Table 1.3.2-1.** Mean ( $\pm$  standard deviation) pharmacokinetic parameters following single 200 mg dose of fidaxomicin (fasted) in healthy adult males (n=14)

Parameter	Fidaxomicin		OP-1118	
	N	Value	N	Value
C <sub>max</sub> (ng/mL)	14	5.20 $\pm$ 2.81	14	12.0 $\pm$ 6.06
T <sub>max</sub> <sup>a</sup> (h)	14	2.00 (1.00-5.00) <sup>a</sup>	14	1.02 (1.00-5.00) <sup>a</sup>
AUC <sub>0-t</sub> (ng*h/mL)	14	48.3 $\pm$ 18.4	14	103 $\pm$ 39.4
AUC <sub>0-inf</sub> (ng*h/mL)	9	62.9 $\pm$ 19.5	10	118 $\pm$ 43.3
t <sub>1/2</sub> (h)	9	11.7 $\pm$ 4.80	10	11.2 $\pm$ 3.01

<sup>a</sup> T<sub>max</sub> reported as median (minimum-maximum)

C<sub>max</sub>, maximum observed concentration; T<sub>max</sub>, time to maximum observed concentration; AUC<sub>0-t</sub>, area under the concentration-time curve from time 0 to last measured concentration; AUC<sub>0-∞</sub>, area under the concentration-time curve from time 0 to infinity; t<sub>1/2</sub>, apparent elimination half-life

In Phase 3 patients treated with fidaxomicin 200 mg Q12h for 10 days (**Table 1.3.2-2**), “peak” plasma concentrations of fidaxomicin and OP-1118 (i.e., obtained within the T<sub>max</sub> window of 1-5 hours) were approximately 2-6 times higher and more variable (contributed by sampling) than C<sub>max</sub> values in healthy subjects. Plasma concentrations of OP-1118, but not fidaxomicin, appeared to increase (by 50-80%) with repeat dose administration in Phase 3 patients.

**Table 1.3.2-2.** Plasma concentrations at 1-5 h (T<sub>max</sub> window per Reviewer) following fidaxomicin 200 mg Q12h for 10 days in Phase 3 patients

	Concentration at 1-5 h (T <sub>max</sub> window) (ng/mL)			
	Fidaxomicin		OP-1118	
	Day 1	End of Therapy	Day 1	End of Therapy
N >LLOQ <sup>a</sup>	347/430 (80.7%)	130/160 (81.3%)	354/430 (82.3%)	133/160 (83.1%)
Mean	22.4	26.7	43.6	79.1
SD	28.3	31.1	54.0	121
Median	13.2	15.7	25.9	40.0
Minimum	0.26	0.31	0.24	1.09
Maximum	237	191	406	871

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

**Absorption:** *In vitro* studies with Caco-2 cells indicate fidaxomicin and OP-1118 are substrates of P-gp, an efflux transporter expressed in the GI tract with a known role in limiting PO bioavailability.

No clinically significant effect was observed with food on the systemic exposures of fidaxomicin and OP-1118, and thus, fidaxomicin may be administered with or without food.

**Distribution:** Fidaxomicin is mainly confined to the GI tract following PO administration. In select Phase 3 patients treated with fidaxomicin 200 mg Q12h for 10 days (n=8), concentrations of fidaxomicin and OP-1118, respectively, ranged 639-2710  $\mu$ g/g and 213-1210  $\mu$ g/g in feces

versus 0.002-0.179 µg/mL and 0.010-0.829 µg/mL in plasma (as “peak” concentrations within the 1-5 hour T<sub>max</sub> window).

**Metabolism:** *In vitro* studies with human intestinal and liver microsomes and hepatocytes indicate fidaxomicin is primarily transformed by hydrolysis at the isobutyryl ester to form the major active metabolite, OP-1118. CYP enzymes do not appear to play a major role in the metabolism of fidaxomicin or formation of OP-1118.

Across Phase 1 studies with single 200 mg doses, OP-1118 was the predominant circulating compound, followed by fidaxomicin, which represented approximately 50% of the metabolite AUC. OP-1118 possesses pharmacological activity that is weaker (by 32-fold) than the parent compound.

**Excretion:** Fidaxomicin and OP-1118 are primarily excreted in the feces. In one Phase 1 study, approximately 26.4% of the dose was recovered in stool as fidaxomicin and 66.2% as OP-1118, following single doses of 200 and 300 mg in healthy adults (n=11). In another Phase 1 study, approximately 0.59% of the dose was recovered in urine as OP-1118 only, following a single 200 mg dose in healthy adults (n=6).

### 1.3.3 Intrinsic Factors

Phase 1 studies were not performed to specifically evaluate the effect of intrinsic factors. Instead, intrinsic factors were assessed in Phase 3 trials, using “peak” plasma concentrations obtained within the 1-5 hour T<sub>max</sub> window following fidaxomicin 200 mg Q12h for 10 days.

**Elderly:** In Phase 3 trials, “peak” concentrations of fidaxomicin and OP-1118 were approximately 2-4 times higher in elderly (≥65 years of age) versus non-elderly (<65 years of age) patients, although values remained in the ng/mL range. There was a trend towards lower efficacy and higher incidence of adverse events with elderly age; however, similar effects were generally also observed for the active comparator. No dose adjustment is recommended in elderly patients.

**Gender:** In Phase 3 trials, “peak” concentrations of fidaxomicin and OP-1118 did not vary by gender. No dose adjustment is recommended based on gender.

**Renal Impairment:** In Phase 3 trials, there was no discernible trend with “peak” concentrations of fidaxomicin and OP-1118 across categories of renal impairment (defined using creatinine clearance, CrCL) as mild (51-79 mL/min), moderate (31-50 mL/min), or severe (≤30 mL/min). Moreover, renal impairment is not anticipated to significantly alter the pharmacokinetics of this non-renally and non-hepatically eliminated compound. No dose adjustment is recommended based on renal function.

### 1.3.4 Extrinsic Factors

Phase 1 DDI studies were conducted to investigate gut-mediated interactions with cyclosporine, digoxin, and midazolam/warfarin/omeprazole, by targeting transporters (P-gp) and enzymes (CYP3A4 followed by CYP2C9 and CYP2C19) prominent at the intestinal level.

**Cyclosporine (P-gp inhibitor):** Co-administration of cyclosporine 200 mg with fidaxomicin 200 mg in healthy adult males (n=14) increased plasma concentrations of fidaxomicin and OP-1118 by approximately 4-9 fold for  $C_{max}$  and 2-4 fold for  $AUC_{0-inf}$ , although values remained in the ng/mL range. In Phase 3 trials, there was a trend towards lower efficacy (in recurrence and global cure, but not clinical cure) and higher incidence of adverse events with P-gp inhibitor use; however, similar effects were generally also observed with the active comparator. It should be noted that efficacy rates of fidaxomicin surpassed those of PO vancomycin for nearly all endpoints and analysis populations, regardless of P-gp inhibitor use.

DDI via P-gp inhibition may decrease concentrations of the microbiologically active fidaxomicin and OP-1118 at the desired site of action/infection; however, the clinical implications of this DDI are unknown. Fidaxomicin may be co-administered with P-gp inhibitors.

**Digoxin (P-gp substrate):** Co-administration of digoxin 0.5 mg with fidaxomicin 200 mg Q12h in healthy adults (n=14) had no significant effect on the pharmacokinetics of digoxin. No dose adjustment is recommended for co-administration with substrates of P-gp.

**Midazolam/Warfarin/Omeprazole (CYP3A4/2C9/2C19 substrates):** Co-administration of midazolam 5 mg + warfarin 10 mg + omeprazole 40 mg (CYP cocktail) with fidaxomicin 200 mg Q12h in healthy adult males (n=24) had no significant effect on the pharmacokinetics of midazolam, warfarin, and omeprazole. No dose adjustment is recommended for co-administration with substrates of CYP enzymes.

## 2. QUESTION-BASED REVIEW

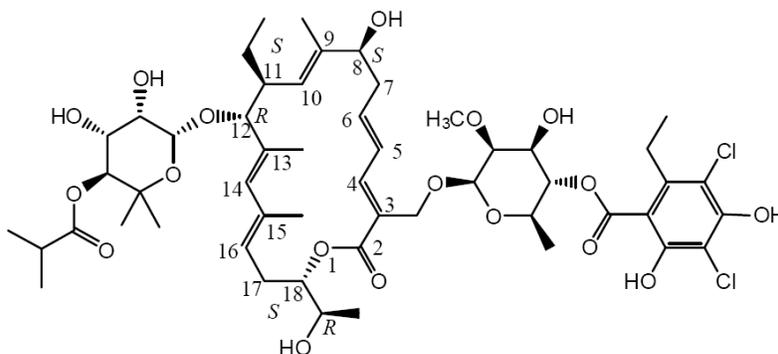
### 2.1 General Attributes of the Drug

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Fidaxomicin (previously OPT-80 and PAR-101) is proposed by the Sponsor (b) (4). Fidaxomicin has chemical properties suggestive of poor solubility and poor permeability, and accordingly, is poorly absorbed from the gastrointestinal (GI) tract.

The molecular formula of fidaxomicin is  $C_{52}H_{74}Cl_2O_{18}$  and the molecular weight is 1058.04 g/mol. Its chemical name is 3-[[[6-deoxy-4-*O*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*O*-methyl- $\beta$ -D-mannopyranosyl]oxy]methyl]-12(*R*)-[[6-deoxy-5-*C*-methyl-4-*O*-(2-methyl-1-oxopropyl)- $\beta$ -D-lyxo-hexopyranosyl]oxy]-11(*S*)-ethyl-8(*S*)-hydroxy-18(*S*)-(1(*R*)-hydroxyethyl)-9,13,15-trimethyloxacyclooctadeca-3,5,9,13,15-pentaene-2-one.

The chemical structure of fidaxomicin is shown below:



Fidaxomicin immediate-release tablets are available as white to off-white, film-coated (b) (4) tablets containing 200 mg of fidaxomicin per tablet (Table 2.1.1-1).

**Table 2.1.1-1.** Composition of fidaxomicin 200 mg tablets

Component	Function	Unit Formula (mg/tablet)
Fidaxomicin	Active ingredient	200.0
Microcrystalline cellulose	(b) (4)	(b) (4)
Pre-gelatinized starch	(b) (4)	(b) (4)
Hydroxypropyl cellulose	(b) (4)	(b) (4)
Butylated hydroxytoluene	(b) (4)	(b) (4)
Sodium starch glycolate	(b) (4)	(b) (4)
Magnesium stearate	(b) (4)	(b) (4)
(b) (4)	(b) (4)	--
(b) (4)	(b) (4)	--
(b) (4)	(b) (4)	(b) (4)

Note: Adapted from Module 2.3.P, Quality Overall Summary – Drug Product, Table 1

### 2.1.2 What are the proposed mechanism(s) of action and therapeutic indications(s)?

The proposed mechanism of action is inhibition of ribonucleic acid (RNA) synthesis by bacterial RNA polymerase. Fidaxomicin possesses a narrow spectrum of activity, specifically against *Clostridium difficile*, and is proposed for the treatment of *C. difficile*-associated diarrhea (CDAD).

### 2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of fidaxomicin is 200 mg (one tablet) orally (PO) twice daily (i.e., every 12 hours, Q12h) for 10 days.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In total, there were ten *in vitro* studies (seven reviewed) and six Phase 1 studies evaluating the clinical pharmacology of fidaxomicin and relevant metabolites (OP-1118, major active metabolite of fidaxomicin). Studies included the evaluation of single- and multiple-dose pharmacokinetics, effect of food, and drug-drug interactions (DDI) (cyclosporine, digoxin, and midazolam/warfarin/omeprazole).

Efficacy of fidaxomicin in the treatment of CDAD was assessed in two pivotal Phase 3 trials (101.1.C.003 and 101.1.C.004) and one supportive Phase 2 trial (OPT-80 Phase 2A) as summarized in Table 2.2.1-1.

**Table 2.2.1-1.** Overview of clinical efficacy trials for fidaxomicin in the treatment of CDAD

Study No.	Design	Fidaxomicin Regimen	Comparator Regimen	Treatment Duration	Population Size
101.1.C.003	Phase 3 -Randomized -Double-blind -Comparative	200 mg Q12h	Vancomycin 125 mg PO Q6h	10 days	Fidaxomicin N=300 Vancomycin N=323
101.1.C.004					Fidaxomicin N=264 Vancomycin N=260
OPT-80 Phase 2A	Phase 2 -Open-label -Dose-ranging -Randomized	50 mg Q12h 100 mg Q12h 200 mg Q12h	None	10 days	Fidaxomicin N=48 (n=16 per dose arm)

Note: Adapted from Module 5.3.5, Integrated Summary of Efficacy, Table 2.3-1 and Table 4-1

### 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

In Phase 3 trials, the patient population was comprised of adults ( $\geq 18$  years of age) with confirmed diagnosis of CDAD, with diarrhea (defined as change in bowel habits, with  $>3$  unformed bowel movements [UBM] in 24 hours before randomization) and the presence of either toxin A or B of *C. difficile* in stool within 48 hours of randomization. The primary

efficacy endpoint was clinical cure at the end-of-therapy visit (EOT), defined as requiring no further CDAD therapy two days after completion of study medication (**Table 2.2.2-1**). Secondary endpoints were (i) recurrence, defined as re-establishment of diarrhea to an extent that was greater than that noted on the last day of study medication, with demonstration of toxin A or B of *C. difficile*, and requiring re-treatment with CDAD anti-infective therapy, and (ii) global cure, defined as those who were evaluated both as cured at EOT and did not have recurrence.

Analysis populations included modified intent-to-treat (mITT), mITT for recurrence, per-protocol (PP), and PP for recurrence. Subjects who had a confirmed diagnosis of CDAD and received at least one dose of study medication were classified as mITT, and all subjects in the mITT population who achieved cure at EOT were classified as mITT for recurrence. Subjects in the mITT population who (i) met all inclusion and no exclusion criteria, (ii) received sufficient course of therapy, (iii) had an EOT clinical evaluation, and (iv) did not have significant protocol violations were classified as PP, and all subjects in the PP population who were cured at EOT and followed for recurrence for >25 days after treatment or experienced recurrence ≤30 days post-treatment were classified as PP for recurrence.

**Table 2.2.2-1.** Efficacy of fidaxomicin (FDX) versus PO vancomycin (VAN) in Phase 3 trials (by Sponsor)

	101.1.C.003		101.1.C.004		Pooled Phase 3		
	FDX	PO VAN	FDX	PO VAN	FDX	PO VAN	Difference (95% CI)
<b>Clinical Cure</b>							
mITT	255/289 (88.2%)	263/307 (85.7%)	222/253 (87.7%)	222/256 (86.7%)	477/542 (88.0%)	485/563 (86.1%)	1.9 (-2.1, 5.8)
PP <sup>a</sup>	247/268 (92.2%)	251/280 (89.6%)	199/217 (91.7%)	212/234 (90.6%)	446/485 (92.0%)	463/514 (90.1%)	1.9 (-1.7, 5.4)
<b>Recurrence</b>							
mITT <sup>a</sup>	40/255 (15.7%)	66/263 (25.1%)	28/222 (12.6%)	60/222 (27.0%)	68/477 (14.3%)	126/485 (26.0%)	-11.7 (-16.7, -6.7)
PP	28/213 (13.1%)	53/219 (24.2%)	23/181 (12.7%)	46/181 (25.4%)	51/394 (12.9%)	99/400 (24.8%)	-11.8 (-17.1, -6.4)
<b>Global Cure</b>							
mITT <sup>a</sup>	215/289 (74.4%)	197/307 (64.2%)	194/253 (76.7%)	162/256 (63.3%)	409/542 (75.5%)	359/563 (63.8%)	11.7 (6.3, 17.0)
PP	208/268 (77.6%)	188/280 (67.1%)	173/217 (79.7%)	153/234 (65.4%)	381/485 (78.6%)	341/514 (66.3%)	12.2 (6.7, 17.6)

<sup>a</sup> Denotes the primary analysis population for the specified efficacy endpoint

Note: Adapted from Module 5.3.5, Integrated Summary of Efficacy, Tables 3.2-1, 3.2-3, 3.2-4

Clinical endpoints were selected by the Sponsor to reflect patient outcome as there is no validated marker for the disease and resolution of CDAD. Selected analysis populations and endpoints were discussed in past correspondences between the Sponsor and the Division. It should be emphasized that efficacy results discussed herein reflect those of the Sponsor and do not necessarily represent the Division. Refer to reviews by the Statistical Reviewer (R Izem, PhD) and Medical Officer (D Iarikov, MD) for complete analysis of fidaxomicin efficacy.

### 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Bioanalytical methods were developed and validated to support the quantification of fidaxomicin and OP-1118 (major active metabolite of fidaxomicin) in samples generated from clinical studies. Details regarding validated liquid chromatography tandem mass spectrometry (LC-MS/MS) for quantification of fidaxomicin and OP-1118 in plasma, urine, and feces were reported and acceptable. See **Section 2.6** for details.

### 2.2.4 Exposure-response

#### 2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

**In Vitro Susceptibility:** Fidaxomicin susceptibility (as minimum inhibitory concentration, MIC) against various collections of *C. difficile*, including clinical isolates from Phase 3 trials, is shown in **Table 2.2.4.1-1**. Overall, MIC<sub>90</sub> (MIC for 90% of the bacterial population) values ranged 0.125-0.25 µg/mL. Against a random sampling of 135 *C. difficile* isolates from Phase 3 trials, MIC<sub>90</sub> for OP-1118 (major active metabolite of fidaxomicin) was 8 µg/mL or 32-fold higher than the parent.

**Table 2.2.4.1-1.** Fidaxomicin susceptibility against *C. difficile* isolates

Reference	N	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	MIC range (µg/mL)
Credito et al. <i>Antimicrob Agents Chemother</i> 2004	21	≤0.016	0.125	≤0.016 - 0.125
Finegold et al. <i>Antimicrob Agents Chemother</i> 2004	23	0.12	0.25	0.06 - 2
Hecht et al. <i>Antimicrob Agents Chemother</i> 2007	110	0.125	0.125	0.015 - 0.25
Karlowsky et al. <i>Antimicrob Agents Chemother</i> 2008	208	0.25	0.5	0.06 - 1
Citron et al. <i>Anaerobe</i> 2009	38	--	0.125	≤ 0.008 - 0.25
Study 101.1.C.003	415	0.125	0.25	0.003 - 0.5
Study 101.1.C.004	376	0.125	0.25	0.007 - 1

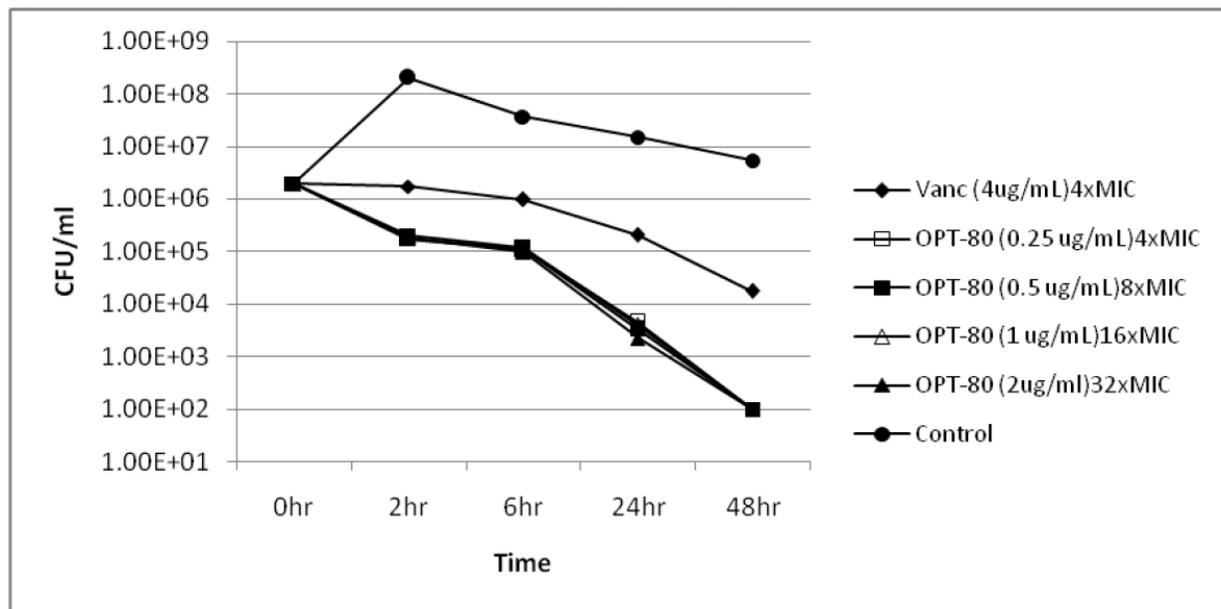
Note: Adapted from Module 2.7.2, Summary of Clinical Pharmacology Studies, Table 2.7.2-18

In the presence of 5% human fecal material, MIC values of fidaxomicin and OP-1118 increased 8-fold (to 2 µg/mL) and 4-fold (to 4 µg/mL), respectively, against *C. difficile* ATCC 700057, likely due to fecal binding of drug.

Fidaxomicin is a narrow spectrum agent with virtually no activity against Gram-negative organisms, as MIC<sub>50</sub> and MIC<sub>90</sub> values were universally >100 µg/mL.

**Time-Kill Kinetics:** Both fidaxomicin and OP-1118 (data not shown) demonstrated bactericidal activity (i.e.,  $\geq 3$ -log kill) in 48 hours at concentrations of 4 times the MIC against *C. difficile* strains (n=4; 2 ATCC and 2 clinical) (**Figure 2.2.4.1-1**). Bacterial kill was maximized at 4 times the MIC, as kill was not further improved with increasing concentration, indicating time-dependent rather than concentration-dependent activity.

**Figure 2.2.4.1-1.** Time-kill kinetics of fidaxomicin against a representative strain, *C. difficile* ATCC 43255



Note: Obtained from Module 2.7.2, Summary of Clinical Pharmacology Studies, Figure 2.7.2-3

**Post-Antibiotic Effect:** Following 1 hour of exposure at 4 times the MIC, the post-antibiotic effect (PAE, length of time required for bacterial titers to increase 1-log after drug exposure) for fidaxomicin and OP-1118 was 9.5-12.5 hours and 3 hours, respectively, against *C. difficile* strains, ATCC 43255 and ATCC 9689. Comparatively, vancomycin and metronidazole PAE ranged 0-3 hours. The Sponsor pursued a dosing frequency of Q12h in light of the PAE exhibited by fidaxomicin.

**Phase 2 Trial:** Regimens of fidaxomicin 50, 100, and 200 mg Q12h were evaluated for 10 days in a dose-ranging Phase 2 trial (**Table 2.2.4.1-2**). Primary efficacy endpoints in the mITT population were (i) clinical cure at EOT, based on the investigator's clinical judgment (even if all signs and symptoms were not entirely normalized), and (ii) relief of symptoms at EOT, defined as  $\leq 3$  UBM/day without other associated signs or symptoms. Secondary endpoints were (i) clinical recurrence within 6 weeks post-treatment, defined as  $\geq 3$  UBM with presence of toxin A or B of *C. difficile*, and (ii) time to resolution of diarrhea, defined as time from first dose of study medication to resolution of diarrhea.

**Table 2.2.4.1-2.** Efficacy of fidaxomicin (for mITT) in a dose-ranging Phase 2 trial (by Sponsor)

	50 mg Q12h ×10 d	100 mg Q12h ×10 d	200 mg Q12h ×10 d
<b>Clinical Cure</b>	12/16 (75.0%)	13/16 (81.3%)	15/15 (100.0%)
<b>Relief of Symptoms</b>			
Relief	6/16 (37.5%)	8/16 (50.0%)	13/15 (86.7%)
No Relief	9/16 (56.3%)	6/16 (37.5%)	2/15 (13.3%)
Unknown	1/16 (6.3%)	2/16 (12.5%)	0/15 (0.0%)
<b>Recurrence</b>	1/6 (16.7%)	0/8 (0.0%)	1/13 (7.7%)
<b>Resolution of diarrhea</b>			
N	10/16 (62.5%)	12/16 (75.0%)	14/15 (93.3%)
Median time (days)	5.5	3.5	3.0

Note: Adapted from Module 5.3.5, OPT-80 Phase 2A Clinical Study Report, Tables 8, 9 and 10

In this small exploratory study, a clear dose-response relationship was evident over the dose range of 50-200 mg Q12h, as efficacy was greatest and nearly maximized with the 200 mg Q12h regimen in clinical cure, symptom relief, and time to resolution of diarrhea. Doses greater than 200 mg Q12h have not been studied in any clinical efficacy studies.

**Susceptibility Breakpoints:** Interpretive criteria for *in vitro* susceptibility testing were not provided by the Sponsor. The Sponsor indicates susceptibility breakpoints for fidaxomicin are not applicable or meaningful as (i) fidaxomicin is a locally-acting product, (ii) concentrations of the active fidaxomicin and OP-1118 are estimated to be many fold higher in the GI tract versus the MIC of *C. difficile*, and (iii) *C. difficile* is representative of a wild-type population only and is not characterized by the existence of other resistant populations.

In pooled Phase 3 trials, majority of *C. difficile* isolates resided at fidaxomicin MIC of 0.06-0.25 µg/mL (Table 2.2.4.1-3). When stratified by MIC and strain, there was a trend towards higher MIC values and poorer clinical outcomes with the BI strain (hyper-virulent strain associated with outbreaks of severe CDAD) versus non-BI strains.

**Table 2.2.4.1-3.** Clinical cure (for mITT) by MIC and strain in pooled Phase 3 trials (by Sponsor)

	MIC (µg/mL)											
	0.007	0.015	0.02	0.03	0.06	0.125	0.25	0.5	1	2	4	8
<b>Clinical Cure for Fidaxomicin</b>												
BI	0/0	0/0	0/0	3/3 (100%)	5/7 (71%)	40/48 (83%)	54/69 (78%)	11/13 (85%)	1/1 (100%)	0/0	0/0	0/0
Non-BI	7/7 (100%)	15/16 (94%)	4/5 (80%)	24/27 (89%)	83/89 (93%)	87/92 (95%)	16/19 (84%)	2/2 (100%)	0/0	0/0	0/0	0/0
<b>Clinical Cure for PO Vancomycin</b>												
BI	0/0	0/0	0/0	0/0	0/0	0/0	0/0	36/45 (80%)	53/65 (82%)	22/24 (92%)	5/8 (63%)	1/1 (100%)
Non-BI	0/0	0/0	0/0	0/0	0/0	0/0	3/3 (100%)	67/72 (93%)	115/129 (89%)	36/41 (88%)	5/7 (71%)	0/0

Note: Adapted from Module 5.3.5, Integrated Summary of Efficacy, Table 3.2-11

Refer to the Clinical Microbiology review (F Marsik, PhD) for complete analysis of fidaxomicin microbiology, including susceptibility interpretive criteria.

**2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.**

In a dose-ranging Phase 2 trial of fidaxomicin 50, 100, and 200 mg Q12h for 10 days, there was no discernible dose-dependent trend in treatment-emergent adverse events (TEAE) (**Table 2.2.4.2-1**). In total, 21 TEAEs were reported by 9 subjects and 6 serious adverse events (SAE) by 5 subjects, none of which were considered related to study drug. No clinically significant mean changes were observed in any laboratory parameter, vital sign parameter, physical exam finding, or electrocardiogram (ECG) parameter in any dose group.

**Table 2.2.4.2-1.** Safety of fidaxomicin in a dose-ranging Phase 2 trial (by Sponsor)

	<b>50 mg Q12h ×10 d</b>	<b>100 mg Q12h ×10 d</b>	<b>200 mg Q12h ×10 d</b>
N with TEAE	4/16 (25.0%)	4/16 (25.0%)	1/16 (6.3%)
N with SAE	2/16 (12.5%)	3/16 (18.8%)	0/16 (0.0%)
Death	0/16 (0.0%)	1/16 (6.3%)	0/16 (0.0%)

Note: Adapted from Module 5.3.5, OPT-80 Phase 2A Clinical Study Report, Table 12.2.2

In Phase 3 trials, overall incidence of TEAE was similar between fidaxomicin (68.3%) and PO vancomycin (65.5%). Most common events were classified as GI disorders (31.4% versus 29.2%), infections and infestations (22.9% versus 20.8%), metabolism and nutrition disorders (18.4% versus 14.9%), and general disorders and administration site conditions (16.0% versus 19.4%). Of note, GI hemorrhage (20/564, 3.5% versus 12/583, 2.1%) and decrease in white blood cell (WBC) count (23/564, 4.1% versus 10/583, 1.7%) were observed in higher frequency with fidaxomicin versus PO vancomycin. There was no discernible relationship between GI hemorrhage (**Table 2.2.4.2-2**) and decrease in WBC count (**Table 2.2.4.2-3**) with “peak” plasma concentrations of fidaxomicin or OP-1118 (i.e., obtained within T<sub>max</sub> window of 1-5 hours, as per the Reviewer).

**Table 2.2.4.2-2.** Incidence of GI hemorrhage by plasma concentrations at 1-5 h (T<sub>max</sub> window per Reviewer) following fidaxomicin 200 mg Q12h for 10 days in Phase 3 patients

	<b>Concentration at 1-5 h (T<sub>max</sub> window)</b>			
	<b>1<sup>st</sup> Quartile</b>	<b>2<sup>nd</sup> Quartile</b>	<b>3<sup>rd</sup> Quartile</b>	<b>4<sup>th</sup> Quartile</b>
<b>Fidaxomicin</b>				
Day 1	5/87 (5.8%)	3/87 (3.5%)	4/86 (4.7%)	3/87 (3.5%)
End of Therapy	1/33 (3.0%)	3/33 (9.1%)	2/31 (6.5%)	2/33 (6.1%)
<b>OP-1118</b>				
Day 1	6/89 (6.7%)	2/88 (2.3%)	3/88 (3.4%)	5/89 (5.6%)
End of Therapy	3/35 (8.6%)	0/32 (0.0%)	2/33 (6.1%)	2/33 (6.1%)

Note: Created from the Reviewer’s analysis

**Table 2.2.4.2-3.** Incidence of **decreased WBC count** by plasma concentrations at 1-5 h (T<sub>max</sub> window per Reviewer) following fidaxomicin 200 mg Q12h for 10 days in Phase 3 patients

	<b>Concentration at 1-5 h (T<sub>max</sub> window)</b>			
	<b>1<sup>st</sup> Quartile</b>	<b>2<sup>nd</sup> Quartile</b>	<b>3<sup>rd</sup> Quartile</b>	<b>4<sup>th</sup> Quartile</b>
<b>Fidaxomicin</b>				
Day 1	4/87 (4.6%)	6/87 (6.9%)	3/86 (3.5%)	4/87 (4.6%)
End of Therapy	1/33 (3.0%)	1/33 (3.0%)	2/31 (6.5%)	3/33 (9.1%)
<b>OP-1118</b>				
Day 1	6/89 (6.7%)	3/88 (3.4%)	3/88 (3.4%)	5/89 (5.6%)
End of Therapy	3/35 (8.6%)	0/32 (0.0%)	1/33 (3.0%)	3/33 (9.1%)

Note: Created from the Reviewer's analysis

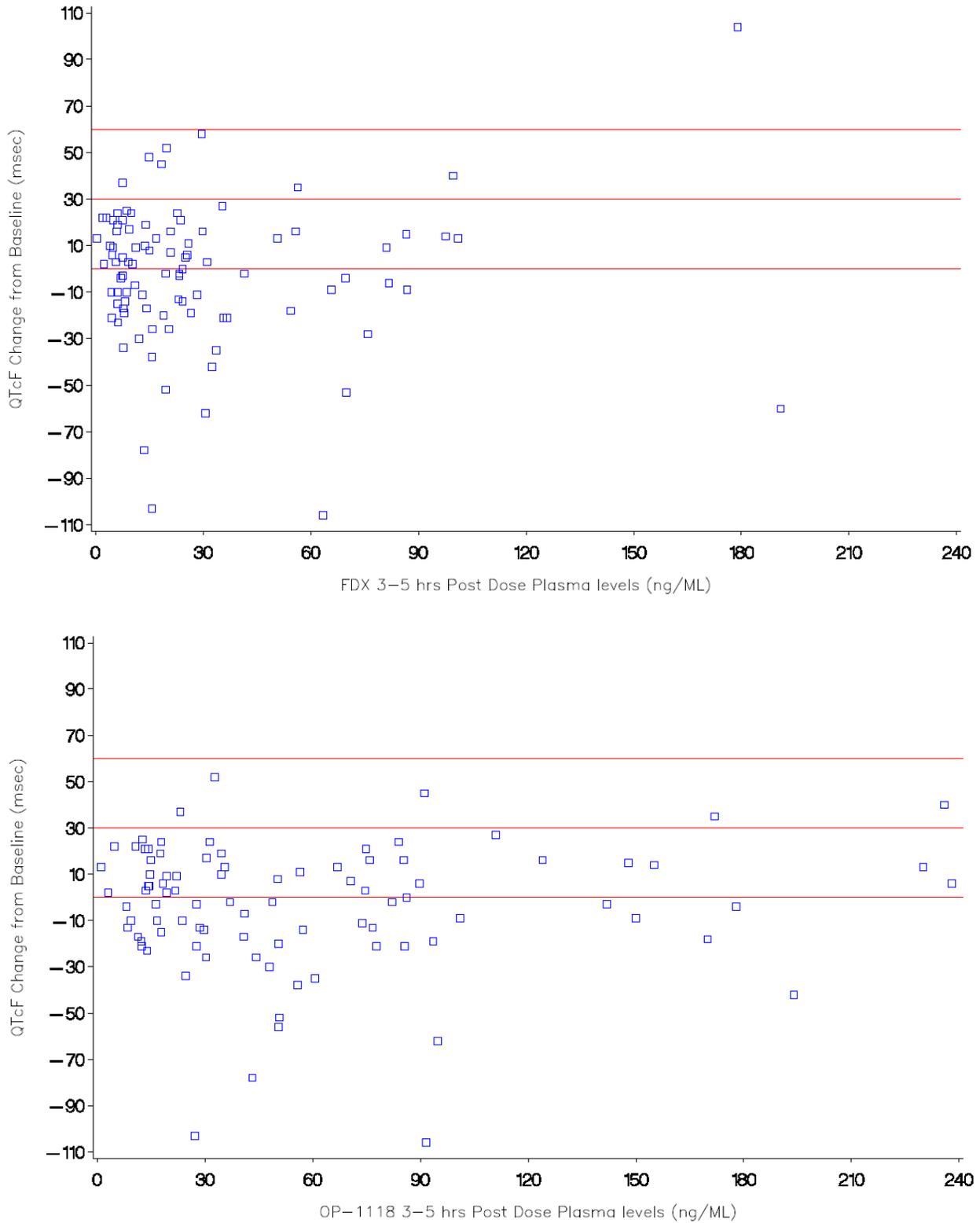
Refer to the Medical Officer's review (D Iarikov, MD) for complete analysis of fidaxomicin safety.

### 2.2.4.3 Does this drug prolong the QT or QTc interval?

An informative thorough QT study was not feasible for fidaxomicin, and thus, was not performed by the Sponsor (with FDA concurrence). Due to *(i)* solubility limitations with dosage, *(ii)* minimal systemic absorption, and *(iii)* lack of significant food effect, it was not possible to generate plasma concentrations in healthy subjects that would approximate or surpass those observed in patients.

Based on pooled data from Phase 3 trials, increasing plasma concentrations of fidaxomicin or metabolite OP-1118 were not associated with an increase in QTcF (corrected QT interval by the Fridericia method) from baseline (**Figure 2.2.4.3-1**).

**Figure 2.2.4.3-1.** Concentrations of **fidaxomicin (top)** and **OP-1118 (bottom)** at 3-5 h at EOT versus  $\Delta$ QTcF in Phase 3 trials



Note1: Red lines indicate either no change (0 msec) or categorical increases QTcF from baseline of 30 and 60 msec  
Note2: Obtained from Module 5.3.5, Integrated Summary of Safety, Figure 9.1-4

#### 2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dose and dosing regimen of fidaxomicin 200 mg PO Q12h for 10 days in the treatment of CDAD is supported by the following:

- A clear dose-response relationship was evident in a dose-ranging Phase 2 trial, as clinical efficacy (in clinical cure, relief of symptoms, and time to resolution of diarrhea) was greatest and nearly maximized with the 200 mg Q12h regimen without any safety concern. (Systemic concentrations are of no utility in assessing the efficacy for this locally-acting product.)
- Clinical efficacy of fidaxomicin in pivotal Phase 3 trials was established with the regimen of 200 mg Q12h for 10 days, with superior results in incidence of recurrence versus the active comparator.

There are no unresolved dosing or administration issues.

#### 2.2.5 What are the PK characteristics of the drug and its major metabolite?

##### 2.2.5.1 What are the single dose and multiple dose PK parameters?

**Single-Dose:** There were two Phase 1 studies in which single-dose pharmacokinetics were evaluated. **Study OPT-80 1A-SD** investigated single doses of 100, 200, 300, and 450 mg, but was limited by an earlier bioanalytical method with a lower limit of quantification (LLOQ) of 5 ng/mL in plasma. **Study OPT-80-005** investigated a single 200 mg dose and utilized a more sensitive method with a LLOQ of 0.2 ng/mL, but pharmacokinetic sampling was insufficient to estimate all relevant parameters in a suitable number of subjects.

Pharmacokinetics of fidaxomicin and metabolite OP-1118 were more appropriately determined following a single 200 mg dose (fasted) in healthy adult males as part of the cyclosporine DDI study (**OPT-80-007**) and are presented in **Table 2.2.5.1-1**, with corresponding concentration-time profiles in **Figure 2.2.5.1-1**. Peak concentrations ( $C_{max}$ ) were observed at 1-5 hours (time to  $C_{max}$ ,  $T_{max}$ ), and systemic exposure (as  $C_{max}$  and area under the concentration-time curve, AUC) of OP-1118 was approximately 2 times that of the parent. Plasma concentrations of OP-1118 appeared to follow the time-course profile of fidaxomicin, along with double peaks that were considered negligible relative to the ng/mL scale.

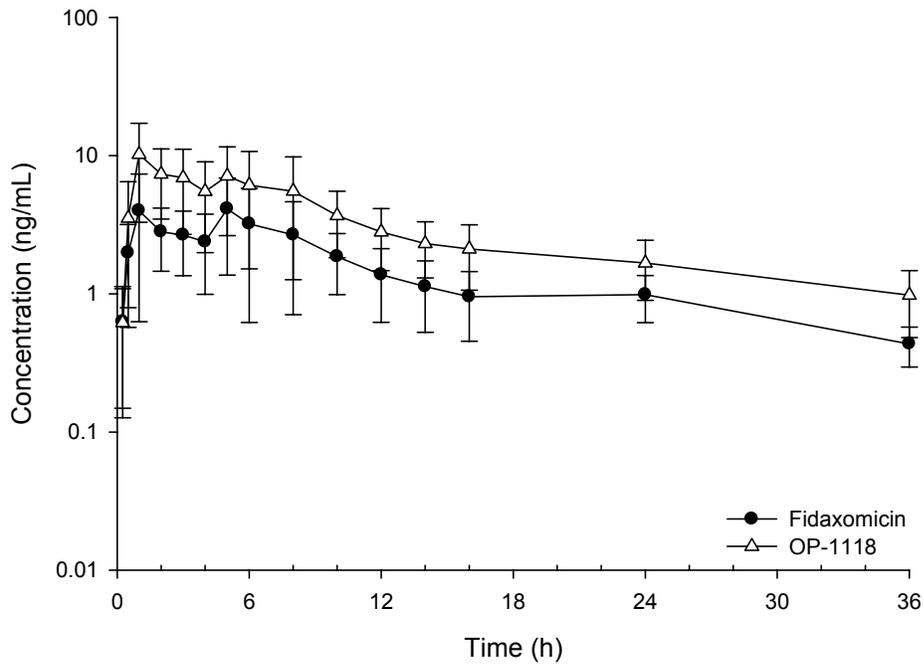
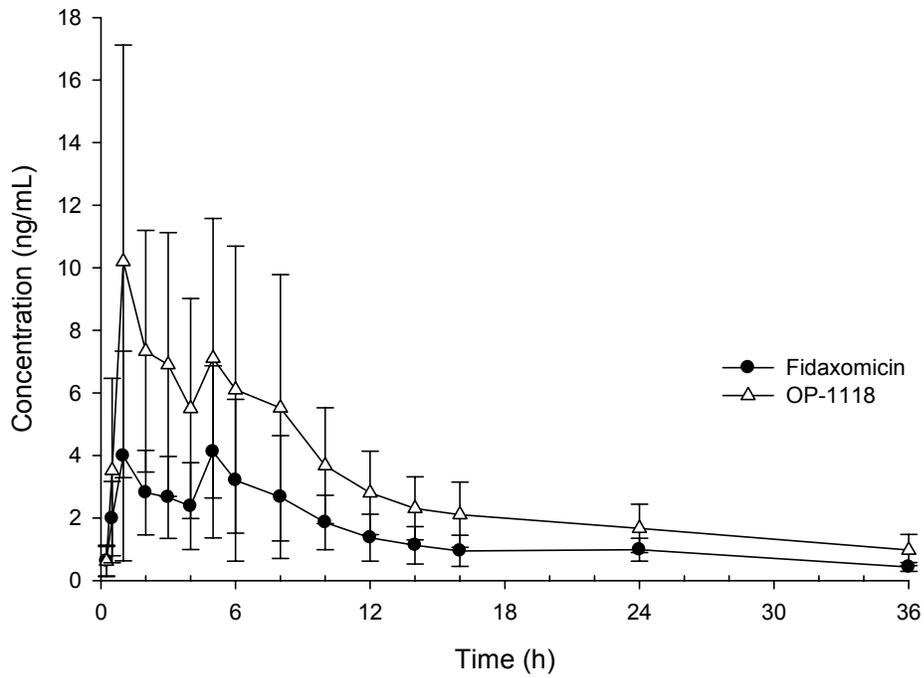
**Table 2.2.5.1-1.** Mean  $\pm$  SD pharmacokinetic parameters following single 200 mg dose of fidaxomicin (fasted) in healthy adult males (n=14)

Parameter	Fidaxomicin		OP-1118	
	N	Value	N	Value
$C_{max}$ (ng/mL)	14	5.20 $\pm$ 2.81	14	12.0 $\pm$ 6.06
$T_{max}$ <sup>a</sup> (h)	14	2.00 (1.00-5.00) <sup>a</sup>	14	1.02 (1.00-5.00) <sup>a</sup>
AUC <sub>0-t</sub> (ng*h/mL)	14	48.3 $\pm$ 18.4	14	103 $\pm$ 39.4
AUC <sub>0-inf</sub> (ng*h/mL)	9	62.9 $\pm$ 19.5	10	118 $\pm$ 43.3
$t_{1/2}$ (h)	9	11.7 $\pm$ 4.80	10	11.2 $\pm$ 3.01

<sup>a</sup>  $T_{max}$  reported as median (minimum-maximum)

Note: Adapted from Module 5.3.3, OPT-80-007 Clinical Study Report, Tables 14.2.2-1 and 14.2.2-3

**Figure 2.2.5.1-1.** Mean  $\pm$  SD concentration-time profiles following single 200 mg dose of fidaxomicin (fasted) in healthy adult males (n=14), in **linear (top)** and **logarithmic (bottom)** form



Note: Created from Module 5.3.3, OPT-80-007 Clinical Study Report, Tables 14.2.1-1 and 14.2.1-3

**Multiple-Dose:** Multiple-dose pharmacokinetics were evaluated in one Phase 1 study (**OPT-80 1B-MD**) following 150, 300, and 450 mg once daily for 10 days, but was similarly limited by the earlier and less sensitive bioanalytical method, and moreover, failed to represent the proposed therapeutic regimen (200 mg Q12h).

Available pharmacokinetic data with multiple dose administration of the proposed therapeutic regimen was provided in Phase 3 trials, where samples were collected pre- and post-dose on Day 1 and EOT in patients treated with fidaxomicin 200 mg Q12h for 10 days. Of collected samples, those obtained within the  $T_{max}$  window of 1-5 hours (defined by the Reviewer) were chosen to most closely approximate “peak” concentrations (**Table 2.2.5.1-2**). In Phase 3 patients, “peak” concentrations of OP-1118 were approximately 2 times that of fidaxomicin, similarly to healthy subjects, and appeared to accumulate with repeat dosing. (Note: The  $T_{max}$  window applied by the Sponsor was 3-5 hours post-dose.)

**Table 2.2.5.1-2.** Plasma concentrations at 1-5 h ( $T_{max}$  window per Reviewer) following fidaxomicin 200 mg Q12h for 10 days in Phase 3 patients

	Concentration at 1-5 h ( $T_{max}$ window) (ng/mL)			
	Fidaxomicin		OP-1118	
	Day 1	End of Therapy	Day 1	End of Therapy
N >LLOQ <sup>a</sup>	347/430 (80.7%)	130/160 (81.3%)	354/430 (82.3%)	133/160 (83.1%)
Mean	22.4	26.7	43.6	79.1
SD	28.3	31.1	54.0	121
Median	13.2	15.7	25.9	40.0
Minimum	0.26	0.31	0.24	1.09
Maximum	237	191	406	871

<sup>a</sup> LLOQ of fidaxomicin and OP-1118 in plasma was 0.2 ng/mL

Note: Created from the Reviewer’s analysis

### 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Comparisons of fidaxomicin and OP-1118 pharmacokinetics in healthy subjects versus patients are restricted to peak concentration data:  $C_{max}$  in Phase 1 subjects and concentrations within the 1-5 hour  $T_{max}$  window in Phase 3 patients. Overall,  $C_{max}$  or “peak” concentrations were approximately 2-6 fold higher (based on mean and median values) and more variable (contributed by sampling) in patients than in healthy subjects, with values ranging from the LLOQ (0.2 ng/mL) to 237 ng/mL for fidaxomicin and to 871 ng/mL for metabolite OP-1118 (**Table 2.2.5.2-1**). Higher plasma concentrations in patients may be attributed to CDAD infection and factors such as elderly age (see **Section 2.3.2.1**) or concomitant use of known inhibitors of P-glycoprotein (P-gp) (see **Section 2.4.2.8**).

Greater systemic exposures of fidaxomicin and OP-1118 in patients are not considered to be a safety concern based on the safety profile established in Phase 3 trials and supporting non-clinical pharmacology/toxicology exposures. Refer to the Pharmacology/Toxicology review (W Schmidt, PhD) for details.

**Table 2.2.5.2-1.** Peak plasma concentrations ( $C_{max}$  or within  $T_{max}$  window) following fidaxomicin 200 mg in healthy subjects versus fidaxomicin 200 mg Q12h for 10 days in Phase 3 patients

	<b>OPT-80-007</b> Healthy adult males 200 mg ×1 Fasted	<b>Pooled Phase 3</b> CDAD patients 200 mg Q12 ×10 d With or without food	
	<b>Day 1</b>	<b>Day 1</b>	<b>End of Therapy</b>
<b>Fidaxomicin <math>C_{max}</math> or Concentration at 1-5 h (<math>T_{max}</math> window) (ng/mL)</b>			
N	14	347	130
Mean	5.20	22.4	26.7
SD	2.81	28.3	31.1
Median	4.52	13.2	15.7
Minimum	2.45	0.26	0.31
Maximum	11.4	237	191
<b>OP-1118 <math>C_{max}</math> or Concentration at 1-5 h (<math>T_{max}</math> window) (ng/mL)</b>			
N	14	354	133
Mean	12.0	43.6	79.1
SD	6.06	54.0	121
Median	11.7	25.9	40.0
Minimum	3.36	0.24	1.09
Maximum	24.5	406	871

Note: Created from (i) Module 5.3.3, OPT-80-007 Clinical Study Report, Tables 14.2.2-1 and 14.2.2-3 and (ii) the Reviewer's analysis

### 2.2.5.3 What are the characteristics of drug absorption?

Systemic absorption from the GI tract is minimal and variable following PO administration, as plasma concentrations ranged from below the LLOQ (0.2 ng/mL) to 237 ng/mL for fidaxomicin and to 871 ng/mL for OP-1118 in Phase 3 patients treated with fidaxomicin 200 mg Q12h. *In vitro* studies with Caco-2 cells indicate fidaxomicin and OP-1118 are substrates of P-gp, an efflux transporter expressed in the GI tract with a known role in limiting PO bioavailability (9OPTIP3).

No clinically significant effect was observed with food on the systemic exposures of fidaxomicin and OP-1118, and accordingly, fidaxomicin may be administered with or without food. See **Section 2.5.3** for details.

### 2.2.5.4 What are the characteristics of drug distribution?

Fidaxomicin is mainly confined to the GI tract following PO administration. In select Phase 3 patients treated with fidaxomicin 200 mg Q12h for 10 days (n=8), fidaxomicin and OP-1118 concentrations ranged 639-2710 µg/g and 213-1210 µg/g, respectively, in fecal samples collected within 24 hours of EOT (**Table 2.2.5.4-1**). Comparatively, “peak” plasma concentrations in the same select patients ranged 0.002-0.179 µg/mL and 0.010-0.829 µg/mL. (Note: Select Phase 3 patients were those whose fecal samples were collected within 24 hours of EOT and were appropriately stored prior to analysis.)

**Table 2.2.5.4-1.** Plasma versus fecal concentrations following fidaxomicin 200 mg Q12h for 10 days in select Phase 3 patients

Subject ID	Fidaxomicin Concentration		OP-1118 Concentration	
	Plasma (µg/mL)	Feces (µg/g)	Plasma (µg/mL)	Feces (µg/g)
	End of Therapy 1-5 h	End of Therapy 0-24 h	End of Therapy 1-5 h	End of Therapy 0-24 h
OPT-80-003-157-002	0.006	1140	0.014	660
OPT-80-004-025-010	--	862	--	371
OPT-80-004-088-028	0.179	817	0.829	944
OPT-80-004-169-007	0.002	2670	0.010	1140
OPT-80-004-177-004	--	2710	--	1210
OPT-80-004-189-004	0.004	639	0.014	213
OPT-80-004-197-002	--	1550	--	480
OPT-80-004-201-013	--	1120	--	514

Note: Created from the Reviewer's analysis

Plasma protein binding was not assessed since free plasma concentrations are not an appropriate marker for the pharmacological effects of this locally-acting product.

### 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was performed for fidaxomicin. See **Section 2.2.5.7** for details on drug excretion.

### 2.2.5.6 What are the characteristics of drug metabolism?

*In vitro* studies with human intestinal microsomes, liver microsomes, and cryopreserved hepatocytes indicate fidaxomicin is primarily transformed by hydrolysis at the isobutyryl ester to form the major active metabolite, OP-1118 (**PF04107** and **XT100005**). Accompanying minor pathways of fidaxomicin metabolism include hydroxylation of fidaxomicin (C5) and isomerization by acyl migration of fidaxomicin (Tiacumicin C and F). CYP enzymes do not appear to play a major role in the metabolism of fidaxomicin or formation of OP-1118 (**XT100005** and **PF04212**).

Across Phase 1 studies with single 200 mg doses of fidaxomicin (**OPT-80-005** and **OPT-80-007**), OP-1118 was the predominant compound systemically available, followed by fidaxomicin, which represented approximately 50% of the metabolite AUC.

### 2.2.5.7 What are the characteristics of drug excretion?

Fidaxomicin and OP-1118 are primarily excreted in the feces. In one Phase 1 study, an average of 26.4% of the dose was recovered in stool as fidaxomicin and 66.2% as OP-1118, following single doses of 200 and 300 mg in healthy adults (n=11) (**OPT-80 1A-SD**). Alternatively, 0.59% of the dose was recovered in urine as OP-1118 while fidaxomicin was undetectable (<5 ng/mL) in another Phase 1 study, following a single 200 mg dose in healthy adults (n=6) (**OPT-80-005**).

### 2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Assessment of linearity is restricted to plasma concentrations of fidaxomicin following single doses of 100, 200, 300, and 450 mg in healthy adults (**OPT-80 1A-SD**). Detectable concentrations of fidaxomicin appeared to increase with increasing dose, although determination of linearity is problematic due to minimal and variable systemic absorption (**Table 2.2.5.8-1**).

**Table 2.2.5.8-1.** Detectable plasma concentrations (>5 ng/mL) of fidaxomicin following single escalating doses in healthy subjects

Subject	Fidaxomicin Concentration (ng/mL)								
	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h
<b>100 mg</b>									
001	-	6.08	-	-	-	-	-	-	-
002	9.74	-	-	-	-	-	-	-	-
003	-	-	-	-	-	-	-	-	-
005	-	5.15	-	-	-	-	-	-	-
006	5.06	5.23	-	-	-	-	-	-	-
008	-	9.42	5.25	-	-	-	-	-	-
<b>200 mg</b>									
009	-	6.38	5.04	-	-	-	-	-	-
010	-	10.4	6.31	-	-	-	-	-	-
011	-	-	5.16	-	-	-	-	-	-
013	-	-	-	-	-	-	-	-	-
014	-	-	-	-	-	-	-	-	-
016	10.6	6.27	-	-	-	-	-	-	-
<b>300 mg</b>									
001	5.95	-	-	-	-	-	-	-	-
002	6.42	5.22	-	-	-	-	-	-	-
003	16.5	8.77	-	-	-	-	-	-	-
005	-	-	16.9	-	-	-	-	-	-
006	-	5.09	-	-	-	-	-	-	-
008	-	-	8.79	7.85	5.79	-	-	-	-
<b>450 mg</b>									
009	17.1	25.3	15.2	5.77	-	-	-	-	-
010	24.8	37.8	21.6	8.62	5.59	-	-	-	-
011	13.8	-	5.36	6.78	-	-	-	-	-
013	17.7	17.7	21.1	22.1	9.00	-	5.06	-	-
014	20.7	15.9	11.6	6.74	5.19	-	-	-	-

Note: Adapted from Module 5.3.3, OPT-80 1A-SD Clinical Study Report, Appendix I

### 2.2.5.9 How do the PK parameters change with time following chronic dosing?

At the proposed regimen of 200 mg Q12h for 10 days, “peak” concentrations from within the 1-5 hour  $T_{max}$  window appeared to increase with repeat dosing for OP-1118 in Phase 3 patients (see **Table 2.2.5.1-2** under **Section 2.2.5.1**). Mean and median values for OP-1118 were approximately 50-80% greater on EOT than Day 1, while unchanged for fidaxomicin.

A comprehensive assessment of time-dependent changes in the pharmacokinetics of fidaxomicin and OP-1118 could not be performed due to limited absorption and inadequate sampling in multiple-dose studies of the proposed therapeutic regimen.

### 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

With single doses of fidaxomicin 200 mg, inter-subject variability (expressed as percent coefficient of variation, % CV) of fidaxomicin and OP-1118 ranged 27.0-54.1% for  $C_{max}$ , 16.7-38.3% for AUC parameters, and 62.4-92.2% for  $T_{max}$  across Phase 1 studies (**Table 2.2.5.10-1**). In Phase 3 patients, inter-subject variability was >100% for estimated “peak” concentrations obtained within the 1-5 hour  $T_{max}$  window on Day 1 of fidaxomicin 200 mg Q12h.

Higher variability in Phase 3 patients may be largely attributable to CDAD infection as well as factors like elderly age (see **Section 2.3.2.1**) or concomitant use of P-gp inhibitors (see **Section 2.4.2.8**). Variability is further contributed to by the fact that “peak” concentrations in Phase 3 trials were single samples obtained around the anticipated  $T_{max}$  and are not truly representative of the actual  $C_{max}$ .

**Table 2.2.5.10-1.** Mean  $\pm$  SD pharmacokinetic parameters and corresponding %CV following single 200 mg dose of fidaxomicin in healthy subjects and Phase 3 patients

	OPT-80-005			OPT-80-007			Pooled Phase 3		
	N	Value	% CV	N	Value	% CV	N	Value	% CV
<b>Fidaxomicin</b>									
$C_{max}$ (ng/mL)	6	9.88 $\pm$ 3.96	40.0%	14	5.20 $\pm$ 2.81	54.1%	347	22.4 $\pm$ 28.3 <sup>a</sup>	126%
$T_{max}$ <sup>b</sup> (h)		1.75 (1.00-8.00) <sup>a</sup>	92.2%	14	2.00 (1.00-5.00) <sup>b</sup>	62.4%	--	--	--
AUC <sub>0-t</sub> (ng*h/mL)	6	69.5 $\pm$ 18.3	26.3%	14	48.3 $\pm$ 18.4	38.1%	--	--	--
AUC <sub>0-inf</sub> (ng*h/mL)	1	68.9	--	9	62.9 $\pm$ 19.5	30.9%	--	--	--
$t_{1/2}$ (h)	1	11.8	--	9	11.7 $\pm$ 4.80	41.1%	--	--	--
<b>OP-1118</b>									
$C_{max}$ (ng/mL)	6	17.6 $\pm$ 4.73	27.0%	14	12.0 $\pm$ 6.06	50.3%	354	43.6 $\pm$ 54.0 <sup>a</sup>	124%
$T_{max}$ <sup>b</sup> (h)	6	1.75 (1.00-8.00) <sup>a</sup>	87.8%	14	1.02 (1.00-5.00) <sup>b</sup>	72.8%	--	--	--
AUC <sub>0-t</sub> (ng*h/mL)	6	136 $\pm$ 26.2	19.2%	14	103 $\pm$ 39.4	38.3%	--	--	--
AUC <sub>0-inf</sub> (ng*h/mL)	3	155 $\pm$ 25.9	16.7%	10	118 $\pm$ 43.3	36.8%	--	--	--
$t_{1/2}$ (h)	3	8.36 $\pm$ 2.03	24.3%	10	11.2 $\pm$ 3.01	26.9%	--	--	--

<sup>a</sup>  $C_{max}$  values represent concentrations within the 1-5 h  $T_{max}$  window for Phase 3 trials

<sup>b</sup>  $T_{max}$  reported as median (minimum-maximum)

Note: Created from (i) Module 5.3.3, OPT-80-005 Clinical Study Report, Tables 14.2.2-1a and 14.2.2-2a, (ii) Module 5.3.3, OPT-80-007 Clinical Study Report, Tables 14.2.2-1 and 14.2.2-3, and (iii) the Reviewer’s analysis

Data for evaluation of intra-subject variability were not available.

## 2.3 Intrinsic Factors

### 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Dedicated Phase 1 studies were not performed to evaluate the effect of intrinsic factors. Instead, intrinsic factors were assessed in Phase 3 trials, using “peak” concentration data obtained within

the 1-5 hour  $T_{max}$  window following fidaxomicin 200 mg Q12h for 10 days. Intrinsic factors that influence exposure and their impact on efficacy or safety are described in **Section 2.3.2**.

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative bases for the recommendation.**

**2.3.2.1 Elderly**

In Phase 3 trials, “peak” concentrations of fidaxomicin and OP-1118 were approximately 2-4 fold greater (based on mean and median values) in elderly ( $\geq 65$  years of age) versus non-elderly ( $< 65$  years of age) patients (**Table 2.3.2.1-1**). Median (range) age of fidaxomicin-treated patients in Phase 3 trials, for whom “peak” concentration data were available, was approximately 63 (18-94) years.

**Table 2.3.2.1-1.** Plasma concentrations at 1-5 h ( $T_{max}$  window per Reviewer) following fidaxomicin 200 mg Q12h for 10 days in Phase 3 patients, stratified by age

	Concentration at 1-5 h ( $T_{max}$ window) (ng/mL)			
	Day 1		End of Therapy	
	<65 years	$\geq 65$ years	<65 years	$\geq 65$ years
<b>Fidaxomicin</b>				
N >LLOQ <sup>a</sup>	191	156	58	72
Mean	14.2	32.5	15.5	35.8
SD	19.7	33.6	17.6	36.3
Median	8.17	24.0	8.67	24.8
Minimum	0.26	0.90	1.76	0.31
Maximum	197	237	86.9	191
<b>OP-1118</b>				
N >LLOQ <sup>a</sup>	191	163	61	72
Mean	27.0	63.1	45.8	107
SD	32.0	66.6	112	121
Median	13.9	44.7	17.8	72.2
Minimum	0.24	0.98	3.01	1.09
Maximum	173	406	871	829

<sup>a</sup> LLOQ of fidaxomicin and OP-1118 in plasma was 0.2 ng/mL

Note: Created from the Reviewer’s analysis

With elderly age, there was a trend towards lower efficacy (**Table 2.3.2.1-2**) and higher incidence of adverse events (**Table 2.3.2.1-3**) with fidaxomicin. However, similar effects were also observed for the active comparator or otherwise occurred in too small frequencies to allow for proper interpretation. This effect is likely indicative of the infected patient population rather than elderly age.

**Table 2.3.2.1-2.** Efficacy of fidaxomicin versus PO vancomycin in pooled Phase 3 trials (by Sponsor), stratified by age

	Fidaxomicin			PO Vancomycin		
	<65 years	≥65 years	Total	<65 years	≥65 years	Total
<b>Clinical Cure</b>						
mITT	252/277 (91.0%)	225/265 (84.9%)	477/542 (88.0%)	247/281 (87.9%)	238/282 (84.4%)	485/563 (86.1%)
PP	243/258 (94.2%)	203/227 (89.4%)	446/485 (92.0%)	240/262 (91.6%)	223/252 (88.5%)	463/514 (90.1%)
<b>Recurrence</b>						
mITT	31/252 (12.3%)	37/225 (16.4%)	68/477 (14.3%)	57/247 (23.1%)	69/238 (29.0%)	126/485 (26.0%)
PP	22/215 (10.2%)	29/179 (16.2%)	51/394 (12.9%)	48/213 (22.5%)	51/187 (27.3%)	99/400 (24.8%)
<b>Global Cure</b>						
mITT	221/277 (79.8%)	188/265 (70.9%)	409/542 (75.5%)	190/281 (67.6%)	169/282 (59.9%)	359/563 (63.8%)
PP	212/258 (82.2%)	169/227 (74.4%)	381/485 (78.6%)	183/262 (69.8%)	158/252 (62.7%)	341/514 (66.3%)

Note: Created from the Reviewer's analysis

**Table 2.3.2.1-3.** Safety of fidaxomicin versus PO vancomycin in pooled Phase 3 trials (by Sponsor), stratified by age

	Fidaxomicin		PO Vancomycin	
	<65 years	≥65 years	<65 years	≥65 years
N	292	272	288	295
N with TEAE	188 (64.4%)	197 (72.4%)	176 (61.1%)	206 (69.8%)
N with SAE	61 (20.9%)	84 (30.9%)	50 (17.4%)	85 (28.8%)
Investigations <sup>a</sup>	26 (8.9%)	47 (17.3%)	17 (5.9%)	41 (13.9%)
Renal & Urinary Disorders <sup>a</sup>	7 (2.4%)	23 (8.5%)	12 (4.2%)	15 (5.1%)
Hematology <sup>a</sup>				
Low lymphocytes	7 (2.7%)	12 (5.3%)	4 (1.7%)	6 (2.4%)
Chemistry <sup>a</sup>				
High glucose	9 (3.3%)	22 (9.4%)	14 (5.5%)	14 (5.6%)

<sup>a</sup> Indicates a notable difference in incidence by elderly age

Note: Adapted from Module 5.3.5, Integrated Summary of Safety, Tables 11.1-1, -2, -3, and -4

No dose adjustment is warranted based on elderly age as greater plasma concentrations of fidaxomicin and OP-1118 in elderly versus non-elderly patients were not accompanied by significant loss in efficacy or any remarkable safety issues.

### 2.3.2.2 Pediatric patients

The pharmacokinetics of fidaxomicin have not been studied in pediatric patients, and accordingly, the proposed indication is limited to patients 18 years of age and older.

(b) (4)

(b) (4)

(b) (4)

### 2.3.2.3 Gender

In Phase 3 trials, “peak” concentrations of fidaxomicin and OP-1118 did not vary by gender (Table 2.3.2.3-1). Thus, no dose adjustment is warranted based on gender.

**Table 2.3.2.3-1.** Plasma concentrations at 1-5 h ( $T_{max}$  window per Reviewer) following fidaxomicin 200 mg Q12h for 10 days in Phase 3 patients, stratified by gender

	Concentration at 1-5 h ( $T_{max}$ window) (ng/mL)			
	Day 1		End of Therapy	
	Male	Female	Male	Female
<b>Fidaxomicin</b>				
N >LLOQ <sup>a</sup>	145	202	50	80
Mean	22.8	22.1	27.7	26.1
SD	26.8	29.4	27.2	33.5
Median	14.3	12.8	17.7	15.3
Minimum	0.40	0.26	1.90	0.31
Maximum	197	237	101	191
<b>OP-1118</b>				
N >LLOQ <sup>a</sup>	150	204	52	81
Mean	41.8	44.9	88.3	73.1
SD	41.8	61.4	135	111
Median	26.9	23.3	38.8	40.0
Minimum	0.50	0.24	4.72	1.09
Maximum	256	406	871	829

<sup>a</sup> LLOQ of fidaxomicin and OP-1118 in plasma was 0.2 ng/mL

Note: Created from the Reviewer’s analysis

### 2.3.2.4 Race

The effect of race could not be assessed for fidaxomicin as majority of subjects in Phase 3 trials were classified as White.

### 2.3.2.5 Renal impairment

In Phase 3 trials, there was no discernible trend with “peak” concentrations of fidaxomicin and OP-1118 across categories of renal impairment, defined using creatinine clearance (CrCL) by Cockcroft-Gault as mild (51-79 mL/min), moderate (31-50 mL/min), or severe ( $\leq 30$  mL/min) (Table 2.3.2.5-1). It should be noted there was no classification of normal renal function to apply for comparative purposes.

However, renal impairment is not anticipated to significantly alter the pharmacokinetics of this non-renally and non-hepatically eliminated compound, and thus, no dose adjustment or restriction is warranted based on renal function.

**Table 2.3.2.5-1.** Plasma concentrations at 1-5 h ( $T_{max}$  window per Reviewer) following fidaxomicin 200 mg Q12h for 10 days in Phase 3 patients, stratified by renal impairment

	Concentration at 1-5 h ( $T_{max}$ window) (ng/mL)					
	Day 1			End of Therapy		
	Mild CrCL 51-79	Moderate CrCL 31-50	Severe CrCL $\leq$ 30	Mild CrCL 51-79	Moderate CrCL 31-50	Severe CrCL $\leq$ 30
<b>Fidaxomicin</b>						
N >LLOQ <sup>a</sup>	82	34	40	40	12	11
Mean	27.0	32.1	33.7	36.1	29.4	31.6
SD	30.7	26.0	37.4	38.8	27.6	17.2
Median	16.7	24.5	24.9	24.4	23.8	32.9
Minimum	1.64	1.10	1.41	0.31	5.90	7.09
Maximum	185	102	197	191	97.6	56.5
<b>OP-1118</b>						
N >LLOQ <sup>a</sup>	87	34	40	37	14	11
Mean	50.4	66.7	75.1	119	91.5	93.2
SD	51.3	64.2	72.8	161	79.4	54.7
Median	30.6	50.7	60.8	70.5	51.6	87.6
Minimum	2.15	2.01	2.98	1.09	16.9	8.14
Maximum	321	363	343	871	248	183

<sup>a</sup> LLOQ of fidaxomicin and OP-1118 in plasma was 0.2 ng/mL

Note: Created from the Reviewer's analysis

### 2.3.2.6 Hepatic impairment

The effect of hepatic impairment has not been studied, as hepatic metabolism and/or excretion does not account for >20% of the elimination of fidaxomicin or OP-1118.

### 2.3.2.7 What pregnancy and lactation use information is there in the application?

No studies with fidaxomicin have been performed in pregnant or lactating females. Information on pregnancy is limited to non-clinical data, and the Sponsor proposes the classification of Pregnancy Category B. The excretion of fidaxomicin in human milk by lactating mothers has not been assessed, and accordingly, the Sponsor recommends caution when fidaxomicin is administered to nursing women.

Refer to the Pharmacology/Toxicology review (W Schmidt, PhD) for complete analysis of fidaxomicin toxicology.

## 2.4 Extrinsic Factors

### 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Phase 1 DDI studies were conducted to investigate gut-mediated interactions with cyclosporine, digoxin, and midazolam/warfarin/omeprazole, by targeting transporters (P-gp) and enzymes (CYP3A4 followed by CYP2C9 and CYP2C19) prominent at the intestinal level. Extrinsic factors that influence exposure and their impact on efficacy or safety are described in **Section 2.4.2.**

## 2.4.2 Drug-drug interactions

### 2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

*In vitro* CYP inhibition and P-gp studies suggest the potential for *in vivo* DDI with fidaxomicin via the GI tract.

### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

*In vitro* studies with human intestinal microsomes, liver microsomes, and cryopreserved hepatocytes indicate fidaxomicin and OP-1118 are not significant substrates of major CYP isoenzymes (XT100005 and PF04212).

### 2.4.2.3 Is the drug an inhibitor and/or inducer of CYP enzymes?

Fidaxomicin and OP-1118 exhibited inhibitory potential for prominent intestinal CYP isoenzymes (CYP3A4, CYP2C9, and CYP2C19) in *in vitro* studies with human liver microsomes, based on estimated intestinal concentrations (fidaxomicin [I]<sub>2</sub>, 800 µg/mL). Fidaxomicin IC<sub>50</sub> (half maximal inhibitory concentration) values for CYP3A4, CYP2C9, and CYP2C19 were >10 µg/mL, 7.2 µg/mL, and >10 µg/mL, respectively; however, fidaxomicin was limited by solubility and experimental concentrations were maximized at 10 µg/mL (XT065019). OP-1118 was not similarly restrained by solubility, and accordingly, IC<sub>50</sub> values were determined for CYP3A4/5 as 620 µg/mL and 42 µg/mL with test substrates, testosterone and midazolam, respectively (XT095062).

In *in vitro* studies with human hepatocytes, fidaxomicin and OP-1118 showed little or no potential for induction of major CYP isoenzymes (including CYP3A4/5, CYP2C9, and CYP2C19) compared to study controls at concentrations up to 10 µg/mL (XT063006).

### 2.4.2.4 Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?

*In vitro* studies with Caco-2 cells indicate fidaxomicin and OP-1118 are substrates of P-gp, as net flux ratios were >2 and effluxes were decreased by >50% in the presence of test P-gp inhibitors, cyclosporine and ketoconazole (9OPTIP3).

Fidaxomicin is also an inhibitor of P-gp, with an IC<sub>50</sub> value of 2.59 µM against test substrate, digoxin, while the IC<sub>50</sub> for OP-1118 was >125 µM in *in vitro* studies with Caco-2 cells (9OPTIP3).

### 2.4.2.5 Are there other metabolic/transporter pathways that may be important?

There are no other *in vitro* metabolic/transporter pathways relevant to fidaxomicin.

### 2.4.2.6 Does the label specify co-administration of another drug, and if so, has the interaction potential between these drugs been evaluated?

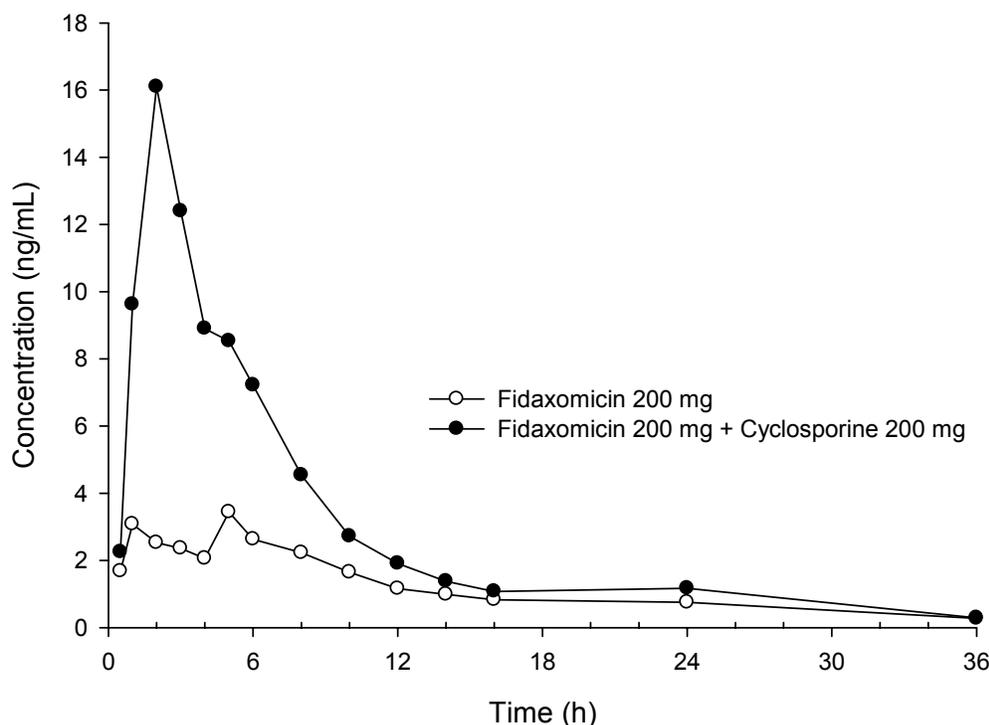
### 2.4.2.7 What other co-medications are likely to be administered to the target patient population?

The target patient population of CDAD range from otherwise healthy patients to patients with significant co-morbidities. Fidaxomicin may be used with a wide variety of co-medications from different drug classes for many different therapeutic indications.

### 2.4.2.8 Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

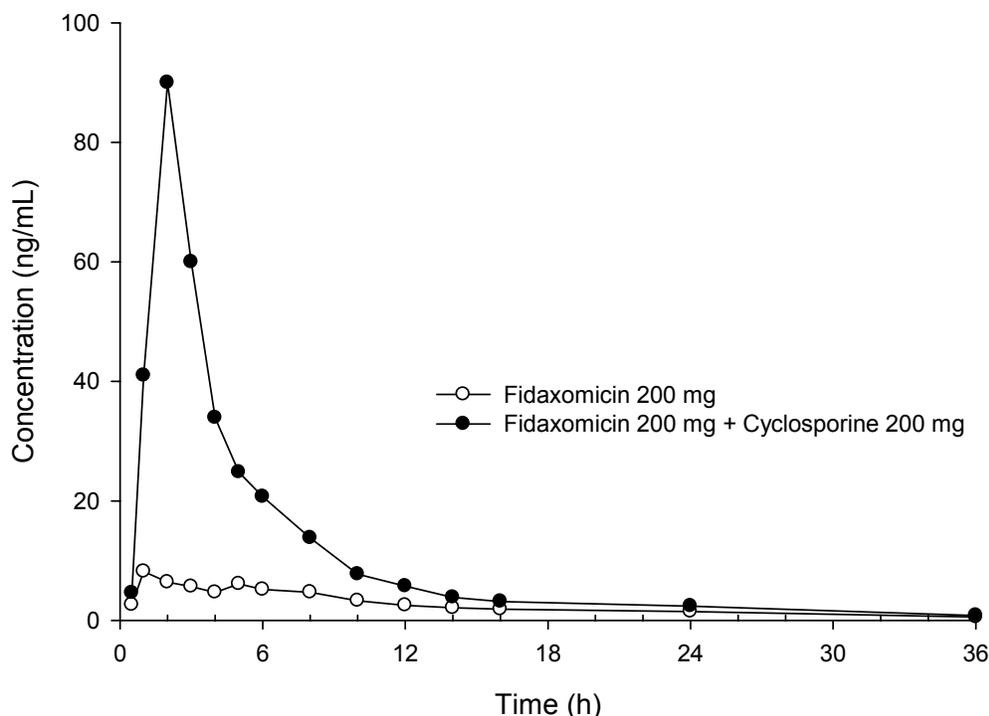
**Cyclosporine (P-gp inhibitor):** The effect of cyclosporine (inhibitor of multiple transporters, including P-gp) on the pharmacokinetics of fidaxomicin and OP-1118 (substrates of P-gp) was evaluated in healthy adult males (n=14) with fidaxomicin 200 mg ×1 alone versus in combination with cyclosporine 200 mg ×1 (staggered administration of cyclosporine followed by fidaxomicin) in a randomized, two-period, crossover fashion (OPT-80-007). Co-administration of cyclosporine increased plasma concentrations of fidaxomicin (Figure 2.4.2.8-1) and OP-1118 (Figure 2.4.2.8-2), by approximately 4-9 fold for  $C_{max}$  and 2-4 fold for  $AUC_{0-inf}$  (Table 2.4.2.8-1).

**Figure 2.4.2.8-1.** Geometric mean concentrations of fidaxomicin following fidaxomicin 200 mg ×1 alone versus in combination with cyclosporine 200 mg ×1 in healthy adult males (n=14)



Note: Created from Module 5.3.3, OPT-80-007 Clinical Study Report, Tables 14.2.1-1 and 14.2.1-2

**Figure 2.4.2.8-2.** Geometric mean concentrations of **OP-1118** following fidaxomicin 200 mg ×1 alone versus in combination with cyclosporine 200 mg ×1 in healthy adult males (n=14)



Note: Created from Module 5.3.3, OPT-80-007 Clinical Study Report, Tables 14.2.1-3 and 14.2.1-4

**Table 2.4.2.8-1.** Statistical DDI analysis of fidaxomicin and OP-1118 with fidaxomicin 200 mg ×1 alone versus in combination with cyclosporine 200 mg ×1 in healthy adult males

	Cyclosporine 200 mg + Fidaxomicin 200 mg <sup>a</sup>		Fidaxomicin 200 mg		Test/Reference
	N	Least Squares Mean	N	Least Squares Mean	Point Estimate (90% CI)
<b>Fidaxomicin</b>					
C <sub>max</sub> (ng/mL)	14	19.4	14	4.67	4.15 (3.23-5.32)
AUC <sub>0-t</sub> (ng*h/mL)	14	111	14	45.3	2.45 (1.96-3.06)
AUC <sub>0-inf</sub> (ng*h/mL)	8	114	9	59.5	1.92 (1.39-2.64)
<b>OP-1118</b>					
C <sub>max</sub> (ng/mL)	14	100	14	10.6	9.51 (6.93-13.05)
AUC <sub>0-t</sub> (ng*h/mL)	14	408	14	95.6	4.27 (3.41-5.34)
AUC <sub>0-inf</sub> (ng*h/mL)	12	438	10	106	4.11 (3.06-5.53)

<sup>a</sup> Staggered administration of cyclosporine dose followed 1 hour later by fidaxomicin dose

Note: Adapted from Module 5.3.3, OPT-80-007 Clinical Study Report, Table 11-3

As observed in the cyclosporine DDI study, “peak” concentrations of fidaxomicin and OP-1118 in Phase 3 trials were also greater in patients who received P-gp inhibitors during fidaxomicin therapy versus those who did not, although to a lesser degree than in healthy subjects (**Table 2.4.2.8-2**). (Note: P-gp inhibitors from Phase 3 trials included atazanavir, atorvastatin, azithromycin\*, carvedilol\*, cefuroxime, cetirizine, clotrimazole, cyclosporine\*, diltiazem\*, esomeprazole, ketoconazole\*, lopinavir\*, omeprazole, paclitaxel, posaconazole, quinidine\*, and

verapamil\*; starred symbol [\*] denotes inhibitors that have shown >25% increase in P-gp substrate AUC.)

**Table 2.4.2.8-2.** Plasma concentrations at 1-5 h ( $T_{max}$  window per Reviewer) following fidaxomicin 200 mg Q12h for 10 days in Phase 3 patients, stratified by concomitant use of P-gp inhibitors

	Concentration at 1-5 h ( $T_{max}$ window) (ng/mL)			
	Day 1		End of Therapy	
	No P-gp Inhibitor	Yes P-gp Inhibitor	No P-gp Inhibitor	Yes P-gp Inhibitor
<b>Fidaxomicin</b>				
N >LLOQ <sup>a</sup>	212	135	77	53
Mean	17.4	30.3	22.2	33.4
SD	21.3	35.4	28.4	33.8
Median	10.9	18.9	11.2	23.4
Minimum	0.26	0.36	0.31	2.96
Maximum	185	237	179	191
<b>OP-1118</b>				
N >LLOQ <sup>a</sup>	214	140	78	55
Mean	33.3	59.3	63.5	101
SD	43.2	64.2	110	132
Median	17.8	41.1	28.1	68.6
Minimum	0.24	0.28	1.09	10.7
Maximum	321	406	829	871

<sup>a</sup> LLOQ of fidaxomicin and OP-1118 in plasma was 0.2 ng/mL

Note: Created from the Reviewer's analysis

The Sponsor indicates the pharmacokinetic interaction with cyclosporine is not likely to be clinically meaningful, as plasma concentrations of fidaxomicin and OP-1118 remained in the ng/mL range, and thus, proposes no dose adjustments or restrictions. However, increase in plasma concentrations via P-gp inhibition may have implications on clinical efficacy as well as safety, as (i) concentrations of the microbiologically active compounds may, in effect, be decreased at the desired site of action/infection, and (ii) variability in the systemic absorption of fidaxomicin may be further compounded in CDAD patients.

Upon examination of Phase 3 trials, there was a trend towards lower efficacy observed with P-gp inhibitor use, in rates of recurrence and global cure (but not clinical cure) (**Table 2.4.2.8-3**). Similar trend of decreased efficacy was also observed for the active comparator, although the impact of P-gp inhibitor use was not as pronounced as it was with fidaxomicin. It should be noted that efficacy rates of fidaxomicin surpassed those of PO vancomycin for nearly all endpoints and analysis populations, regardless of P-gp inhibitor use.

Incidence of adverse events also trended higher with P-gp inhibitor use in Phase 3 patients, but this effect was generally comparable between fidaxomicin and PO vancomycin or otherwise occurred in too small frequencies to allow for proper interpretation (**Table 2.4.2.8-4**). This effect is likely indicative of the co-morbid conditions of this patient population rather than concomitant P-gp inhibitor use.

**Table 2.4.2.8-3.** Efficacy of fidaxomicin versus PO vancomycin in pooled Phase 3 trials (by Sponsor), stratified by concomitant use of P-gp inhibitors

	Fidaxomicin			PO Vancomycin		
	P-gp Inhibitor Use		Total	P-gp Inhibitor Use		Total
	No	Yes		No	Yes	
<b>Clinical Cure</b>						
mITT	281/312 (90.1%)	196/230 (85.2%)	477/542 (88.0%)	289/331 (87.3%)	196/232 (84.5%)	485/563 (86.1%)
PP	265/285 (93.0%)	181/200 (90.5%)	446/485 (92.0%)	276/299 (92.3%)	187/215 (87.0%)	463/514 (90.1%)
<b>Recurrence</b>						
mITT	31/281 (11.0%)	37/196 (18.9%)	68/477 (14.3%)	69/289 (23.9%)	57/196 (29.1%)	126/485 (26.0%)
PP	23/238 (9.7%)	28/156 (17.9%)	51/394 (12.9%)	53/242 (21.9%)	46/158 (29.1%)	99/400 (24.8%)
<b>Global Cure</b>						
mITT	250/312 (80.1%)	159/230 (69.1%)	409/542 (75.5%)	220/331 (66.5%)	139/232 (59.9%)	359/563 (63.8%)
PP	235/285 (82.5%)	146/200 (73.0%)	381/485 (78.6%)	209/299 (69.9%)	132/215 (61.4%)	341/514 (66.3%)

Note: Created from the Reviewer's analysis

**Table 2.4.2.8-4.** Safety of fidaxomicin versus PO vancomycin in pooled Phase 3 trials (by Sponsor), stratified by concomitant use of P-gp inhibitors

	Fidaxomicin		PO Vancomycin	
	No P-gp Inhibitor	Yes P-gp Inhibitor	No P-gp Inhibitor	Yes P-gp Inhibitor
N	324	240	341	242
N with TEAE	208 (64.2%)	177 (73.8%)	207 (60.7%)	175 (72.3%)
N with SAE	72 (22.2%)	73 (30.4%)	52 (15.2%)	83 (34.3%)
<b>Hematology<sup>a</sup></b>				
Low lymphocytes	5 (1.8%)	14 (7.0%)	6 (2.1%)	4 (2.0%)
<b>Chemistry<sup>a</sup></b>				
High glucose	13 (4.3%)	18 (8.7%)	14 (4.7%)	14 (6.9%)
Low bicarbonate	3 (1.0%)	6 (2.9%)	3 (1.0%)	0 (0.0%)
High urate	1 (0.3%)	7 (3.3%)	2 (0.6%)	2 (1.0%)

<sup>a</sup> Indicates a notable difference in incidence by P-gp inhibitor use

Note: Adapted from Module 5.3.5, Integrated Summary of Safety, Tables 10.1-15,-16, -17, and -18

Here, the traditional approach of dose adjustment based on matching plasma exposures is not an appropriate option, given that (i) plasma concentrations are poor markers for concentrations at the site of action/infection for this locally-acting product, (ii) reduction of fidaxomicin dose may compromise clinical efficacy, and (iii) the degree to which the P-gp inhibitor dose should be adjusted would be problematic, if not impossible, to determine.

Based on the clinical experience of fidaxomicin efficacy and safety in Phase 3 trials (which included patients on P-gp inhibitors), it does not appear concomitant use of P-gp inhibitors needs to be restricted for fidaxomicin. Language should be included into the label to inform clinicians of the potential DDI with P-gp inhibitors, but that the clinical implications are unknown.

**Digoxin (P-gp substrate):** The effect of fidaxomicin (P-gp inhibitor) on the pharmacokinetics of digoxin (P-gp substrate) was evaluated in healthy subjects (n=14) with digoxin 0.5 mg ×1 (in tablet form) alone versus in combination with fidaxomicin 200 mg Q12h for 6 days (staggered administration of fidaxomicin followed by digoxin) in a mono-sequence crossover fashion (**OPT-80-008**). With co-administration of fidaxomicin, digoxin  $C_{max}$  and AUC increased by <15% and 90% CI around point estimates for  $AUC_{0-inf}$  and  $AUC_{0-3}$  (an alternative exposure to  $C_{max}$ ) were within the no-effect boundary of 0.80-1.25 (**Table 2.4.2.8-5**). Moreover, the geometric mean value of digoxin  $C_{max}$  remained in the desired therapeutic range of 0.8-2.0 ng/mL with concomitant fidaxomicin.

**Table 2.4.2.8-5.** Statistical DDI analysis of digoxin with digoxin 0.5 mg ×1 alone versus in combination with fidaxomicin 200 mg Q12h for 6 days in healthy subjects

	Fidaxomicin 200 mg Q12h + Digoxin 0.5 mg <sup>a</sup>		Digoxin 0.5 mg		Test/Reference
	N	Least Squares Mean	N	Least Squares Mean	Point Estimate (90% CI)
<b>Digoxin</b>					
$C_{max}$ (ng/mL)	14	1.66	14	1.46	1.14 (0.99-1.31)
$AUC_{0-3}$ (ng*h/mL)	14	3.26	14	3.01	1.08 (0.98-1.20)
$AUC_{0-inf}$ (ng*h/mL)	14	33.6	14	30.0	1.12 (1.03-1.22)

<sup>a</sup> Staggered administration of fidaxomicin dose followed 1 hour later by digoxin dose

Note: Adapted from Module 5.3.3, OPT-80-008 Clinical Study Report, Table 11-4

No dose adjustment or restriction is warranted with substrates of P-gp, including digoxin.

**Midazolam/Warfarin/Omeprazole (CYP3A4/2C9/2C19 substrates):** The effect of fidaxomicin (CYP inhibitor) on the pharmacokinetics of midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) was evaluated in healthy adult males (n= 24) with a single-dose CYP cocktail of midazolam 5 mg + warfarin 10 mg + omeprazole 40 mg alone versus in combination with fidaxomicin 200 mg Q12h for 4 days in a mono-sequence crossover fashion (**OPT-80-009**). Exposure parameters for all CYP substrates and their respective metabolites showed <20% difference with co-administration of fidaxomicin and 90% CI around nearly all point estimates were within the no-effect boundary of 0.80-1.25 (**Table 2.4.2.8-6**).

**Table 2.4.2.8-6.** Statistical DDI analysis of midazolam, warfarin, and omeprazole with single-dose CYP cocktail alone versus in combination with fidaxomicin 200 mg Q12h for 4 days in healthy adult males

	Fidaxomicin 200 mg Q12h + Midazolam 5 mg Warfarin 10 mg Omeprazole 40 mg		Midazolam 5 mg Warfarin 10 mg Omeprazole 40 mg		Test/Reference
	N	Least Squares Mean	N	Least Squares Mean	Point Estimate (90% CI)
<b>Midazolam</b>					
C <sub>max</sub> (ng/mL)	23	25.1	24	27.4	0.92 (0.83-1.02)
AUC <sub>0-inf</sub> (ng*h/mL)	23	63.9	24	66.2	0.96 (0.88-1.06)
<b>1-hydroxymidazolam</b>					
C <sub>max</sub> (ng/mL)	23	13.4	24	13.0	1.03 (0.91-1.16)
AUC <sub>0-inf</sub> (ng*h/mL)	18	36.2	19	31.0	1.17 (1.07-1.28)
<b>R-warfarin</b>					
C <sub>max</sub> (ng/mL)	23	661	24	606	1.09 (1.05-1.14)
AUC <sub>0-inf</sub> (ng*h/mL)	22	40862	24	35902	1.14 (1.11-1.17)
<b>S-warfarin</b>					
C <sub>max</sub> (ng/mL)	23	668	24	611	1.09 (1.04-1.15)
AUC <sub>0-inf</sub> (ng*h/mL)	21	23171	24	20495	1.13 (1.10-1.17)
<b>Omeprazole</b>					
C <sub>max</sub> (ng/mL)	23	561	24	603	0.93 (0.82-1.06)
AUC <sub>0-inf</sub> (ng*h/mL)	22	1132	24	1100	1.03 (0.93-1.14)
<b>5-hydroxyomeprazole</b>					
C <sub>max</sub> (ng/mL)	23	377	24	378	1.00 (0.91-1.09)
AUC <sub>0-inf</sub> (ng*h/mL)	23	961	24	895	1.07 (1.03-1.12)

Note: Adapted from Module 5.3.3, OPT-80-009 Clinical Study Report, Tables 11-3, -5, -7, -9, -11, and -13

No dose adjustment or restriction is warranted with CYP substrates, including midazolam (CYP3A4), warfarin (CYP2C9), and omeprazole (CYP2C19).

#### 2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Antimicrobials are routinely tested for potential synergy in combination with other agents. Combinations of fidaxomicin and metabolite OP-1118 were tested with various agents against *C. difficile* ATCC 43255 by *in vitro* checkerboard technique, where synergy was defined as the inhibition of organism growth by a combination of antimicrobials at concentrations significantly below the MIC of either agent alone (i.e., fractional inhibitory concentration [FIC] ≤0.5). Both fidaxomicin and OP-1118 showed synergy with rifamycins, which are also known RNA polymerase inhibitors, as well as ampicillin and metronidazole.

#### 2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no significant unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding for fidaxomicin. Plasma protein binding was not assessed but is of minimal clinical relevance for this locally-acting product.

### **2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?**

Labeling language for concomitant use of P-gp inhibitors proposed by the Reviewer are different from those proposed by the Sponsor (see **Section 2.4.2.8** for details). There are no other unresolved issues related to dose, dosing regimens, or administration that represent significant omissions to this application.

## **2.5 General Biopharmaceutics**

### **2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?**

Both fidaxomicin and metabolite OP-1118 are BCS Class IV compounds, i.e., neither highly soluble nor highly permeable. *In vitro* studies with Caco-2 cells indicate the apparent permeability coefficients ( $P_{app}$ ) for fidaxomicin and OP-1118 are low in comparison to the highly permeable control compound, minoxidil.

Refer to the ONDQA review (E Chikhale, PhD) for further details on the solubility, permeability, and dissolution data in support of this classification.

### **2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?**

Fidaxomicin tablets were over-encapsulated in Phase 3 trials for purposes of blinding. Due to minimal systemic absorption, bridging of the formulation used in pivotal Phase 3 trials to the to-be-marketed formulation was limited to *in vitro* dissolution studies. Refer to the ONDQA review (E Chikhale, PhD) for further details.

#### **2.5.2.1 What data support or do not support a waiver of *in vivo* BE data?**

Not applicable.

#### **2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

Not applicable.

#### **2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?**

Not applicable.

**2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

Food effect on the pharmacokinetics of fidaxomicin and OP-1118 was evaluated in healthy subjects (n=28) with a single 400 mg dose under fed (within 0.5 hour of a high-fat meal) versus fasted conditions (**OPT-80-005**). When administered with food, fidaxomicin and OP-1118  $C_{max}$  decreased by 21.5% and 33.4%, respectively, while  $AUC_{0-t}$  was unchanged as 90% CI around point estimates were within the no-effect boundary of 0.80-1.25 (**Table 2.5.3-1**). This decrease in  $C_{max}$  is not considered clinically significant for this locally-acting product, and thus, fidaxomicin may be administered with or without food.

**Table 2.5.3-1.** Statistical food effect analysis of fidaxomicin and OP-1118 with single 400 mg dose of fidaxomicin under fed versus fasted conditions in healthy subjects

	400 mg Fed		400 mg Fasted		Test/Reference
	N <sup>a</sup>	Least Squares Mean	N	Least Squares Mean	Point Estimate (90% CI)
<b>Fidaxomicin</b>					
$C_{max}$ (ng/mL)	27	7.02	28	8.94	0.79 (0.67-0.92)
$AUC_{0-t}$ (ng*h/mL)	27	70.6	28	73.0	0.97 (0.87-1.07)
<b>OP-1118</b>					
$C_{max}$ (ng/mL)	27	14.9	28	22.4	0.67 (0.58-0.76)
$AUC_{0-t}$ (ng*h/mL)	27	146	28	162	0.90 (0.83-0.98)

<sup>a</sup> Data from Subject 017 for Period 2 were excluded due to positive pre-dose values

Note: Adapted from Module 5.3.3, OPT-80-005 Clinical Study Report, Tables 11-4 and 11-8

**2.5.4 When would a fed BE study be appropriate and was one conducted?**

Not applicable.

**2.5.5 How do the dissolution conditions and specifications ensure *in vivo* performance and quality of the product?**

Refer to the ONDQA review (E Chikhale, PhD).

**2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?**

Not applicable.

**2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?**

Not applicable.

**2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or *in vivo* data to evaluate BE?**

PO vancomycin (active control) was over-encapsulated in Phase 3 trials for purposes of blinding. Due to minimal systemic absorption, bridging of the product used in pivotal Phase 3 trials to the approved product was limited to *in vitro* dissolution studies. Refer to the ONDQA review (E Chikhale, PhD) for further details.

**2.5.9 What other significant, unresolved issues related to *in vitro* dissolution or *in vivo* BA and BE need to be addressed?**

Refer to the ONDQA review (E Chikhale, PhD) for details on *in vitro* dissolution, including any significant, unresolved issues. No *in vivo* BA or BE studies were completed, and there are no significant, unresolved issues related to any such studies.

**2.6 Analytical Section**

**2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?**

Fidaxomicin and metabolite OP-1118 were quantified in plasma, urine, and feces by validated LC-MS/MS assays and were acceptable for intended purposes.

**2.6.2 Which metabolites have been selected for analysis and why?**

In addition to fidaxomicin, OP-1118 was measured in plasma, urine, and feces. OP-1118 is the major and active metabolite of fidaxomicin and represents the majority of circulating and recovered moieties.

**2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

Total drug concentrations of fidaxomicin and OP-1118 were measured in all clinical studies, as concentrations corrected for plasma protein binding are not relevant for this locally-acting product.

**2.6.4 What bioanalytical methods are used to assess concentrations?**

Validated LC-MS/MS assays were used for quantitation of fidaxomicin and OP-1118. See **Table 2.6.4-1** for details.

**2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?**

See **Table 2.6.4-1**. When concentrations exceeded the standard curve range, samples were diluted, then assayed. Dilution integrity was verified within each clinical pharmacology study when sample dilutions were performed.

Power or quadratic equations were applied for curve fitting purposes, with a weighting factor of  $1/x^2$  for some methods.

#### **2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?**

See **Table 2.6.4-1**.

#### **2.6.4.3 What are the accuracy, precision, and selectivity at these limits?**

Accuracy was expressed as percent deviation from the nominal concentration, and precision as % CV. See **Table 2.6.4-1**.

#### **2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?**

See **Table 2.6.4-1**. Majority of fecal samples collected in clinical studies exceeded the duration for which sample stability was established. As such, fecal pharmacokinetic data for labeling will be limited to descriptive terms in instances where sample integrity could not be verified (e.g., data from Study OPT-80 1A-SD).

#### **2.6.4.5 What is the QC sample plan?**

See **Table 2.6.4-1**. Low, medium, and high concentration QC samples were run in 2-6 replicates.

**Table 2.6.4-1.** Summary of analytical methods for quantification of fidaxomicin and OP-1118

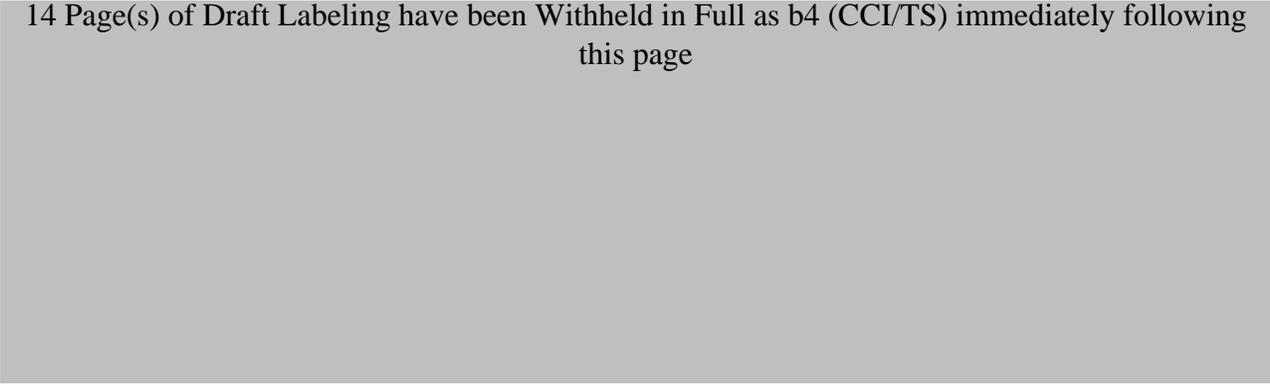
Matrix	Plasma				Urine		Feces
Validation Report	FB-2003-110	MC04186	MC05071	TSLR06-123	MC04248	MC09B-0192	MC04249
Clinical Studies	OPT-80 1A-SD	OPT-80 1B-MD	OPT-80 Phase 2A	OPT-80-005 OPT-80-007 101.1.C.003 101.1.C.004	OPT-80 1B-MD	OPT-80-005	OPT-80 1A-SD OPT-80 1B-MD OPT-80-005  OPT-80 Phase 2A 101.1.C.003 101.1.C.004
Method	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Analytes	Fidaxomicin	Fidaxomicin	Fidaxomicin OP-1118	Fidaxomicin OP-1118	Fidaxomicin	Fidaxomicin OP-1118	Fidaxomicin OP-1118
Linearity	≥0.992	≥0.9989	≥0.9994	≥0.9945	≥0.9993	≥0.999	≥0.9990
Standard Curve (ng/mL)	5-5000	5-1000	5-1000	0.2-100	5-1000	5-1000	10-2000 50-10000
LLOQ (ng/mL)	5	5	5	0.2	5	5	10 50
ULOQ (ng/mL)	5000	1000	1000	100	1000	1000	2000 10000
QC Samples (ng/mL)	10, 2000, 4000	15, 75, 800	15, 75, 800	0.6, 50, 80	15, 75, 800	15, 150, 800	30, 250, 1600 150, 1250, 8000
Accuracy							
Intra-day	± 12.0%	± 9.3%	± 4.0%	± 12.8%	± 2.8%	± 9.3%	± 8.1%
Inter-day	± 5.5%	± 9.6%	± 2.7%	± 8.8%	± 1.3%	± 4.7%	± 10.1%
Precision							
Intra-day	≤ 10.7%	≤ 2.6%	≤ 6.3%	≤ 9.3%	≤ 6.4%	≤ 9.3%	≤ 4.8%
Inter-day	≤ 10.7%	≤ 8.5%	≤ 5.9%	≤ 8.5%	≤ 5.6%	≤ 7.0%	≤ 5.5%
Stability							
Freeze-thaw	3 cycles	3 cycles	3 cycles	4 / 5 cycles	3 cycles	4 cycles	3 cycles
At -70 °C	21 weeks	21 weeks	370 days	838 / 1133 days	--	32 days	93 / 31 days <sup>a</sup>
At -20 °C	--	--	--	32 days	33 days	32 days	368 days
At room temperature	--	4.5 hours	4 / 24 hours	5 / 6 hours	24 hours	26 hours	24 hours

<sup>a</sup> Stability at -70 °C is in reference to un-homogenized fecal samples

Note: Created from the Reviewer's analysis

### **3. DETAILED LABELING RECOMMENDATIONS**

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



## **4. APPENDICES**

### **4.1 Individual Study Reviews**

#### **4.1.1 *In Vitro* Studies**

APPEARS THIS WAY ON  
ORIGINAL

STUDY NO.: PF04107

REPORT NO.: MC04107

## Determination of the potential metabolites of OPT-80 using intestinal and liver microsomes from rat, dog, monkey and human

Laboratory Site: (b) (4)

**STUDY DESCRIPTION:** This study investigated the *in vitro* metabolism of OPT-80 in intestinal and liver microsomes from Sprague-Dawley rat, beagle dog, cynomolgus monkey, and human.

### METHODS

**Study Procedures:** OPT-80 was incubated with microsomes suspended in an NADPH regenerating system at a final concentration of 1  $\mu\text{M}$  (or 1.06  $\mu\text{g/mL}$ ). Samples were obtained at 0, 30, 60, and 120 minutes of incubation at 37  $^{\circ}\text{C}$ . Similar reactions were run with metabolic controls representing low (tolbutamide, 3  $\mu\text{M}$ ), moderate (desipramine, 3  $\mu\text{M}$ ), and high (testosterone, 3  $\mu\text{M}$ ) clearance compounds.

**Analytical Methods:** Samples were analyzed by high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometry. Analysis was conducted in three parts.

- MRM (multiple reaction monitoring) quantitation of metabolism controls: The disappearance of metabolism controls was determined by comparing peak heights at each time point to peak heights at 0 min.
- MS scanning for potential metabolites: Samples from 0, 30, 60, and 120 min of incubation were subjected to scanning over 100-1120 amu for identification of potential metabolites. The disappearance of OPT-80 and appearance of potential metabolites over time were determined by comparing peak heights at each time point to peak heights at 0 min.
- Product ion scanning of potential metabolites: Spectra from product ion scans of potential metabolite peaks were compared to OPT-80 to determine the degree of molecular similarity between the potential metabolites and OPT-80.

### RESULTS

OPT-80 was consumed at various rates depending on the type of microsomes and species (**Table 1**). Seven putative metabolites (M1-M7) were revealed, two of which (M2 and M4) were eliminated from further consideration because of their presence in standards and/or because they did not exhibit a suitable trend over time. Based on mass differences, potential metabolites were tentatively assigned as a hydrolysis product (M1) and hydroxylated OPT-80 (M3). M1 was confirmed as related to OPT-80 by product ion spectra (not available for any other metabolite) and as the hydrolysis product by authentic standard analysis.

**Table 1.** Degradation of OPT-80 and formation of potential metabolites

	Time (min)	OPT-80 (% of 0-min control)	OPT-80 <i>m/z</i> 1056.8 7.3 min	M1 <i>m/z</i> 985.4 7.06 min	M3 <i>m/z</i> 1072.4 7.19 min	M5 <i>m/z</i> 271.5 7.12 min	M6 <i>m/z</i> 344.0 7.72 min	M7 <i>m/z</i> 297.7 7.79 min
<b>LIVER</b>								
Human	0	100	6234639	-	-	148064	-	-
	30	19	1177453	2313032	-	3755504	632518	2116768
	60	14	886534	1803346	-	5701047	514742	3546250
	120	22	1341133	2347768	-	2465386	-	1069044
Monkey	0	100	7533470	-	-	-	-	-
	30	40	2990385	2181981	495973	3243267	823060	770256
	60	15	1109548	2129346	404255	5259614	1057395	1166157
	120	7	500184	1503233	368464	5548942	1090738	1213438
Dog	0	100	9966020	-	-	-	-	-
	30	75	7449977	939491	176977	3699747	-	1415837
	60	45	4493672	1319231	262760	4754233	125858	2372189
	120	31	3108289	2298146	219758	7194484	120629	3375972
Rat	0	100	9006989	-	104671	-	-	-
	30	17	1561636	2542785	-	2956076	521922	668453
	60	11	994157	2475491	-	4596960	421929	1025085
	120	14	1280784	2213175	-	3256981	-	625712
<b>INTESTINAL</b>								
Human	0	100	7671875	-	-	-	-	-
	30	92	7074767	316857	-	-	-	-
	60	83	6363693	524403	-	-	-	-
	120	73	5623694	602000	81810	-	-	-
Monkey	0	100	10799327	-	-	-	-	-
	30	61	6586860	602808	-	-	-	-
	60	54	5878629	1586547	-	-	-	-
	120	39	4263829	2168714	-	-	-	-
Dog	0	100	10316283	-	-	-	-	-
	30	83	8608493	105294	-	-	-	131872
	60	70	7253908	141634	-	-	-	-
	120	77	7968331	183913	-	-	-	-
Rat	0	100	8939578	-	142059	-	-	-
	30	12	1031699	2154001	-	-	-	-
	60	1	127130	2340203	-	238133	-	-
	120	3	254693	2371225	-	-	-	100962

**SPONSOR'S CONCLUSIONS:** OPT-80 was generally consumed more rapidly by liver microsomes than by intestinal microsomes. M1, the predominant metabolite, was generated by both types of microsomes from tested species. M1 was confirmed to be related to OPT-80 as the hydrolysis product.

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results.

STUDY NO.: **XT100005**

## Characterization of OPT-80 and OP-1118 metabolite in human and dog microsomes and hepatocytes

Laboratory Site: (b) (4)

**STUDY DESCRIPTION:** This study investigated the metabolism of OPT-80 and OP-1118 in pooled liver microsomes and cryopreserved hepatocytes from beagle dog and human.

### METHODS

**Study Procedures:** With liver microsomes, OPT-80 (10  $\mu$ M or 10.6  $\mu$ g/mL) and OP-1118 (10  $\mu$ M) were incubated at 37 °C with 0-4 mg/mL microsomal protein and an NADPH-generating system; samples were obtained over 0-120 minutes. With cryopreserved hepatocytes, OPT-80 (10  $\mu$ M or 10.6  $\mu$ g/mL) and OP-1118 (10  $\mu$ M) were incubated at 37 °C; samples were obtained over 0-240 minutes. Similar reactions were run with 7-hydroxycoumarin (100  $\mu$ M), midazolam (100  $\mu$ M), and phenacetin (100  $\mu$ M) to determine metabolic competency of test systems.

**Analytical Methods:** Samples were analyzed by liquid chromatography tandem quadrupole time of flight mass spectrometry (LC/MS/MS) with electrospray ionization (ESI) and in-line UV/visible spectrophotometric detection.

### RESULTS

In liver microsomes from human and dog, metabolism of OPT-80 was protein concentration-dependent but not NADPH-dependent, while OP-1118 metabolism was dependent on both protein concentration and NADPH (**Table 1**). OPT-80 was metabolized to a greater extent in human liver microsomes than dog, while OP-1118 was minimally metabolized in both.

**Table 1.** Metabolic stability of OPT-80 and OP-1118 in NADPH-fortified liver microsomes

Species	Protein Concentration (mg/mL)	Incubation Time (min)	% Remaining	
			+ NADPH	- NADPH
<b>OPT-80</b>				
Human	0	10	106.9	--
	0.25	10	84.2	77.7
	0.5	15	47.4	47.9
	1	10	41.4	36.6
Dog	0	30	95.3	--
	1	30	90.7	86.2
	2	60	64.6	51.1
	4	30	92.7	55.6
<b>OP-1118</b>				
Human	0	30	106.1	--
	0.5	30	97.0	105.7
	1	120	74.7	91.1
	2	30	90.5	86.2
Dog	0	30	104.3	--
	0.5	30	85.4	104.1
	1	120	57.7	92.9
	2	30	78.7	98.4

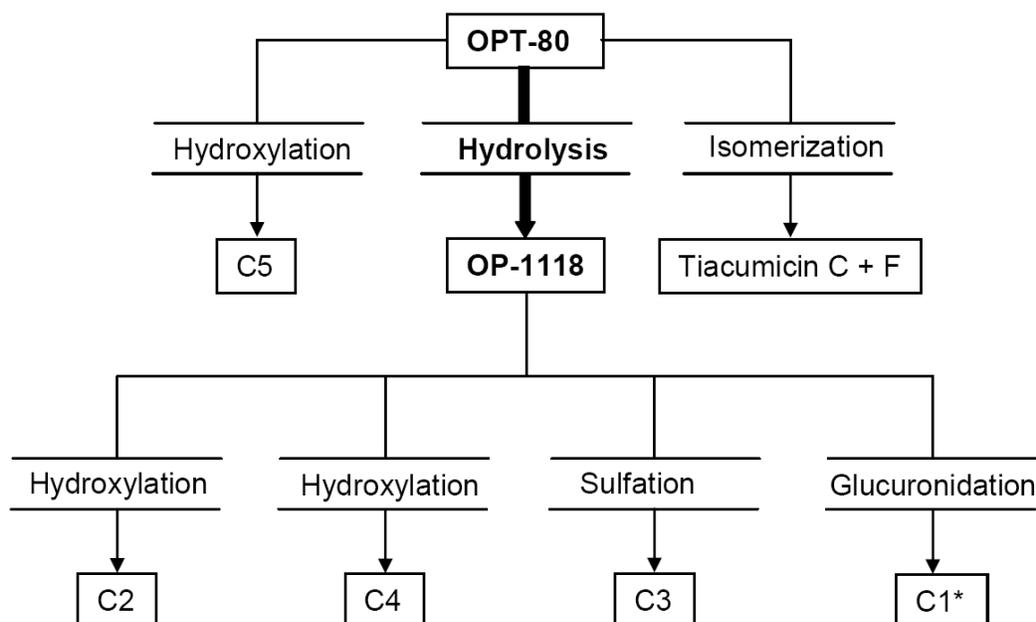
In hepatocytes, the extent of OPT-80 metabolism was comparable between human and dog, while OP-1118 was metabolically stable in human hepatocytes relative to dog (**Table 2**).

**Table 2.** Metabolic stability of OPT-80 and OP-1118 in cryopreserved hepatocytes

Incubation Time (min)	% Remaining	
	Human	Dog
<b>OPT-80</b>		
60	65.7	80.5
120	57.6	64.0
240	41.5	38.3
240 (boiled)	115.5	101.4
<b>OP-1118</b>		
60	101.8	89.0
120	102.3	90.5
240	103.4	85.4
240 (boiled)	95.9	96.5

In liver microsomes and hepatocytes from both human and dog, the major metabolite of OPT-80 detected was OP-1118, a product of ester hydrolysis (**Figure 1**). Two minor pathways of OPT-80 metabolism were also identified: (i) hydroxylation of OPT-80 to metabolite C5 and (ii) isomerization by acyl migration of OPT-80 to Tiacumicin C and F (hepatocytes only) (**Table 3**). OP-1118 was further metabolized to 4 secondary metabolites: two hydroxylated metabolites (C2 and C4) and two conjugates (C3, sulfate conjugate; C1, glucuronide conjugate) (**Table 4**). No human-specific or disproportionate components were detected.

**Figure 1.** *In vitro* biotransformation of OPT-80 and OP-1118



**Table 3.** *In vitro* biotransformation of OPT-80 in liver microsomes and hepatocytes

	Proposed Identity	Proposed Biotransformation	Liver Microsomes		Hepatocytes			
			Human	Dog	Human	Dog		
OPT-80		(b) (4)	+	+	+	+		
OP-1118			+	+	+	+		
C1						+		
C2								
C3						+	+	
C4						+	+	
C5					+	+	+	+
Tiacumicin C							+	+
Tiacumicin F							+	+

**Table 4.** *In vitro* biotransformation of OP-1118 in liver microsomes and hepatocytes

	Proposed Identity	Proposed Biotransformation	Liver Microsomes		Hepatocytes		
			Human	Dog	Human	Dog	
OP-1118		(b) (4)	+	+	+	+	
C1						+	
C2			+	+			
C3						+	+
C4			+	+			+

**SPONSOR’S CONCLUSIONS:** The major route of metabolism of OPT-80 was hydrolysis to OP-1118. Formation of OP-1118 did not require NADPH, suggesting non-CYP enzymes were responsible.

**REVIEWER ASSESSMENT:** The Sponsor’s conclusions are appropriate based on study results.

STUDY NO.: PF04212  
REPORT NO.: MC04212

## Reaction phenotyping of OPT-80 using human intestinal and liver microsomes and CYP450-specific chemical inhibitors

Laboratory Site: (b) (4)

**STUDY DESCRIPTION:** This study investigated whether CYP isoenzymes significantly contribute to the *in vitro* metabolism of OPT-80 in human liver and intestinal microsomes.

### METHODS

**Study Procedures:** OPT-80 and CYP-specific metabolism controls were incubated with microsomes suspended in an NADPH regenerating system at a final concentration of 1  $\mu$ M (or 1.06  $\mu$ g/mL for OPT-80). Samples were obtained at 0, 30 (for liver microsomes), and 120 (for intestinal microsomes) minutes of incubation at 37  $^{\circ}$ C. Similar reactions were run in the presence of CYP-specific inhibitors (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a final concentration of 20  $\mu$ M.

**Analytical Methods:** Samples were analyzed by high-performance liquid chromatography (HPLC) in conjunction with mass spectrometric detection. The disappearance of OPT-80 and formation of M1 were determined by comparing peak heights at each time point to peak heights at 0 min. Peak heights were compared in the presence and absence of chemical inhibitors.

### RESULTS

Human intestinal microsomes exhibited little activity toward substrate controls, indicating CYP activity was not significant in microsome preparation. Despite low CYP activity, approximately 40-50% of OPT-80 was consumed in intestinal microsomes.

In human liver microsomes, sufficient metabolism of substrate controls was observed for CYP1A2, CYP2C9, CYP2D6, and CYP3A4, but not for CYP2C19 (**Table 1**). Activities of CYP1A2, CYP2C9, and CYP2D6 were blocked by each corresponding inhibitor, while CYP3A4 was only partially inhibited. OPT-80 was quickly consumed in human liver microsomes and was not affected by inhibitors, although slowed by ketoconazole (CYP3A4) and sulfaphenazole (CYP2C9). Formation of M1 was similarly unaffected by inhibitors, although it was reduced to a minor extent by ketoconazole (CYP3A4).

**Table 1.** Percent remaining of controls and OPT-80 in human liver microsomes incubations

Isoform	Inhibitor	% Remaining <sup>a</sup>			
		Control		OPT-80	
		Alone	With Inhibitor	Alone	With Inhibitor
CYP1A2	Furafylline	68.3	97.7	16.1	9.3
CYP2C9	Sulfaphenazole	1.8	66.7	14.3	36.1
CYP2C19	n-Benzyltirivanol	88.9	80.9	19.3	10.8
	Omeprazole	88.9	85.1	19.3	10.6
CYP2D6	Quinidine	70.6	154.6	15.7	14.0
CYP3A4	Ketoconazole	22.4	39.9	23.7	38.6

<sup>a</sup> % remaining = peak height at final time point / peak height at 0 min

**SPONSOR'S CONCLUSIONS:** Based on activity displayed towards OPT-80 by intestinal microsomes, which did not have very good CYP activity, and the inability of inhibitors to significantly affect OPT-80 metabolism by liver microsomes, it is likely that CYP enzymes do not play a major role in the metabolism of OPT-80 and formation of M1.

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results.

STUDY NO.: **XT065019**

***In vitro* evaluation of PAR-101 and OP-1118 as inhibitors of human cytochrome P450 enzymes**

Laboratory Site: (b) (4)

**STUDY DESCRIPTION:** This study investigated the ability of PAR-101 and OP-1118 to inhibit major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) in pooled human liver microsomes.

**METHODS**

**Study Procedures:** For evaluation of direct inhibition, PAR-101 and OP-1118 were incubated at 37 °C with pooled human liver microsomes, NADPH-generating system, and marker substrates at final concentrations of 0.01-10 µg/mL. (Note: Concentration of 10 µg/mL was the solubility limit for PAR-101.) For evaluation of time-/metabolism-dependent inhibition, PAR-101 was pre-incubated with human liver microsomes and an NADPH-generating system for 30 minutes to allow for generation of metabolites that may inhibit CYP activity. Known direct and time-dependent inhibitors of CYP enzymes were included as positive controls.

**Analytical Methods:** All analyses were performed using validated HPLC/MS/MS methods.

**RESULTS**

PAR-101 caused direct inhibition of CYP2C9 with IC<sub>50</sub> of 7.2 µg/mL, and there was evidence of direct inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, and CYP3A4 although IC<sub>50</sub> values were >10 µg/mL (**Table 1**). PAR-101 showed possible evidence of time-dependent inhibition for CYP2B6 and CYP3A4/5, as % inhibition at the highest concentration increased more than 2-fold with 30-min pre-incubation. OP-1118 also caused direct inhibition of CYP2C9 although IC<sub>50</sub> was >10 µg/mL, and there was little or no direct inhibition of any other enzyme (**Table 2**).

**Table 1.** *In vitro* CYP inhibition by PAR-101 in human liver microsomes

Enzyme	Direct Inhibition		Time-Dependent Inhibition		Potential
	IC <sub>50</sub> (µg/mL)	Max Inhibition at 10 µg/mL (%)	IC <sub>50</sub> (µg/mL)	Max Inhibition at 10 µg/mL (%)	
<b>PAR-101</b>					
CYP1A2	>10	12	>10	16	Little/No
CYP2B6	>10	15	>10	32	Yes
CYP2C8	>10	25	>10	39	Little/No
CYP2C9	7.2	58	9.9	51	Little/No
CYP2C19	>10	19	>10	24	Little/No
CYP2D6	>10	21	>10	27	Little/No
CYP2E1	>10	3.8	>10	9.0	Little/No
CYP3A4/5 (testosterone)	>10	--	>10	20	Yes
CYP3A4/5 (midazolam)	>10	8.3	>10	32	Yes
CYP3A4/5 (nifedipine)	>10	13	>10	43	Yes

**Table 2.** *In vitro* CYP inhibition by OP-1118 in human liver microsomes

Enzyme	Direct Inhibition	
	IC <sub>50</sub> (µg/mL)	Max Inhibition at 10 µg/mL (%)
<b>OP-1118</b>		
CYP1A2	>10	2.1
CYP2B6	>10	5.0
CYP2C8	>10	--
CYP2C9	>10	17
CYP2C19	>10	8.9
CYP2D6	>10	2.2
CYP2E1	>10	--
CYP3A4/5 (testosterone)	>10	--
CYP3A4/5 (midazolam)	>10	--
CYP3A4/5 (nifedipine)	>10	--

**SPONSOR'S CONCLUSIONS:** PAR-101 and OP-1118 were weak inhibitors of CYP enzymes under experimental conditions. PAR-101 caused direct inhibition of CYP2C9 with an IC<sub>50</sub> value of 7.2 µg/mL.

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results. However, the highest tested concentration of 10 µg/mL does not reflect the highest intestinal concentration anticipated at the clinical dose ([I]<sub>2</sub>, 800 µg/mL). Thus, the potential for inhibition of prominent gut CYP enzymes (i.e., CYP3A4, CYP2C9, and CYP2C19) by PAR-101 and OP-1118 cannot be excluded.

STUDY NO.: **XT095062**

***In vitro* evaluation of OP-1118 as an inhibitor of cytochrome P450 (CYP) 3A4/5 in human liver microsomes**

Laboratory Site: (b) (4)

**STUDY DESCRIPTION:** This study investigated the ability of OP-1118 to inhibit CYP3A4/5 in pooled human liver microsomes.

**METHODS**

**Study Procedures:** For evaluation of direct inhibition, OP-1118 was incubated at 37 °C with pooled human liver microsomes, NADPH-generating system, and the marker substrate at final concentrations of 5-1000 µg/mL. (Note: Unlike OP-1118, the parent compound was limited by solubility at the concentration of 10 µg/mL, and was thus, not re-evaluated.) For evaluation of time- and metabolism-dependent inhibition, OP-1118 was pre-incubated with human liver microsomes in the presence and absence of an NADPH-generating system for 30 minutes. Known direct and time-dependent inhibitors of CYP enzymes were included as positive controls.

**Analytical Methods:** All analyses were performed using validated HPLC/MS/MS methods.

**RESULTS**

OP-1118 directly inhibited CYP3A4/5, as measured by testosterone 6β-hydroxylation and midazolam 1'-hydroxylation, with IC<sub>50</sub> of 620 and 42 µg/mL, respectively (**Table 1**). OP-1118 was a time- and metabolism-dependent inhibitor of CYP3A4/5, as IC<sub>50</sub> values decreased with pre-incubation +/- NADPH.

**Table 1.** *In vitro* CYP3A4/5 inhibition by OP-1118 in human liver microsomes

Enzyme	Direct Inhibition (No Pre-Incubation)		Time-Dependent Inhibition (Pre-Incubation, -NADPH)		Metabolism-Dependent Inhibition (Pre-Incubation, +NADPH)	
	IC <sub>50</sub> (µg/mL)	Max Inhibition at 1000 µg/mL (%)	IC <sub>50</sub> (µg/mL)	Max Inhibition at 1000 µg/mL (%)	IC <sub>50</sub> (µg/mL)	Max Inhibition at 1000 µg/mL (%)
CYP3A4/5 (testosterone)	620	58	370	94	78	100
CYP3A4/5 (midazolam)	42	94	36	99	16	100

**SPONSOR'S CONCLUSIONS:** OP-1118 directly inhibited CYP3A4/5 with IC<sub>50</sub> values of 620 µg/mL (testosterone) and 42 µg/mL (midazolam).

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results. The potential for gut-mediated CYP3A4/5 inhibition by OP-1118 cannot be excluded, and the clinical significance of this potential drug-drug interaction requires investigation.

STUDY NO.: **XT063006**

***In vitro* evaluation of PAR-101 and OP-1118 as inducers of cytochrome P450 expression in cultured human hepatocytes**

Laboratory Site: (b) (4)

**STUDY DESCRIPTION:** This study investigated the effect of PAR-101 and OP-1118 on the expression of CYP enzymes in primary cultures of human hepatocytes.

**METHODS**

**Study Procedures:** Three preparations of cultured human hepatocytes from three separate human livers were treated once daily for three consecutive days with dimethyl sulfoxide (DMSO, 0.1%), PAR-101 or OP-1118 (0.1, 1, or 10 µg/mL), or known CYP inducer (omeprazole 100 µM, phenobarbital 750 µM, or rifampin 10 µM). After treatment, cells were harvested to prepare microsomes for analysis of phenacetin O-dealkylation (CYP1A2), bupropion hydroxylation (CYP2B6), diclofenac 4'-hydroxylation (CYP2C9), S-phenytoin 4'-hydroxylation (CYP2C19), and testosterone 6β-hydroxylation (CYP3A4/5).

**Analytical Methods:** All analyses were performed using validated HPLC/MS/MS methods.

**RESULTS**

Treatment of hepatocytes with known inducers caused anticipated increases in CYP enzyme activity (**Table 1**). Treatment with 0.1, 1, or 10 µg/mL of PAR-101 or OP-1118 had little or no effect on the activity of CYP enzymes tested.

**Table 1.** *In vitro* CYP induction by PAR-101 and OP-1118 in cultured human hepatocytes

Treatment	Concentration (µg/mL)	Mean Fold Induction				
		CYP1A2	CYP2B6	CYP2C9	CYP2C19	CYP3A4/5
DMSO (– control)	--	1.00	1.00	1.00	1.00	1.00
PAR-101	0.1	1.12	1.06	1.14	1.01	1.05
	1	1.16	1.01	1.12	1.03	0.92
	10	0.99	0.83	1.10	0.93	0.94
OP-1118	0.1	1.03	0.93	1.05	1.00	1.03
	1	1.05	0.93	1.04	0.87	0.96
	10	1.05	0.84	0.95	0.90	0.93
Omeprazole (+ control)	--	20.6	8.15	1.55	1.30	2.31
Phenobarbital (+ control)	--	2.31	16.1	1.86	2.61	6.16
Rifampin (+ control)	--	2.30	9.69	2.24	9.81	6.11

**SPONSOR’S CONCLUSIONS:** PAR-101 and OP-1118 have little or no potential to cause induction of human CYP enzymes.

**REVIEWER ASSESSMENT:** The Sponsor’s conclusions are appropriate based on study results.

**STUDY NO.: 9OPTIP3**

**P-gp substrate and inhibitor assessment of fidaxomicin and main metabolite (OP-1118)**

Laboratory Site: (b) (4)

**STUDY DESCRIPTION:** This study investigated the extent to which fidaxomicin and OP-1118 act as a substrate or inhibitor of P-gp in Caco-2 cell monolayers by bidirectional permeability.

**METHODS**

**Study Procedures:** For P-gp substrate studies, fidaxomicin and OP-1118 were evaluated in Caco-2 cells, with digoxin as a positive control (**Table 1**). Further studies were performed in the absence and presence of known P-gp inhibitors, cyclosporine A and ketoconazole (**Table 2**).

**Table 1.** P-gp substrate assessment assay conditions (Step 1)

Pre-incubation with Dosing Solution	AP-to-BL	Matrix Composition		Sampling Volume (µL)		Sampling Time Points (minute)	
		AP	BL	AP	BL	AP	BL
Y	Fidaxomicin (1, 5, 10 µM) or OP-1118 (1.25, 12.5, 125 µM)	HBSSg	HBSSg BSA	50	200	0, 120	30, 60, 90, 120
N	Digoxin (10 µM)	HBSSg	HBSSg			5, 120	120
<b>BL-to-AP</b>							
Y	Fidaxomicin (1, 5, 10 µM) or OP-1118 (1.25, 12.5, 125 µM)	HBSSg BSA	HBSSg	200	50	30, 60, 90, 120	0, 120
N	Digoxin (10 µM)	HBSSg	HBSSg			120	5, 120

AP, apical side; BL, basolateral side; BSA, bovine serum albumin; HBSSg, Hanks Balanced Salt Solution containing 10 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) and 15 mM glucose

**Table 2.** P-gp substrate assessment assay conditions (Step 2)

Treatments	30-minute Pre-incubation		A-B Directional Permeability		B-A Directional Permeability	
	AP	BL	AP	BL	AP	BL
5 µM Fidaxomicin, or 125 µM OP-1118	HBSSg (7.4)	HBSSg (7.4)	Test Compound	HBSSg (1% BSA)	HBSSg (1% BSA)	Test Compound
	5 µM CsA	5 µM CsA	Test Compound + CsA	HBSSg (1% BSA) + CsA	HBSSg (1% BSA) + CsA	Test Compound + CsA
	20 µM Ketoconazole	20 µM Ketoconazole	Test Compound + Ketoconazole	HBSSg (1% BSA) + Ketoconazole	HBSSg (1% BSA) + Ketoconazole	Test Compound + Ketoconazole
10 µM Digoxin	HBSSg (7.4)	HBSSg (7.4)	10 µM Digoxin	HBSSg (7.4)	HBSSg (7.4)	10 µM Digoxin
	5 µM CsA	5 µM CsA	Digoxin + CsA	HBSSg + CsA	HBSSg + CsA	Digoxin + CsA
	20 µM Ketoconazole	20 µM Ketoconazole	Digoxin + Ketoconazole	HBSSg + Ketoconazole	HBSSg + Ketoconazole	Digoxin + Ketoconazole

AP, apical side; BL, basolateral side; BSA, bovine serum albumin; CsA, cyclosporine A; HBSSg, Hanks Balanced Salt Solution containing 10 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) and 15 mM glucose

P-gp inhibitor studies (**Table 3**) and studies for IC<sub>50</sub> determination (**Table 4**) were conducted for fidaxomicin and OP-1118 with cyclosporine A and ketoconazole as positive controls.

**Table 3.** P-gp inhibitor assessment assay conditions

30-minute Pre-incubation with Test or Control Compound Solution	Matrix Composition		Sampling Volume (μL)		Sampling Time Points (minute)	
	AP	BL	AP	BL	AP	BL
Plain HBSSg buffer, 5 μM CsA, 20 μM ketoconazole, 10 μM fidaxomicin, or 125 μM OP-1118	Digoxin (10 μM) in the absence and presence of 5 μM CsA, 20 μM ketoconazole, 10 μM fidaxomicin, or 125 μM OP-1118	HBSSg in the absence and presence of 5 μM CsA, 20 μM ketoconazole, 10 μM fidaxomicin, or 125 μM OP-1118	50	200	5, 120	120
Plain HBSSg buffer, 5 μM CsA, 20 μM ketoconazole, 10 μM fidaxomicin, or 125 μM OP-1118	HBSSg in the absence and presence of 5 μM CsA, 20 μM ketoconazole, 10 μM fidaxomicin, or 125 μM OP-1118	Digoxin (10 μM) in the absence and presence of 5 μM CsA, 20 μM ketoconazole, 10 μM fidaxomicin, 125 μM or OP-1118	200	50	120	5, 120

AP, apical side; BL, basolateral side; CsA, cyclosporine A; HBSSg, Hanks Balanced Salt Solution containing 10 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) and 15 mM glucose

**Table 4.** P-gp IC<sub>50</sub> assessment assay conditions

30-minute Pre-incubation	Matrix Composition		Sampling Volume (μL)		Sampling Time Points (minutes)	
	AP	BL	AP	BL	AP	BL
Plain HBSSg buffer, 5 μM CsA, 20 μM ketoconazole, or series of concentrations of fidaxomicin	Digoxin (10 μM) in the absence and presence of 5 μM CsA, 20 μM ketoconazole, or series of concentrations of fidaxomicin	HBSSg in the absence and presence of 5 μM CsA, 20 μM ketoconazole, or series of concentrations of fidaxomicin	50	200	5, 120	120
Plain HBSSg buffer, 5 μM CsA, 20 μM ketoconazole, or series of concentrations of fidaxomicin	HBSSg in the absence and presence of 5 μM CsA, 20 μM ketoconazole, or series of concentrations of fidaxomicin	Digoxin (10 μM) in the absence and presence of 5 μM CsA, 20 μM ketoconazole, or series of concentrations of fidaxomicin	200	50	120	5, 120

AP, apical side; BL, basolateral side; CsA, cyclosporine A; HBSSg, Hanks Balanced Salt Solution containing 10 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) and 15 mM glucose

**Analytical Methods:** All analyses were performed using validated LC-MS/MS methods.

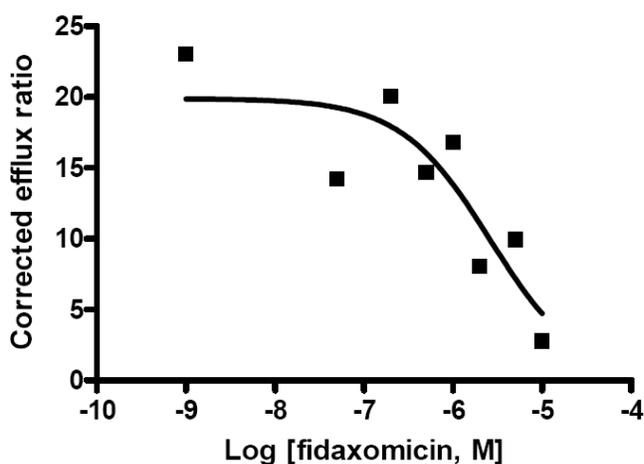
## RESULTS

Both fidaxomicin and OP-1118 had efflux ratios in excess of 2, indicating that these compounds were likely substrates of efflux transporters. The maximum efflux ratio was observed at 5 μM for fidaxomicin (44.9) and the efflux ratio could only be quantified at 125 μM for OP-1118 (6.36). Comparatively, efflux ratio for digoxin (known P-gp substrate) was 17.2 in Caco-2 cells.

With fidaxomicin 5  $\mu\text{M}$ , the presence of cyclosporine A and ketoconazole decreased its efflux by 98.8% and 89.8%, respectively. With OP-1118 125  $\mu\text{M}$ , the presence of cyclosporine A and ketoconazole decreased its efflux by 44.2% and 88.6%, respectively. Since efflux ratios were reduced by >50% (or marginally lower than 50% for OP-1118 with cyclosporine A), fidaxomicin and likely OP-1118 are substrates of P-gp.

In the presence of fidaxomicin 10  $\mu\text{M}$  and OP-1118 125  $\mu\text{M}$ , efflux ratio of digoxin (known P-gp substrate) was decreased by 81.2% and 43.1%, respectively. The  $\text{IC}_{50}$  value of fidaxomicin towards digoxin was 2.59  $\mu\text{M}$  (or 2.74  $\mu\text{g}/\text{mL}$ ) and  $R^2$  was 0.7650, suggesting fidaxomicin may have a non-specific effect on P-gp (**Figure 1**). The  $\text{IC}_{50}$  value of OP-1118 towards digoxin was not determined.

**Figure 1.** Inhibitory effect of fidaxomicin on digoxin transport



**SPONSOR'S CONCLUSIONS:** Fidaxomicin and likely OP-1118 are substrates of P-gp. Fidaxomicin was an inhibitor of P-gp, with an  $\text{IC}_{50}$  of 2.59  $\mu\text{M}$ , while OP-1118 was a weak inhibitor ( $\text{IC}_{50} > 125 \mu\text{M}$ , highest tested concentration).

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results. Clinical drug-drug interaction studies of fidaxomicin as a P-gp substrate and as a P-gp inhibitor are warranted due to high intestinal concentrations anticipated at the clinical dose ( $[\text{I}]_2$ , 800  $\mu\text{g}/\text{mL}$ ).

## 4.1.2 General Pharmacokinetics

APPEARS THIS WAY ON  
ORIGINAL

**STUDY NO.: OPT-80 1A-SD**

**A Phase 1A, single dose-escalating safety study of OPT-80 in healthy volunteers**

Date(s): 30 Sep 2003 – 12 Nov 2003

Investigator(s): RA Preston, M.D.

Clinical Site(s): Division of Clinical Pharmacology, University of Miami; Miami, FL, US

Analytical Site(s): (b) (4)

**OBJECTIVE(S):** To determine the safety, tolerability, and pharmacokinetics of OPT-80 in healthy volunteers following a single oral dose

**METHODS**

**Study Design:** This was a single oral (PO) dose, double-blind, randomized, placebo-controlled, dose escalation study in healthy volunteers (n=16). Each subject received two escalating doses of the study drug in a crossover manner with a washout period of at least one week (**Table 1**).

**Table 1.** Study design of Study OPT-80 1A-SD

	Group 1 (n=8; 6 active, 2 placebo)		Group 2 (n=8; 6 active, 2 placebo)		Evaluation
	Period 1	Period 2	Period 1	Period 2	
100 mg	X				Inpatient/Outpatient
200 mg			X		Inpatient
300 mg		X			Inpatient
450 mg				X	Inpatient/Outpatient

**Inclusion Criteria:** Healthy volunteers, 18-65 years of age, with body mass index (BMI) 19-27 kg/m<sup>2</sup> were enrolled. Subjects who had were on a regular course of medications within 2 weeks of dosing, used antibiotics or had a bowel infection in past 3 months were excluded.

**Treatment:** Subjects were administered doses of OPT-80 PO approximately 0.5 h after morning breakfast, followed by a 4-h fast post-dose with water *ad libitum*. OPT-80 was supplied as 50 mg hard gelatin capsules, containing 50 mg OPT-80 in 0.5 g Labrasol<sup>®</sup>.

**Sample Collection:** Blood, urine, and fecal samples were collected (**Table 2**), but only plasma and fecal samples were analyzed for pharmacokinetic purposes. (Note: A suitable assay for urine was still under development due to poor drug stability in freshly caught unbuffered urine.)

**Table 2.** Pharmacokinetic sampling scheme for single PO doses of OPT-80

<b>Blood</b>	0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 48, 72, 96, and 120 h post-dose
<b>Urine</b>	0-24, 24-48, 48-72, 72-96, 96-120 h post-dose
<b>Feces</b>	0-24, 24-48, 48-72, 72-96, 96-120 h post-dose

**Analytical Methods:** Pharmacokinetic samples were analyzed for OPT-80 and OP-1118 (major active metabolite of OPT-80) by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) in plasma (b) (4) and feces (b) (4) (b) (4) (**Table**

3). Concentrations below the lower limit of quantification (LLOQ) were excluded from pharmacokinetic analysis.

**Table 3.** Bioanalytical results of OPT-80 and OP-1118 in plasma and feces

Criterion	OPT-80	OP-1118 <sup>a</sup>	Comments
<b>PLASMA</b>			
Range	5-5000 ng/mL	--	Satisfactory
LLOQ	5 ng/mL	--	Satisfactory
Linearity	≥0.996	--	Satisfactory
Accuracy	± 7.7%	--	Satisfactory
Precision	11.3% CV	--	Satisfactory
Stability	<ul style="list-style-type: none"> <li>• Study Dates: 30 Sep 2003 – 12 Nov 2003</li> <li>• Analysis Dates: 22 Oct 2003 – 26 Nov 2003               <ul style="list-style-type: none"> <li>• Stability: 21 weeks at -80 °C</li> </ul> </li> </ul>		Satisfactory
<b>FECES</b>			
Range	2-400 µg/g (100x dilution tested)	10-2000 µg/g	Satisfactory
LLOQ	2 µg/g	10 µg/g	Satisfactory
Linearity	≥0.9991	≥0.9988	Satisfactory
Accuracy	Missing	Missing	<b>Unsatisfactory</b>
Precision	Missing	Missing	<b>Unsatisfactory</b>
Stability	<ul style="list-style-type: none"> <li>• Study Dates: 30 Sep 2003 – 12 Nov 2003</li> <li>• Analysis Dates: 10 May 2004 – 12 May 2004               <ul style="list-style-type: none"> <li>• Stability: 93 days / 31 days at -70 °C</li> </ul> </li> </ul>		<b>Unsatisfactory</b>

<sup>a</sup> No bioanalytical method was available for assessing OP-1118 in plasma

*Reviewer Comment: Due to unsatisfactory storage duration of fecal samples and missing accuracy and precision information, pharmacokinetic data of OPT-80 and OP-1118 in feces will be limited to descriptive terms for labeling.*

**Pharmacokinetic Assessment:** Pharmacokinetic parameters for OPT-80 and OP-1118 were determined using single-dose data with non-compartmental methods. Parameters included the following:

- $C_{max}$ , peak observed plasma concentration
- $T_{max}$ , time to  $C_{max}$
- $t_{1/2}$ , apparent elimination half-life
- $AUC_{0-t}$ , area under the concentration-time curve from time 0 to last measured concentration
- $AUC_{0-inf}$ , area under the concentration-time curve from time 0 to infinity
- Fecal recovery, percent of dose recovered in feces

## RESULTS

**Study Population:** In total, 16 subjects were enrolled with equal number of males and females. Subjects were predominantly Hispanic, with only 1/16 Caucasian. Mean ± SD age of all subjects was 49.3 ± 9.6 years, while mean ± SD weight and BMI were 72.8 ± 9.2 kg and 26.0 ± 1.7 kg/m<sup>2</sup>, respectively.

Of enrolled subjects, 15/16 completed the study. Subject 016 was withdrawn (due to abnormal pre-dose lipase values) after receiving the designated 200 mg dose, and thus, failed to receive the planned 450 mg dose following crossover.

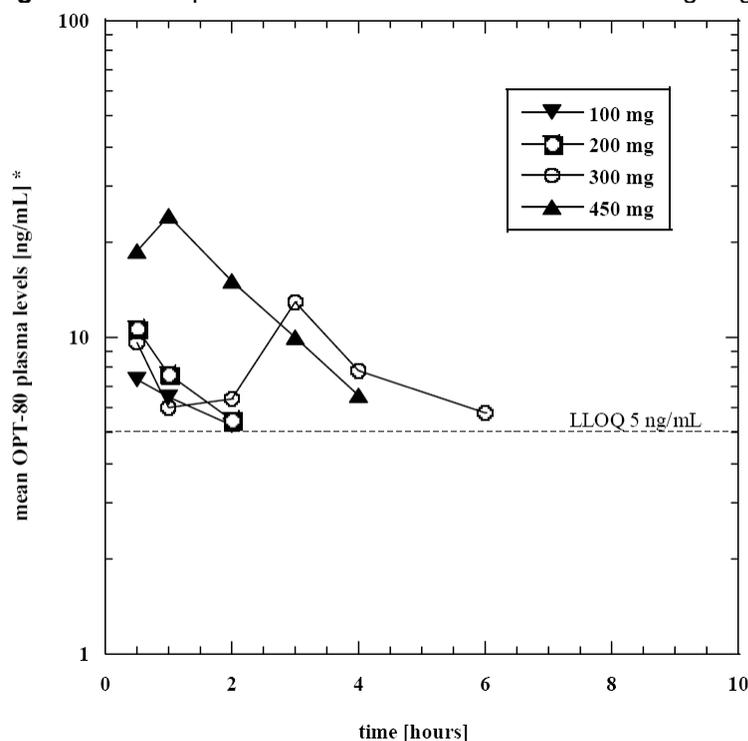
**Pharmacokinetics: (i) Plasma** – Individual and mean plasma concentrations of OPT-80 following single PO doses are shown in **Table 4** and **Figure 1**, respectively. Plasma concentrations of OPT-80 appeared to increase with increasing dose. For 100 and 200 mg doses, plasma concentrations were undetectable after 2 h, while there was only one subject with detectable concentrations at 4 h for 300 mg and another at 8 h for 450 mg.

**Table 4.** Individual plasma concentrations of OPT-80 following single PO doses in healthy subjects

Subject	OPT-80 Concentration (ng/mL)									
	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	
<b>100 mg</b>										
001	-	6.08	-	-	-	-	-	-	-	-
002	9.74	-	-	-	-	-	-	-	-	-
003	-	-	-	-	-	-	-	-	-	-
005	-	5.15	-	-	-	-	-	-	-	-
006	5.06	5.23	-	-	-	-	-	-	-	-
008	-	9.42	5.25	-	-	-	-	-	-	-
<b>200 mg</b>										
009	-	6.38	5.04	-	-	-	-	-	-	-
010	-	10.4	6.31	-	-	-	-	-	-	-
011	-	-	5.16	-	-	-	-	-	-	-
013	-	-	-	-	-	-	-	-	-	-
014	-	-	-	-	-	-	-	-	-	-
016	10.6	6.27	-	-	-	-	-	-	-	-
<b>300 mg</b>										
001	5.95	-	-	-	-	-	-	-	-	-
002	6.42	5.22	-	-	-	-	-	-	-	-
003	16.5	8.77	-	-	-	-	-	-	-	-
005	-	-	16.9	-	-	-	-	-	-	-
006	-	5.09	-	-	-	-	-	-	-	-
008	-	-	8.79	7.85	5.79	-	-	-	-	-
<b>450 mg</b>										
009	17.1	25.3 <sup>a</sup>	15.2 <sup>a</sup>	5.77 <sup>a</sup>	-	-	-	-	-	-
010	24.8	37.8 <sup>a</sup>	21.6 <sup>a</sup>	8.62 <sup>a</sup>	5.59 <sup>a</sup>	-	-	-	-	-
011	13.8	-	5.36	6.78	-	-	-	-	-	-
013	17.7	17.7	21.1 <sup>a</sup>	22.1 <sup>a</sup>	9.00 <sup>a</sup>	-	5.06 <sup>a</sup>	-	-	-
014	20.7 <sup>a</sup>	15.9 <sup>a</sup>	11.6 <sup>a</sup>	6.74 <sup>a</sup>	5.19 <sup>a</sup>	-	-	-	-	-

<sup>a</sup> Used in characterization of terminal elimination phase (i.e., determination of  $t_{1/2}$ )

**Figure 1.** Mean plasma concentrations of OPT-80 following single PO doses in healthy subjects



Only 4 subjects (all at the 450 mg dose) had sufficient plasma concentration-time data suitable for pharmacokinetic analysis (**Table 5**). The apparent elimination  $t_{1/2}$  for OPT-80 ranged 0.94-2.77 h.

**Table 5.** OPT-80 pharmacokinetic parameters following single PO dose of 450 mg in healthy subjects

Subject	$C_{max}$ (ng/mL)	$T_{max}$ (h)	$AUC_{0-t}$ (ng*h/mL)	$AUC_{0-inf}$ (ng*h/mL)	$t_{1/2}$ (h)
009	25.30	1.00	44.43	52.24	0.94
010	37.80	1.00	71.92	80.33	1.04
013	22.10	3.00	96.23	116.42	2.77
014	20.70	0.50	42.79	55.73	1.73
<b>N</b>	4	4	4	4	4
<b>Mean</b>	26.48	1.38	63.84	76.18	1.62
<b>SD</b>	7.79	1.11	25.39	29.60	0.84
<b>%CV</b>	29.4	80.6	39.8	38.9	52.0

*Reviewer Comment: Ideally, calculation of  $t_{1/2}$  should be based on regression of  $\geq 3$  concentrations, not including the  $C_{max}$  value. Because systemic absorption of OPT-80 is minimal and measurable concentrations are limited,  $t_{1/2}$  values herein should be interpreted with caution.*

**(ii) Feces** – Fecal recovery data were restricted to 200 and 300 mg doses (**Table 6**) due to incomplete sample collection for 100 and 450 mg, which were evaluated on a combined inpatient/outpatient basis. On average, 26% of the dose (for 200 and 300 mg) was excreted unchanged in feces as parent OPT-80 over the 120-h collection period and 66% as OP-1118.

**Table 6.** Fecal data (peak concentration and fecal recovery) of OPT-80 and OP-1118 following single PO doses of 200 and 300 mg in healthy subjects

Subject <sup>a</sup>	Dose (mg)	Peak OPT-80 Concentration (µg/g)	Dose-Normalized Peak OPT-80 Concentration (µg/g/100 mg dose)	Fecal Recovery (% of dose)		
				OPT-80	OP-1118	Total
009	200	225.5	112.8	31.63	118.31	149.93
010	200	161.1	80.6	24.85	97.50	122.35
011	200	252.8	126.4	22.66	54.84	77.50
013	200	247.3	123.7	45.42	94.35	139.76
014	200	299.8	149.9	27.56	59.75	87.31
016	200	221.7	110.9	27.01	95.67	122.68
001	300	269.4	89.8	12.16	19.74	31.89
002	300	173.1	57.7	28.92	46.25	75.17
003	300	251	83.7	15.99	51.14	67.13
005	300	158.4	52.8	13.03	11.00	24.03
008	300	480.7	160.2	41.17	79.25	120.43
<b>N</b>			11	11	11	11
<b>Mean</b>			104.39	26.40	66.16	92.56
<b>SD</b>			34.94	10.59	33.95	42.04
<b>%CV</b>			33.5	40.1	51.3	45.4

<sup>a</sup> Subject 006 (active) excluded due to possible sample misplacement with Subject 007 (placebo)

**Safety:** In total, 5 adverse events were reported by 3/16 (19%) subjects; none were considered related to study drug. Subject 001 experienced an open wound to the left upper leg during the washout period due to fall on the floor. Subject 005 had a headache and running nose that occurred pre-dose. Subject 016 exhibited elevated amylase and lipase pre-dose and was subsequently withdrawn from the scheduled 450 mg dose (subject had already completed the 200 mg dose at time of reporting).

No clinically significant abnormalities in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, or electrocardiogram were observed.

**SPONSOR'S CONCLUSIONS:** Following single PO doses of OPT-80 100, 200, 300, and 450 mg in healthy subjects (n=16):

- Low concentrations of OPT-80 were detected in plasma, most of which fell below the LLOQ (5 ng/mL) after 2 h for 100 and 200 mg, 4 h for 300 mg, and 8 h for 450 mg.
- Plasma concentrations of OPT-80 appeared to increase with increasing dose.
- Apparent elimination  $t_{1/2}$  for OPT-80 ranged 0.94-2.77 h based on limited data with 450 mg.
- Mean total fecal recovery (OPT-80 plus OP-1118) was 92.6% for 200 and 300 mg doses.
- OPT-80 was well-tolerated at studied single PO doses in healthy subjects.

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results. Due to limitations with pharmacokinetic data provided in Study OPT-80 1A-SD by bioanalytical methods (insufficient LLOQ in plasma and inappropriate storage duration in feces), plasma data for labeling will be obtained from Study OPT-80-007 and fecal data for labeling will be limited to descriptive terms.

**STUDY NO.:** OPT-80 IB-MD

**A Phase 1B, multiple dose-escalating safety study of OPT-80 in healthy volunteers**

Date(s): 29 Apr 2004 – 21 Jun 2004

Investigator(s): RA Preston, M.D.

Clinical Site(s): Division of Clinical Pharmacology, University of Miami; Miami, FL, US

Analytical Site(s): (b) (4)

**OBJECTIVE(S):** To determine the safety, tolerability, and pharmacokinetics of OPT-80 in healthy volunteers following the administration of a series of oral doses for 10 consecutive days

**METHODS**

**Study Design:** This was a multiple oral (PO) dose, double-blind, randomized, placebo-controlled, dose escalation study in healthy subjects (n=24). Subjects received 150, 300, or 450 mg QD for 10 days (n=8/cohort; 6 active, 2 placebo) and were evaluated on a combined inpatient/outpatient basis.

**Inclusion Criteria:** Healthy volunteers, 18-65 years of age, with body mass index (BMI) 19-27 kg/m<sup>2</sup> were enrolled. Subjects who were on a regular course of medications within 2 weeks of dosing, used antibiotics or had a bowel infection in past 3 months were excluded.

**Treatment:** Subjects were administered doses of OPT-80 PO approximately 0.5 h after morning breakfast, followed by a 4-h fast post-dose with water *ad libitum*. OPT-80 was supplied as 50 mg capsules, containing 50 mg OPT-80 in 110 mg Avicel<sup>®</sup>PH-102 (microcrystalline cellulose, NF).

*Reviewer Comment: OPT-80 formulation in Study OPT-80 1B-MD differed from the earlier Study OPT-80 1A-SD; specifically, in excipient (Avicel<sup>®</sup>PH-102 versus Labrasol<sup>®</sup>, respectively).*

**Sample Collection:** Blood, urine, and fecal samples were collected and analyzed for pharmacokinetic purposes (**Table 1**).

**Table 1.** Pharmacokinetic sampling scheme for multiple PO doses of OPT-80

<b>Blood</b>	Day1: 0, 1, 2, 4, 6, 12, 24 h post-dose Day10: 0, 1, 2, 4, 6, 12, 24 h post-dose
<b>Urine</b>	Day1: 4-8 h post-dose Day10: 4-8 h post-dose
<b>Feces</b>	Day10: 0-24 h post-dose

**Analytical Methods:** Pharmacokinetic samples were analyzed for OPT-80 and OP-1118 (major active metabolite of OPT-80) by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) in plasma (b) (4), (b) (4), (b) (4) for stability), urine (b) (4), (b) (4) and feces (b) (4), (b) (4) (**Table 2**). Concentrations below the lower limit of quantification (LLOQ) were excluded from pharmacokinetic analysis.

**Table 2.** Bioanalytical results of OPT-80 and OP-1118 in plasma, urine, and feces

Criterion	OPT-80	OP-1118 <sup>a</sup>	Comments
<b>PLASMA</b>			
Range	5-1000 ng/mL	--	Satisfactory
LLOQ	5 ng/mL	--	Satisfactory
Linearity	≥0.9994	--	Satisfactory
Accuracy	± 8.8%	--	Satisfactory
Precision	2.7% CV	--	Satisfactory
Stability	<ul style="list-style-type: none"> <li>Study Dates: 29 Apr 2004 – 21 Jun 2004</li> <li>Analysis Dates: 01 Jun 2004 – 22 Jun 2004</li> <li>Stability: 21 weeks at -80 °C</li> </ul>		Satisfactory
<b>URINE</b>			
Range	5-1000 ng/mL	--	Satisfactory
LLOQ	5 ng/mL	--	Satisfactory
Linearity	≥0.9993	--	Satisfactory
Accuracy	± 6.2%	--	Satisfactory
Precision	7.6% CV	--	Satisfactory
Stability	<ul style="list-style-type: none"> <li>Study Dates: 29 Apr 2004 – 21 Jun 2004</li> <li>Analysis Dates: 23 Jun 2004 – 24 Jun 2004</li> <li>Stability: 33 days at -20 °C</li> </ul>		<b>Unsatisfactory</b>
<b>FECES</b>			
Range	2-400 µg/g (100x dilution tested)	10-2000 µg/g	Satisfactory
LLOQ	2 µg/g	10 µg/g	Satisfactory
Linearity	≥0.9992	≥0.9993	Satisfactory
Accuracy	± 11.7%	± 11.5%	Satisfactory
Precision	11.9% CV	10.6% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>Study Dates: 29 Apr 2004 – 21 Jun 2004</li> <li>Analysis Dates: 15 Jun 2004 – 22 Jun 2004</li> <li>Stability: 93 days / 31 days at -70 °C</li> </ul>		<b>Unsatisfactory</b>

<sup>a</sup> No bioanalytical method was available for assessing OP-1118 in plasma

*Reviewer Comment: Doses in Study OPT-80 1B-MD do not include the proposed therapeutic regimen of 200 mg BID. As such, unsatisfactory storage durations for urine and fecal samples are of little consequence as these pharmacokinetic data will not be used for labeling purposes.*

**Pharmacokinetic Assessment:** Pharmacokinetic parameters for OPT-80 and OP-1118 were determined using single- and multiple-dose data with non-compartmental methods. Parameters included the following:

- $C_{max}$ , peak observed plasma concentration
- $T_{max}$ , time to  $C_{max}$
- $t_{1/2}$ , apparent elimination half-life
- $AUC_{0-t}$ , area under the concentration-time curve from time 0 to last measured concentration
- $AUC_{0-inf}$ , area under the concentration-time curve from time 0 to infinity
- $C_{min}$ , minimum plasma concentration at steady-state
- $AUC_{ss}$ , area under the concentration-time curve at steady-state
- Drug accumulation, ratio of  $AUC_{ss}$  to  $AUC_{0-inf}$
- Urinary excretion rate (over the 4-8 h interval)
- Renal clearance (approximated at 6 h)

## RESULTS

**Study Population:** In total, 24 subjects were enrolled with equal number of males and females. Subjects were predominantly Hispanic, with only 5/24 Caucasian. Mean  $\pm$  SD age of all subjects was  $51.6 \pm 7.5$  years, while mean  $\pm$  SD weight and BMI were  $71.5 \pm 9.2$  kg and  $26.3 \pm 1.3$  kg/m<sup>2</sup>, respectively.

Of enrolled subjects, 23/24 completed the study. Subject 014 was withdrawn after receiving the second 300 mg dose on Day 3 (later identified as placebo) due to adverse events of rash and pruritis.

**Pharmacokinetics: (i) Plasma** – Plasma concentrations of OPT-80 were mostly below the LLOQ across the multiple dose range. There were 12 samples from 6 subjects (300 mg QD, n=2; 450 mg QD, n=4) with detectable concentrations at various time points, all within 6 h post-dose (**Table 3**). Of these 12 concentrations, 2 were well above the LLOQ (Subject 021, 11.1 and 48.0 ng/mL), while others barely exceeded the LLOQ of 5 ng/mL. Due to insufficient plasma concentration-time data points, no pharmacokinetic parameters were determined.

**Table 3.** Detectable plasma concentrations of OPT-80 following multiple PO doses (QD for 10 days) in healthy subjects

Subject	OPT-80 Concentration (ng/mL)											
	Day 1					Day 10						
	0 h	1 h	2 h	4 h	6 h	12 h	0 h	1 h	2 h	4 h	6 h	12 h
300 mg QD x 10 d												
009	-	-	-	5.06	-	-	-	-	-	-	-	-
015	-	-	6.63	-	5.89	-	-	-	-	-	-	-
450 mg QD x 10 d												
017	-	-	-	-	-	-	-	5.50	5.04	-	-	-
020	-	-	-	6.19	-	-	-	-	-	6.25	5.93	-
021	-	11.1	-	-	-	-	48.0	-	-	6.43	-	-
022	-	-	-	-	-	-	-	-	-	-	5.13	-

*Reviewer comment: The Sponsor indicates that plasma concentrations from this multiple-dose study were considerably lower than those from the single-dose study (Study OPT-80 1A-SD). Samples from all 6 active subjects had undetectable OPT-80 concentrations with multiple doses of 150 mg QD, while there were 7 detectable concentrations with single doses of 100 mg (from 5 subjects) and 200 mg (from 4 subjects). The Sponsor attributes this difference to the use of OPT-80 formulations with different absorption characteristics. In this multiple-dose study, powder-filled capsules with microcrystalline cellulose (Avicel® PH-102) were used versus liquid-filled capsules with Labrasol® in the single-dose study. Pharmacokinetic data necessary for labeling will be obtained from Study OPT-80-007 at the therapeutic dose of 200 mg with the intended to-be-marketed formulation.*

**(ii) Urine** – All collected urine samples had OPT-80 concentrations below the LLOQ, 5 ng/mL.

**(iii) Feces** – On average, fecal concentrations of OPT-80 and OP-1118 were  $916.0 \pm 450.2$  µg/g and  $267.4 \pm 175.2$  µg/g (normalized to 150 mg dose), respectively, following 10 days of multiple QD doses (**Table 4**).

**Table 4.** Fecal data of OPT-80 and OP-1118 following multiple PO doses (QD for 10 days) in healthy subjects

Subject	Dose (mg)	Fecal Concentration (µg/g)		Dose-Normalized Concentration (µg/g/150 mg dose)	
		OPT-80	OP-1118	OPT-80	OP-1118
001	150	628.9	217.8	628.9	217.8
002	150	1554.1	770.3	1554.1	770.3
003	150	724.5	394.8	724.5	394.8
006	150	1127.1	-	1127.1	-
007	150	430.7	157.0	430.7	157.0
008	150	472.4	125.3	472.4	125.3
009	300	2909.2	1142.3	1454.6	571.2
010	300	1124.5	240.5	562.3	120.3
011	300	1491.2	523.6	745.6	261.8
013	300	1139.2	647.3	569.6	323.7
015	300	2342.8	444.1	1171.4	222.1
016	300	2162.7	321.6	1081.4	160.8
017	450	2106.2	736.3	702.1	245.4
019	450	3179.6	605.9	1059.9	202.0
020	450	4565.4	834.4	1521.8	278.1
021	450	2325.9	602.2	775.3	200.7
022	450	5306.8	729.7	1768.9	243.2
023	450	415.1	153.2	138.4	51.1
<b>N</b>				18	18
<b>Mean</b>				916.0	267.4
<b>SD</b>				450.2	175.2
<b>%CV</b>				49.1	65.5

**Safety:** In total, 13 adverse events were reported by 9/24 (37.5%) subjects: 150 mg QD (headache, dizziness, weakness, conjunctivitis, difficulty swallowing, pharyngitis), 450 mg QD (headache, upper respiratory tract infection), and placebo (fatigue, upper respiratory tract infection, nasal congestion, rash, pruritis). Subject 014 (placebo) who experienced rash and pruritis was withdrawn from the study due to hypersensitivity concerns.

No clinically significant abnormalities in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, or electrocardiogram were observed.

**SPONSOR’S CONCLUSIONS:** Following multiple PO doses of OPT-80 150, 300, and 450 mg QD for 10 days in healthy subjects (n=24):

- Low concentrations of OPT-80 were detected in plasma, most of which fell below the LLOQ (5 ng/mL).
- Due to low plasma concentrations, no intact OPT-80 was detected in collected urine samples.
- Normalized to 150 mg dose, fecal concentrations of OPT-80 and OP-1118 averaged 916.0 and 267.4 µg/g, respectively.
- OPT-80 was well-tolerated at studied multiple PO doses in healthy subjects.

**REVIEWER ASSESSMENT:** The Sponsor’s conclusions are appropriate based on study results. Since (i) plasma OPT-80 exposure appeared to vary with different drug formulations and (ii) the proposed therapeutic regimen (200 mg BID) was not evaluated in Study OPT-80 1B-MD, pharmacokinetic data necessary for labeling will be obtained rather from Study OPT-80-007.

**STUDY NO.:** OPT-80-005

**A single center, open-label, randomized, two-period crossover 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**

Date(s): 07 Aug 2009 – 21 Sep 2009

Investigator(s): W Lewis, M.D.

Clinical Site(s): Covance Clinical Research Unit Inc.; Dallas, TX, US

Analytical Site(s): (b) (4)

**OBJECTIVE(S):**

- To investigate the bioavailability of OPT-80 when administered with or without a high-fat meal to healthy individuals
- To analyze and summarize the levels of both OPT-80 and its major metabolite OP-1118 in plasma, urine, and feces
- To calculate total recovery of OPT-80 and OP-1118 from excreta

**METHODS**

**Study Design:** For Group 1, this was a single-dose, single-period, pharmacokinetic study of OPT-80 200 mg PO (fasted state) in healthy subjects (n=6). For Group 2, this was a randomized, single-dose, two-period, two-way crossover study (with 7-day washout) of OPT-80 400 mg PO under fed and fasted conditions in healthy subjects (n=28).

**Inclusion Criteria:** Males and females, 18-50 years of age (inclusive), 18.5-32.0 kg/m<sup>2</sup> in body mass index (BMI) (inclusive), and in good health as determined by medical history, physical exam, and laboratory evaluations were enrolled.

**Treatment:** For fasting conditions, subjects were administered doses of OPT-80 PO after an 8-h fast followed by a minimum 4-h fast from food post-dose. For fed conditions, subjects were administered doses of OPT-80 PO within 0.5 h of a high-fat breakfast (150, 250, and 500-600 calories from protein, carbohydrates, and fat, respectively) followed by a minimum 4-h fast from food post-dose. For all doses, water was restricted for 1 h pre-dose and 2 h post-dose; *ad libitum* for all other times. OPT-80 was supplied in the to-be-marketed formulation as 200 mg tablets manufactured by (b) (4) (Lot# R024B001).

*Reviewer Comment: Fed and fasting conditions are consistent with those recommended in the "Food-Effect Bioavailability and Fed Bioequivalence Studies" Guidance for Industry, dated Dec 2002.*

Prescription medications/products were prohibited from 14 days prior to Check-In. Non-prescription/over-the-counter (OTC) preparations (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) were prohibited from 7 days prior to Check-

In. Alcohol-, grapefruit-, or caffeine-containing foods or beverages were prohibited from 48 hours prior to Check-In.

**Sample Collection:** Blood, urine, and fecal samples were collected and analyzed for pharmacokinetic purposes (**Table 1**).

**Table 1.** Pharmacokinetic sampling scheme for single PO doses of OPT-80

<b>Blood</b>	Group1: 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 h post-dose Group2: 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 h post-dose
<b>Urine</b>	Group1: 0-4, 4-8, 8-12, 12-24 h post-dose Group2: 0-4, 4-8, 8-12, 12-24 h post-dose
<b>Feces</b>	Group1: 0-24, 24-48, 48-72, 72-96, 96-120 h post-dose Group2: 0-24, 24-48, 48-72, 72-96, 96-120 h post-dose (for Period 1 only)

**Analytical Methods:** Pharmacokinetic samples were analyzed for OPT-80 and OP-1118 (major active metabolite of OPT-80) by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) in plasma ( (b) (4) ), urine ( (b) (4) ), and feces ( (b) (4) ) (**Table 2**). Concentrations below the lower limit of quantification (LLOQ) were excluded from pharmacokinetic analysis.

**Table 2.** Bioanalytical results of OPT-80 and OP-1118 in plasma, urine, and feces

<b>Criterion</b>	<b>OPT-80</b>	<b>OP-1118</b>	<b>Comments</b>
<b>PLASMA</b>			
Range	0.2-100 ng/mL	0.2-100 ng/mL	Satisfactory
LLOQ	0.2 ng/mL	0.2 ng/mL	Satisfactory
Linearity	≥0.9842	≥0.9932	Satisfactory
Accuracy	± 7.2%	± 2.3%	Satisfactory
Precision	8.8% CV	7.2% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>Study Dates: 07 Aug 2009 – 21 Sep 2009</li> <li>Analysis Dates: 07 Aug 2009 – 10 Feb 2010</li> <li>Stability: 838 days / 1133 days at -70 °C</li> </ul>		Satisfactory
<b>URINE</b>			
Range	5-1000 ng/mL	5-1000 ng/mL	Satisfactory
LLOQ	5 ng/mL	5 ng/mL	Satisfactory
Linearity	≥1.00	≥1.00	Satisfactory
Accuracy	± 3.3%	± 6.0%	Satisfactory
Precision	4.6% CV	5.0% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>Study Dates: 07 Aug 2009 – 21 Sep 2009</li> <li>Analysis Dates: 21 Aug 2009 – 30 Sep 2009</li> <li>Stability: 32 days at -70 °C</li> </ul>		Satisfactory
<b>FECES</b>			
Range	2-400 µg/g (100x dilution tested)	10-2000 µg/g	Satisfactory
LLOQ	2 µg/g	10 µg/g	Satisfactory
Linearity	≥0.999	≥0.999	Satisfactory
Accuracy	± 3.3%	± 2.6%	Satisfactory
Precision	7.7% CV	10.2% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>Study Dates: 07 Aug 2009 – 21 Sep 2009</li> <li>Analysis Dates: 21 Aug 2009 – 31 Mar 2010</li> <li>Stability: 93 days / 31 days at -70 °C</li> </ul>		<b>Unsatisfactory</b>

*Reviewer Comment: Due to unsatisfactory storage duration of fecal samples, pharmacokinetic data of OPT-80 and OP-1118 in feces will be limited to descriptive terms for labeling.*

**Pharmacokinetic Assessment:** Pharmacokinetic parameters for OPT-80 and OP-1118 were determined using single-dose data with non-compartmental methods. Parameters included the following:

- $C_{max}$ , peak observed plasma concentration
- $T_{max}$ , time to  $C_{max}$
- $t_{1/2}$ , apparent elimination half-life
- $AUC_{0-t}$ , area under the concentration-time curve from time 0 to last measured concentration
- $AUC_{0-24}$ , area under the concentration-time curve from 0 to 24 hours
- $AUC_{0-\infty}$ , area under the concentration-time curve from time 0 to infinity

**Statistical Methods:** Food effect was examined between fed state (test) and fasted state (reference) where pharmacokinetic data were available. An analysis of variance (ANOVA) was performed using natural log-transformed  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  with a fixed linear mixed model. The 90% confidence intervals (CI) of the test means relative to the reference means were obtained by taking the antilog of the corresponding 90% CIs for the differences between means on the log scale. Food effect was assessed by examining the 90% CI for the ratios of the test means relative to the reference means.

## RESULTS

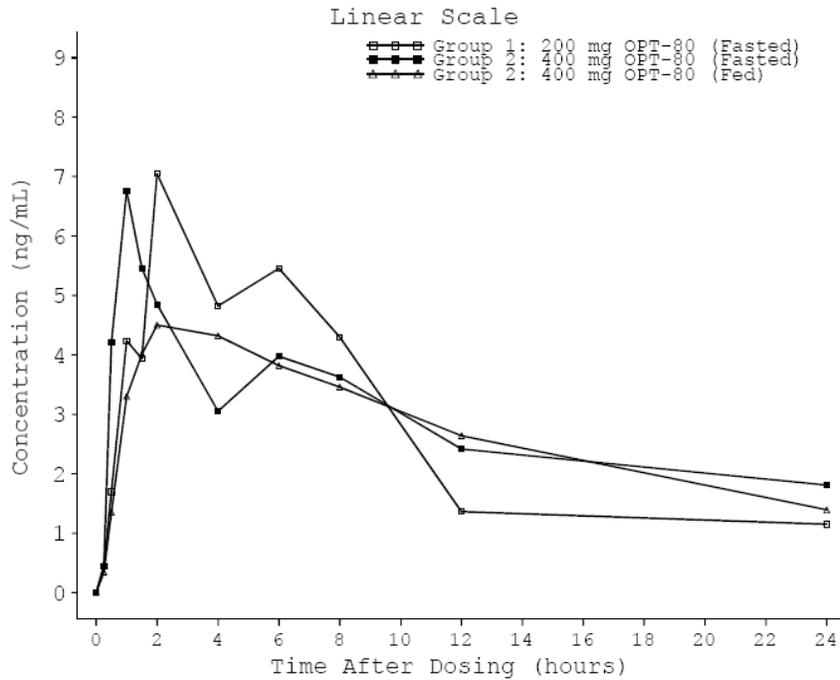
**Study Population:** In total, 34 subjects were enrolled with 6 subjects in Group 1 and 28 subjects in Group 2 (**Table 3**). Overall, there were equal number of males and females with mean age and weight of 33 years and 78 kg, respectively. No subjects were withdrawn prematurely from the study.

**Table 3.** Demographic characteristics of enrolled subjects

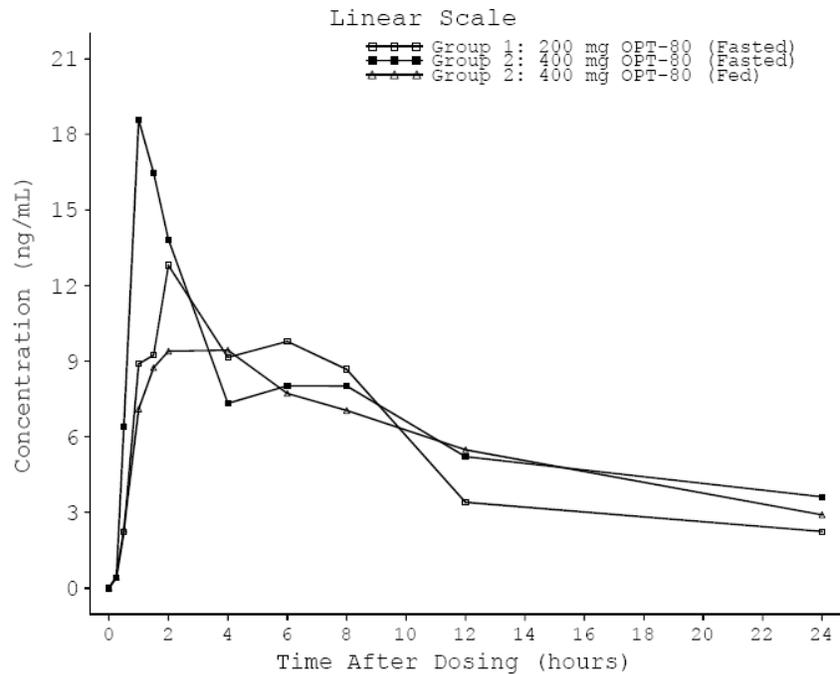
Demographic Variable	Group 1	Group 2
Mean age in years (range)	35 (18 - 44)	32 (18 - 48)
Mean weight in kg (range)	80.9 (60.8 - 94.0)	75.1 (48.9 - 110.2)
Mean height in cm (range)	172.7 (156.9 - 186.3)	168.8 (152.2 - 191.2)
BMI in kg/m <sup>2</sup> (range)	27.0 (24.7 - 28.3)	26.2 (19.0 - 31.6)
Gender (n[%])		
Male	3 (50.0%)	14 (50.0%)
Female	3 (50.0%)	14 (50.0%)
Ethnicity (n[%])		
Hispanic or Latino	- - -	14 (50.0%)
Not Hispanic or Latino	6 (100.0%)	14 (50.0%)
Race (n[%])		
White	1 (16.7%)	23 (82.1%)
Black or African American	5 (83.3%)	5 (17.9%)

**Pharmacokinetics: (i) Plasma** – Geometric mean concentration-time profiles of OPT-80 and OP-1118 following single 200 mg (fasted) or 400 mg (fasted and fed) doses are displayed in **Figure 1** and **Figure 2**, respectively.

**Figure 1.** Geometric mean plasma concentrations of **OPT-80** following single PO doses in healthy subjects (Group 1, n=6; Group 2, n=28)



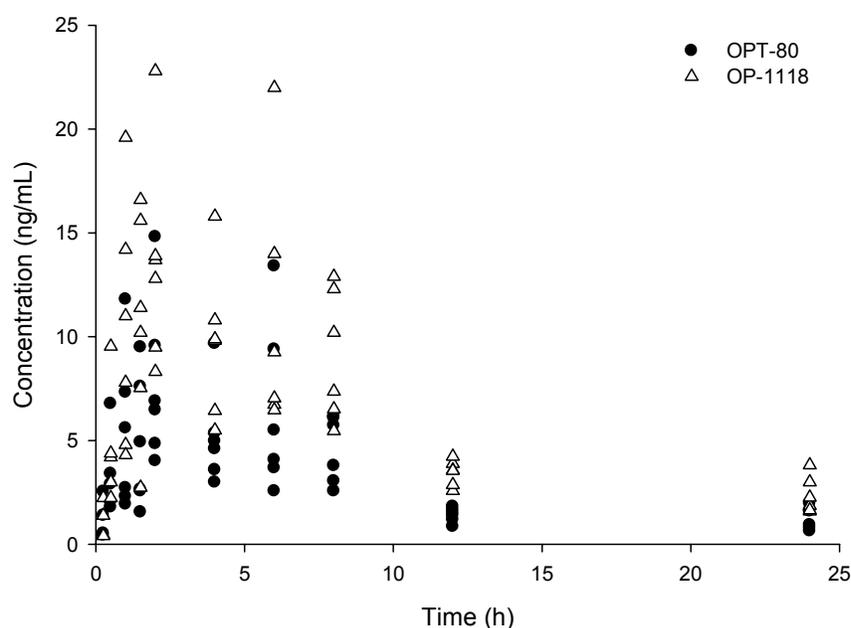
**Figure 2.** Geometric mean plasma concentrations of **OP-1118** following single PO doses in healthy subjects (Group 1, n=6; Group 2, n=28)



For the evaluation of single-dose pharmacokinetics (Group 1), plasma concentrations of OPT-80 and OP-1118 were variable (18.0-112.7% CV) following a single 200 mg dose (fasted) (**Figure 3**) but quantifiable at most time points due to a more sensitive bioanalytical method with a LLOQ of 0.2 ng/mL versus the previous method used in single- and multiple-dose studies (OPT-80 1A-SD and OPT-80 1B-MD) with a LLOQ of 5 ng/mL.

Systemic exposures ( $C_{max}$  and AUC) of the metabolite OP-1118 were approximately 2 times that of the parent OPT-80 based on mean values (**Table 4**).  $T_{max}$  occurred between 1-8 h for both OPT-80 and OP-1118, while the terminal phase could only be characterized for OP-1118 in 3/6 subjects, and accordingly, determination of  $AUC_{0-\infty}$  and  $t_{1/2}$  were limited.

**Figure 3.** Scatter plot of individual OPT-80 and OP-1118 concentration-time points following single 200 mg PO dose in healthy subjects (n=6) under fasting conditions



**Table 4.** Plasma pharmacokinetic parameters of OPT-80 and OP-1118 following single 200 mg PO dose in healthy subjects (n=6) under fasting conditions

	$C_{max}$ (ng/mL)	$T_{max}$ <sup>a</sup> (h)	$AUC_{0-t}$ (ng*h/mL)	$AUC_{0-24}$ (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	$t_{1/2}$ (h)
<b>OPT-80</b>						
N	6	6	6	6	1	1
Mean	9.88	1.75 <sup>a</sup>	69.5	69.4	--	--
SD	3.96	(1.00-8.00)	18.3	18.2	--	--
%CV	40.0%	92.2%	26.3%	26.3%	--	--
<b>OP-1118</b>						
N	6	6	6	6	3	3
Mean	17.6	1.75 <sup>a</sup>	136	136	155	8.36
SD	4.73	(1.00-8.00)	26.2	26.1	25.9	2.03
%CV	27.0%	87.8%	19.2%	19.2%	16.7%	24.3%

<sup>a</sup>  $T_{max}$  reported as median (minimum-maximum)

For the evaluation of food effect (Group 2), 90% CI around point estimates for  $AUC_{0-t}$  under fed versus fasted conditions with a single 400 mg dose were within the standard no-effect boundary of 0.80-1.25 for both OPT-80 and OP-1118 (**Table 5**). For  $AUC_{0-\infty}$ , 90% CI around point estimates were outside 0.80-1.25; however,  $AUC_{0-\infty}$  may be an inappropriate parameter to interpret due to inadequate characterization of the terminal phase. With food,  $C_{max}$  for OPT-80 and OP-1118 was decreased by 21.5% and 33.4%, respectively, while median (range)  $T_{max}$  was slightly delayed (fed state, 2 h [0.5-8 h] versus fasted state, 1 h [0.5-8 h]). (Note: Data from Subject 017 for Period 2 were excluded from all primary pharmacokinetic and statistical analyses due to positive pre-dose values of 1.21 and 1.94 ng/mL for OPT-80 and OP-1118, respectively.)

**Table 5.** Statistical analysis of food effect for OPT-80 and OP-1118 with single 400 mg PO dose under fed versus fasted conditions in healthy subjects (n=28)

Parameter	400 mg Fed (Test)		400 mg Fasted (Reference)		Point Estimate of Test/Reference (90% CI)
	N <sup>a</sup>	Least Squares Mean	N	Least Squares Mean	
<b>OPT-80</b>					
$C_{max}$ (ng/mL)	27	7.02	28	8.94	0.785 (0.673-0.917)
$AUC_{0-t}$ (ng*h/mL)	27	70.6	28	73.0	0.967 (0.870-1.074)
$AUC_{0-\infty}$ (ng*h/mL)	10	68.2	5	77.9	0.875 (0.689-1.112)
<b>OP-1118</b>					
$C_{max}$ (ng/mL)	27	14.9	28	22.4	0.666 (0.584-0.760)
$AUC_{0-t}$ (ng*h/mL)	27	146	28	162	0.897 (0.825-0.977)
$AUC_{0-\infty}$ (ng*h/mL)	11	169	10	217	0.781 (0.626-0.976)

<sup>a</sup> Data from Subject 017 for Period 2 were excluded due to positive pre-dose values of OPT-80 and OP-1118

Concentration-time profiles of OPT-80 (**Figure 4**) and OP-1118 (**Figure 5**) indicate significant variability and also an overlap between fed and fasted states in individual subjects.

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(ii) **Urine** – OPT-80 was not detectable (<LLOQ of 5 ng/mL) in any collected urine sample from any subject. Concentrations of OP-1118 were quantifiable in urine and accounted for  $0.59 \pm 0.36\%$  and  $0.32 \pm 0.22\%$  of the administered dose for Group 1 (200 mg) and Group 2 (400 mg) subjects, respectively.

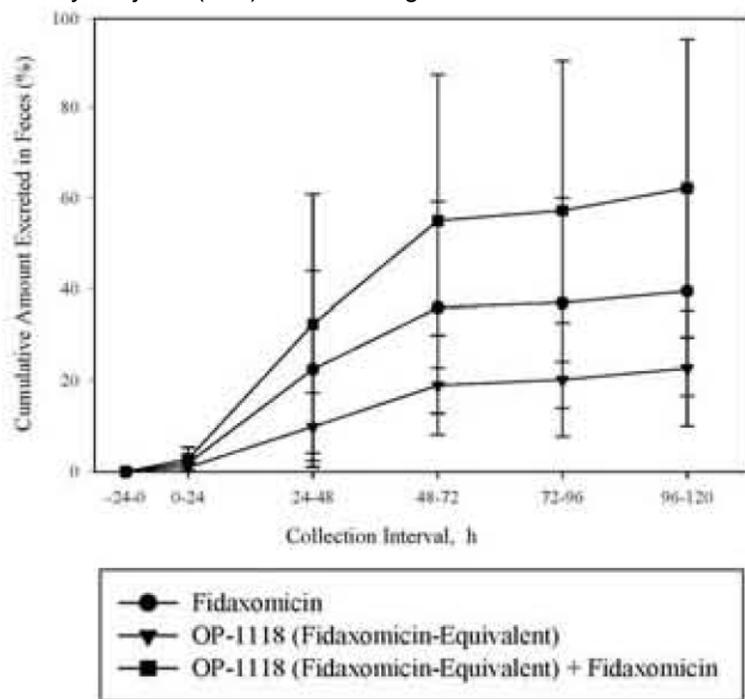
(iii) **Feces** – Peak fecal concentrations of OPT-80 and OP-1118 ranged 391-1240  $\mu\text{g/g}$  and 214-947  $\mu\text{g/g}$ , respectively, following a single 200 mg dose, with the exception of Subject 003 who produced only one fecal sample during the 120-h collection period (**Table 6**). On average, 39.5% of the dose was excreted unchanged in feces as OPT-80 and 22.7% as OP-1118 (**Figure 6**).

**Table 6.** Fecal data of OPT-80 and OP-1118 following single 200 mg PO dose in healthy subjects under fasting conditions

Subject <sup>a</sup>	Peak Concentration ( $\mu\text{g/g}$ )		Fecal Recovery (% of dose)		
	OPT-80	OP-1118	OPT-80	OP-1118	Total
001	943	947	35.9	37.6	73.5
002	391	229	32.8	22.8	55.6
003	11.1	--	0.455	--	0.455
004	893	482	45.8	27.2	73.0
005	741	214	56.0	19.5	75.5
006	1240	475	66.0	29.1	95.1
<b>N</b>	6	5	6	6	6
<b>Mean</b>	703.2	391.2	39.5	22.7	62.2
<b>SD</b>	438.1	327.1	22.8	12.7	32.7
<b>%CV</b>	62.3	83.6	57.7	56.0	52.6

<sup>a</sup> Subject 003 produced only a single fecal sample

**Figure 6.** Fecal recovery (% of dose) of OPT-80 and OP-1118 following single 200 mg PO dose in healthy subjects (n=6) under fasting conditions



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Mean fecal recoveries following a single 400 mg dose were comparable, albeit variable, between fed and fasted states for OPT-80 and OP-1118 (**Table 7**).

**Table 7.** Fecal recovery (% of dose) of OPT-80 and OP-1118 following single 400 mg PO dose in healthy subjects under fed versus fasted conditions

	Fecal Recovery (% of dose)					
	Fasted			Fed		
	OPT-80	OP-1118	Total	OPT-80	OP-1118	Total
N	14	14	14	14	14	14
Mean	31.3	8.63	39.9	47.0	15.5	62.5
SD	21.1	6.73	26.4	34.4	8.82	39.6
%CV	67.4	78.0	66.2	73.2	56.9	63.4

*Reviewer Comment: The Sponsor indicates the wide range of fecal recoveries obtained may be attributable to incomplete collection as some subjects were still excreting past the collection period and variable recovery due to potentially inconsistent extraction of drug in fecal matter.*

**Safety:** In total, 24 adverse events were reported by 13/34 (38.2%) subjects; all were considered mild in severity except for one case of moderate pain in the antecubital fossa secondary to venipuncture. Of reported events, 10 from 5 subjects were considered related to study drug. Most commonly reported events were vessel puncture site pain (6/34, 17.6%) and headache (5/34, 14.7%).

There were 3 subjects in Group 2 with QTcB and/or QTcF intervals of >450 msec: Subject 024 (pre-dose, 3 h post-dose in fasted state, discharge; 452-459 msec), Subject 030 (3 h post-dose in fasted state; 460 msec), and Subject 033 (3 h post-dose in fasted state; 451-460 msec). All electrocardiograms were considered not clinically significant by the investigator.

No clinically significant abnormalities in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, or electrocardiogram were observed.

**SPONSOR'S CONCLUSIONS:** Following single PO dose of 200 mg under fasting conditions (Group 1, n=6) and 400 mg under fed and fasting conditions (Group 2, n=28) in healthy subjects:

- OPT-80 and OP-1118 had AUC<sub>0-t</sub> (but not C<sub>max</sub>) values that were equivalent in the fed versus the fasted state.
- OPT-80 and OP-1118 C<sub>max</sub> values were 21.5 and 33.4% lower, respectively, and median T<sub>max</sub> was 1 h longer in the fed versus the fasted state.
- Urinary excretion represented a minor route of elimination (<1% on average as OP-1118).
- Fecal excretion was the major route of elimination.
- OPT-80 was well-tolerated at studied single PO doses under both fasted and fed conditions.

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results. Although C<sub>max</sub> was decreased and T<sub>max</sub> was delayed with food, this effect is not clinically significant/relevant for this locally-acting product; thus, OPT-80 may be administered with or without food. Plasma pharmacokinetic data provided in Study OPT-80-005 may be considered for labeling due to (i) more sensitive LLOQ of 0.2 ng/mL and (ii) use of the proposed therapeutic dose (200 mg) in the to-be-marketed formulation. Pharmacokinetic data of fecal samples, however, will not be used for labeling because of incomplete collection/extraction issues.

**STUDY NO.:** 101.1.C.003

**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 *Clostridium difficile*-associated diarrhea**

Date(s): 09 May 2006 – 21 Aug 2008

Analytical Site(s): [REDACTED] (b) (4)

**OBJECTIVE(S):**

- To demonstrate that the cure rate of *C. difficile* infection following treatment with OPT-80 is non-inferior to that following treatment with vancomycin
- To evaluate the safety and tolerability of OPT-80 in subjects with *C. difficile* infection

**METHODS**

**Study Design:** This was a multi-center, randomized, double-blind, parallel-group, Phase 3 study. Subjects were randomized to receive either OPT-80 200 mg BID or PO vancomycin 125 mg QID for 10 days.

**Inclusion Criteria:** Males or females,  $\geq 16$  years of age, with diarrhea (defined as change in bowel habits with  $>3$  unformed bowel movements in 24 hours before randomization) and presence of toxin A or B of *C. difficile* in stool within 48 hours of randomization were enrolled.

**Treatment:** OPT-80 and PO vancomycin were over-encapsulated and packaged in blister cards with matching placebo for blinding purposes. OPT-80 was otherwise supplied in the to-be-marketed formulation as 200 mg tablets manufactured by [REDACTED] (b) (4) (Lot# 181338, 183194, and 184834) and by [REDACTED] (b) (4) (Lot# C1236001) using an identical manufacturing process.

**Sample Collection:** For each subject, blood samples were obtained before dosing and after dosing (targeting 3-5 hours post-dose to approximate the likely  $T_{max}$ ) on Day 1 and again during End-of-Therapy/Early Termination visit up to Day 13.

**Analytical Methods:** Pharmacokinetic samples were analyzed for OPT-80 and OP-1118 (major active metabolite of OPT-80) by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) in plasma ([REDACTED] (b) (4) [REDACTED] (b) (4)) and feces ([REDACTED] (b) (4) [REDACTED] (b) (4)) (Table 1).

**Table 1.** Bioanalytical results of OPT-80 and OP-1118 in plasma and feces

Criterion	OPT-80	OP-1118	Comments
<b>PLASMA</b>			
Range	0.2-100 ng/mL	0.2-100 ng/mL	Satisfactory <sup>a</sup>
LLOQ	0.2 ng/mL	0.2 ng/mL	Satisfactory
Linearity	≥0.9907	≥0.9875	Satisfactory
Accuracy	± 5.0%	± 2.2%	Satisfactory
Precision	13.5% CV	13.1% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>• Study Dates: 09 May 2006 – 21 Aug 2008</li> <li>• Analysis Dates: 24 Oct 2006 – 07 Feb 2009</li> <li>• Stability: 838 days / 1133 days at -70 °C</li> </ul>		Satisfactory
<b>FECES</b>			
Range	2-400 µg/g (100x dilution tested)	10-2000 µg/g	Satisfactory
LLOQ	2 µg/g	10 µg/g	Satisfactory
Linearity	≥0.998	≥0.999	Satisfactory
Accuracy	± 1.3%	± 4.0%	Satisfactory
Precision	17.0% CV	10.7% CV	Satisfactory <sup>b</sup>
Stability	<ul style="list-style-type: none"> <li>• Study Dates: 09 May 2006 – 21 Aug 2008</li> <li>• Analysis Dates: 05 Feb 2007 – 21 Jan 2009</li> <li>• Stability: 93 days / 31 days at -70 °C</li> </ul>		<b>Unsatisfactory</b>

<sup>a</sup> Dilution factor of 10 tested with 800 ng/mL for OPT-80 and OP-1118

<sup>b</sup> At least 4 of every 6 QC samples were within 15% of the respective nominal value

**REVIEWER ASSESSMENT:** Plasma concentrations of OPT-80 and OP-1118 were limited to the T<sub>max</sub> window of 1-5 hour post-dose for pharmacokinetic analysis by the Reviewer. Fecal concentrations of OPT-80 and OP-1118 were limited to only those subjects whose fecal samples were appropriately stored. Refer to Section 2.2.5 of the Question-Based Review for complete summary and discussion of the pharmacokinetic results from Studies 101.1.C.003 and 101.1.C.004.

**STUDY NO.:** 101.1.C.004

**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 *Clostridium difficile*-associated diarrhea**

Date(s): 19 Apr 2007 – 11 Dec 2009

Analytical Site(s): [REDACTED] (b) (4)

**OBJECTIVE(S):**

- To demonstrate that the cure rate of *C. difficile* infection following treatment with OPT-80 is non-inferior to that following treatment with vancomycin
- To evaluate the safety and tolerability of OPT-80 in subjects with *C. difficile* infection

**METHODS**

**Study Design:** This was a multi-center, randomized, double-blind, parallel-group, Phase 3 study. Subjects were randomized to receive either OPT-80 200 mg BID or PO vancomycin 125 mg QID for 10 days.

**Inclusion Criteria:** Males or females,  $\geq 16$  years of age, with diarrhea (defined as change in bowel habits with  $>3$  unformed bowel movements in 24 hours before randomization) and presence of toxin A or B of *C. difficile* in stool within 48 hours of randomization were enrolled.

**Treatment:** OPT-80 and PO vancomycin were over-encapsulated and packaged in blister cards with matching placebo for blinding purposes. OPT-80 was otherwise supplied in the to-be-marketed formulation as 200 mg tablets manufactured by [REDACTED] (b) (4) (Lot# 184942) and by [REDACTED] (b) (4) (Lot# C1236001, C1589001, and C1707001) using an identical manufacturing process.

**Sample Collection:** For each subject, blood samples were obtained before dosing and after dosing (targeting 3-5 hours post-dose to approximate the likely  $T_{max}$ ) on Day 1 and again during End-of-Therapy/Early Termination visit up to Day 13.

**Analytical Methods:** Pharmacokinetic samples were analyzed for OPT-80 and OP-1118 (major active metabolite of OPT-80) by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) in plasma [REDACTED] (b) (4) and feces [REDACTED] (b) (4) (**Table 1**).

**Table 1.** Bioanalytical results of OPT-80 and OP-1118 in plasma and feces

Criterion	OPT-80	OP-1118	Comments
<b>PLASMA</b>			
Range	0.2-100 ng/mL	0.2-100 ng/mL	Satisfactory <sup>a</sup>
LLOQ	0.2 ng/mL	0.2 ng/mL	Satisfactory
Linearity	≥0.9896	≥0.9928	Satisfactory
Accuracy	± 4.0%	± 3.8%	Satisfactory
Precision	14.3% CV	9.2% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>• Study Dates: 19 Apr 2007 – 11 Dec 2009</li> <li>• Analysis Dates: 10 Aug 2007 – 22 Feb 2010</li> <li>• Stability: 838 days / 1133 days at -70 °C</li> </ul>		Satisfactory
<b>FECES</b>			
Range	2-400 µg/g (100x dilution tested)	10-2000 µg/g	Satisfactory
LLOQ	2 µg/g	10 µg/g	Satisfactory
Linearity	≥0.999	≥0.999	Satisfactory
Accuracy	± 4.0%	± 0.8%	Satisfactory
Precision	14.9% CV	9.2% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>• Study Dates: 19 Apr 2007 – 11 Dec 2009</li> <li>• Analysis Dates: 25 Apr 2008 – 05 Jan 2010</li> <li>• Stability: 93 days / 31 days at -70 °C</li> </ul>		<b>Unsatisfactory</b>

<sup>a</sup> Dilution factor of 10 tested with 800 ng/mL for OPT-80 and OP-1118

**REVIEWER ASSESSMENT:** Plasma concentrations of OPT-80 and OP-1118 were limited to the T<sub>max</sub> window of 1-5 hour post-dose for pharmacokinetic analysis by the Reviewer. Fecal concentrations of OPT-80 and OP-1118 were limited to only those subjects whose fecal samples were appropriately stored. Refer to Section 2.2.5 of the Question-Based Review for complete summary and discussion of the pharmacokinetic results from Studies 101.1.C.003 and 101.1.C.004.

### 4.1.3 Extrinsic Factors

APPEARS THIS WAY ON  
ORIGINAL

**STUDY NO.:** OPT-80-007

**A Phase 1, open-label, two-period, randomized crossover study to evaluate the effect of a single dose of cyclosporine on the single-dose pharmacokinetic profile of fidaxomicin (OPT-80) in healthy male subjects**

Date(s): 01 Jun 2010 – 16 Jun 2010

Investigator(s): W Lewis, M.D.

Clinical Site(s): Covance Clinical Research Unit Inc.; Dallas, TX, US

Analytical Site(s): (b) (4)

**OBJECTIVE:**

- To examine the effect of a single dose of cyclosporine on the single dose pharmacokinetics of fidaxomicin in healthy male subjects
- To compare the safety and tolerability of a single dose of fidaxomicin in the presence of a single dose of cyclosporine in healthy male subjects

**METHODS**

**Study Design:** This was an open-label, two-period, randomized, crossover (with 7-day washout), drug-drug interaction (DDI) study of fidaxomicin (P-gp substrate) and cyclosporine (inhibitor of multiple transporters, including P-gp) in healthy males (n=14).

- Treatment A: Fidaxomicin 200 mg ×1
- Treatment B: Cyclosporine 200 mg ×1, followed 1 h later by Fidaxomicin 200 mg ×1

**Inclusion Criteria:** Males, 18-40 years of age (inclusive), 18.0-30.0 kg/m<sup>2</sup> in body mass index (BMI) (inclusive), and in good health as determined by medical history, physical exam, and laboratory evaluations were enrolled.

**Treatment:** Subjects were administered doses of fidaxomicin and cyclosporine after a 10-h fast followed by a 4-h fast from food post-dose. Water was restricted for 1 h pre-dose and 2 h post-dose; *ad libitum* for all other times. Fidaxomicin was supplied in the to-be-marketed formulation as 200 mg tablets manufactured by (b) (4) (Lot# R0242001). Cyclosporine (Neoral<sup>®</sup>) was provided as commercially-available 100 mg capsules.

No drugs or substances known to be strong inducers or inhibitors of CYP450 enzymes or P-gp were permitted from 30 days prior to Check-In. Prescription medications/products were prohibited from 14 days prior to Check-In, and non-prescription/over-the-counter (OTC) preparations (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) were prohibited from 30 days prior to Check-In. Grapefruit or grapefruit/apple/orange juice were prohibited from 7 days prior to Check-In, while alcohol- or caffeine-containing foods or beverages were prohibited from 48 hours prior to Check-In.

**Sample Collection:** Blood samples were collected and analyzed for pharmacokinetic purposes (Table 1).

**Table 1.** Pharmacokinetic sampling scheme for single PO dose of fidaxomicin with/without cyclosporine

<b>Fidaxomicin &amp; OP-1118</b>	Day1: 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 36 h post-dose Day9: 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 36 h post-dose
<b>Cyclosporine</b>	Day1: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h post-dose Day9: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h post-dose

**Analytical Methods:** Pharmacokinetic samples were analyzed for fidaxomicin and OP-1118 (major active metabolite of OPT-80) by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) in plasma <sup>(b) (4)</sup> (Table 2). Concentrations below the lower limit of quantification (LLOQ) were set as 0 or missing (when in between two quantifiable concentrations or when following the last quantifiable concentration) for pharmacokinetic analysis.

**Table 2.** Bioanalytical results of fidaxomicin and OP-1118 in plasma

Criterion	Fidaxomicin	OP-1118	Comments
<b>PLASMA</b>			
Range	0.2-100 ng/mL	0.2-100 ng/mL	Satisfactory <sup>a</sup>
LLOQ	0.2 ng/mL	0.2 ng/mL	Satisfactory
Linearity	≥0.9900	≥0.9933	Satisfactory
Accuracy	± 5.3%	± 5.4%	Satisfactory
Precision	8.2% CV	10.7% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>• Study Dates: 01 Jun 2010 – 16 Jun 2010</li> <li>• Analysis Dates: 14 Jun 2010 – 07 Jul 2010</li> <li>• Stability: 838 days / 1133 days at -70 °C</li> </ul>		Satisfactory

<sup>a</sup> Dilution factor of 10 tested with 800 ng/mL for fidaxomicin and OP-1118

Concentrations of cyclosporine were determined using validated high-performance liquid chromatography (HPLC) with tandem mass spectrometric detection.

**Pharmacokinetic Assessment:** Pharmacokinetic parameters for fidaxomicin, OP-1118, and cyclosporine were determined using single-dose data with non-compartmental methods. Parameters included the following:

- $C_{max}$ , peak observed plasma concentration
- $T_{max}$ , time to  $C_{max}$
- $t_{1/2}$ , apparent elimination half-life
- $AUC_{0-t}$ , area under the concentration-time curve from time 0 to last measured concentration
- $AUC_{0-\infty}$ , area under the concentration-time curve from time 0 to infinity

**Statistical Methods:** DDI was examined between staggered administration of cyclosporine and fidaxomicin (test) and fidaxomicin administered alone (reference). An analysis of variance (ANOVA) with sequence, period, and treatment as fixed effects and subject as a random effect was performed using natural log-transformed ( $\ln$ )  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ . The 90% confidence intervals (CI) of the test means relative to the reference means were obtained by taking the antilog of the corresponding 90% CIs for the differences between means on the log scale. DDI was assessed by examining the 90% CI for the ratios of the test means relative to the reference means. Lack of DDI would be concluded if the antilog of 90% CI from  $\ln$ -transformed  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  were entirely contained within the 0.80-1.25 interval.

## RESULTS

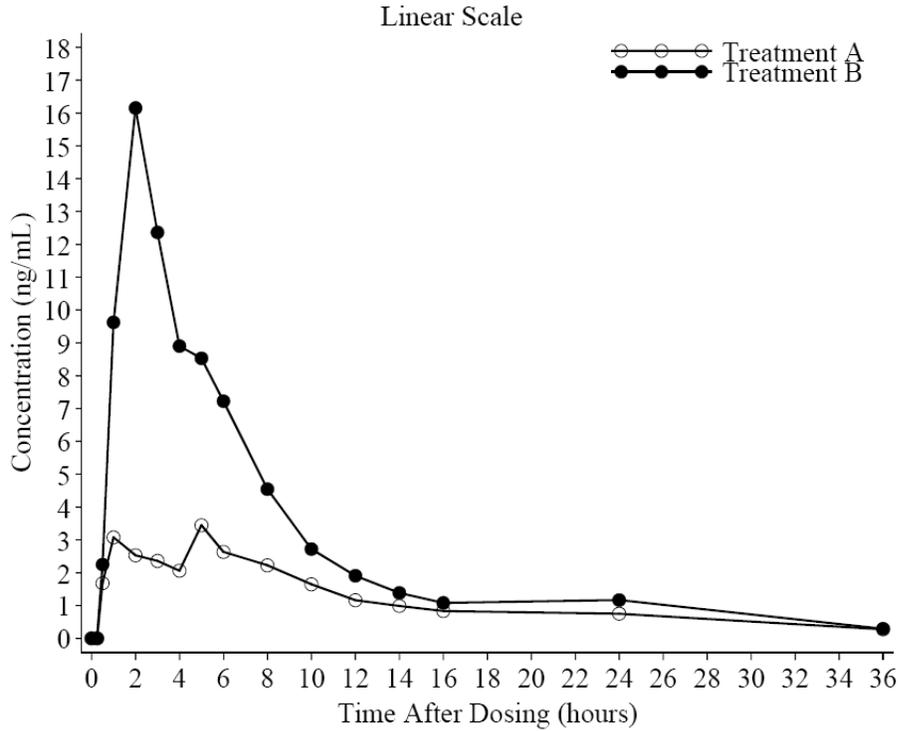
**Study Population:** In total, 14 subjects were enrolled and all completed the study (**Table 3**).

**Table 3.** Demographic characteristics of enrolled subjects

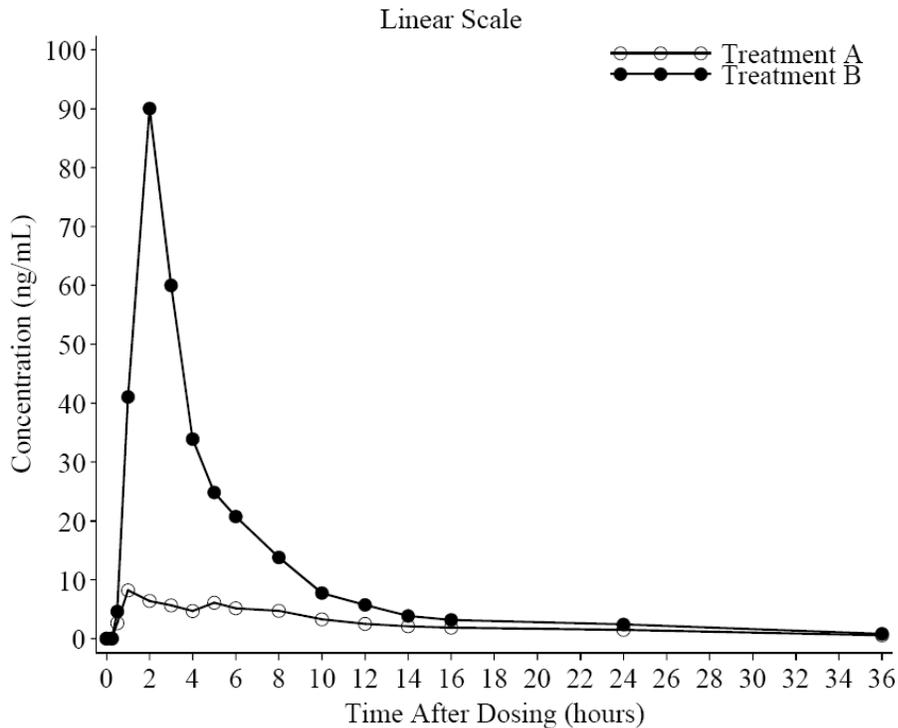
<b>Demographic Variable</b>	
Mean age in years	30 (range 21 to 40 years)
Mean weight in kg	75.3 (range 59.0 to 91.9 kg)
Mean height in cm	173.6 (range 156.8 to 184.5 cm)
BMI in kg/m <sup>2</sup>	25.0 (range 20.9 to 28.7 kg/m <sup>2</sup> )
Gender (n[%])	
Male	14 (100%)
Ethnicity (n[%])	
Hispanic or Latino	7 (50%)
Not Hispanic or Latino	7 (50%)
Race (n[%])	
White	9 (64.3%)
Black or African American	5 (35.7%)

**Pharmacokinetics:** Geometric mean concentration-time profiles of fidaxomicin and OP-1118 following a single 200 mg dose alone or in combination with cyclosporine are respectively shown in **Figure 1** and **Figure 2**. Individual and geometric mean values are further portrayed for exposure parameters of fidaxomicin and OP-1118 as  $C_{max}$  (**Figure 3** and **Figure 4**),  $AUC_{0-t}$  (**Figure 5** and **Figure 6**), and  $AUC_{0-\infty}$  (**Figure 7** and **Figure 8**).

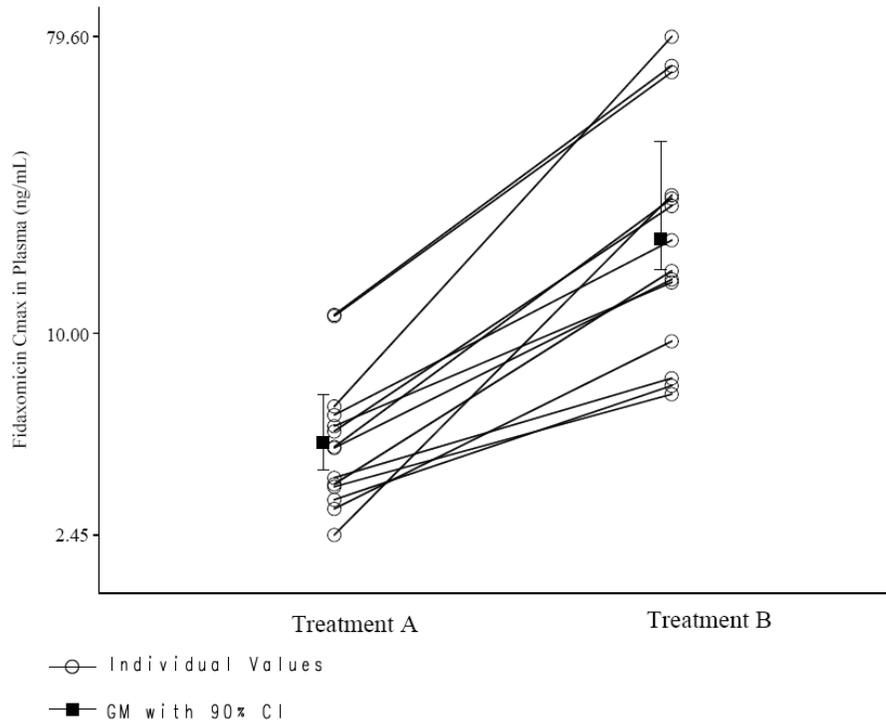
**Figure 1.** Geometric mean plasma concentrations of **fidaxomicin** following single 200 mg PO dose of fidaxomicin alone (Treatment A) or with cyclosporine 200 mg (Treatment B) in healthy males (n=14)



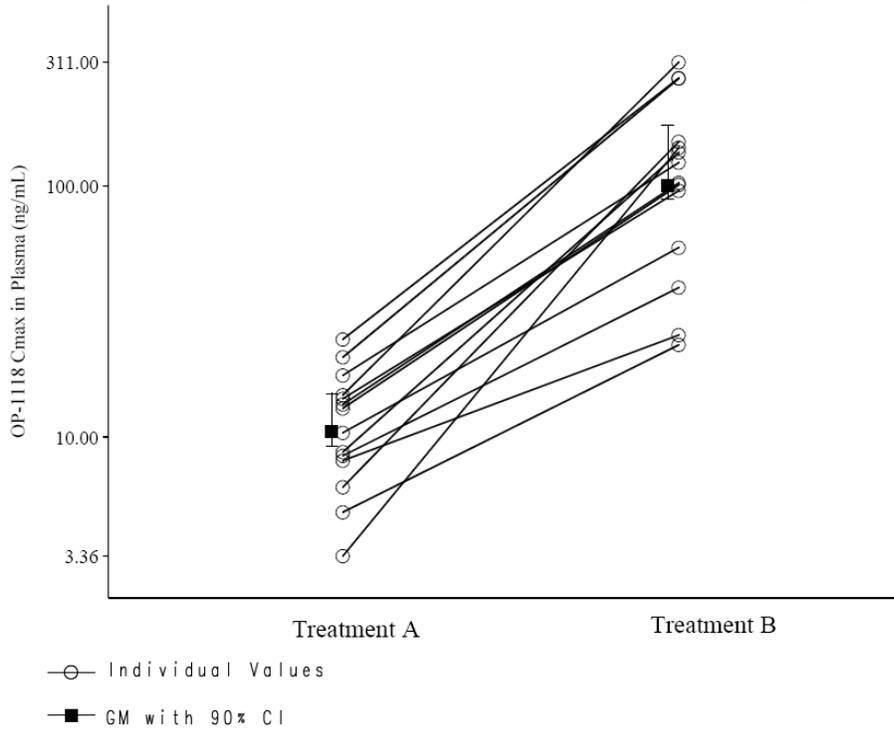
**Figure 2.** Geometric mean plasma concentrations of **OP-1118** following single 200 mg PO dose of fidaxomicin alone (Treatment A) or with cyclosporine 200 mg (Treatment B) in healthy males (n=14)



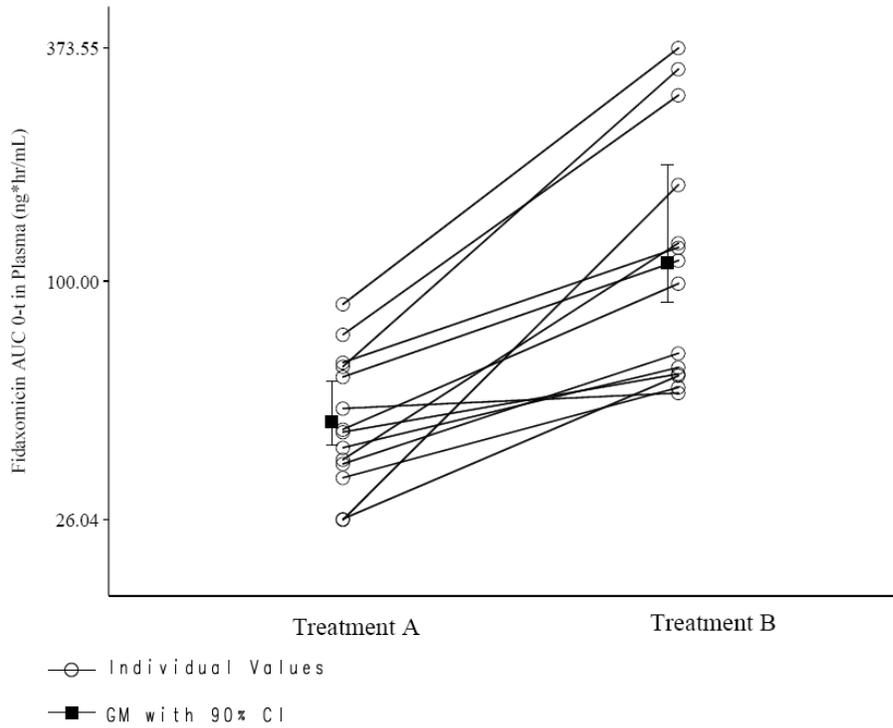
**Figure 3.** Individual and geometric mean with 90% CI for **fidaxomicin C<sub>max</sub>** following single 200 mg PO dose of fidaxomicin alone (Treatment A) or with cyclosporine 200 mg (Treatment B) in healthy males



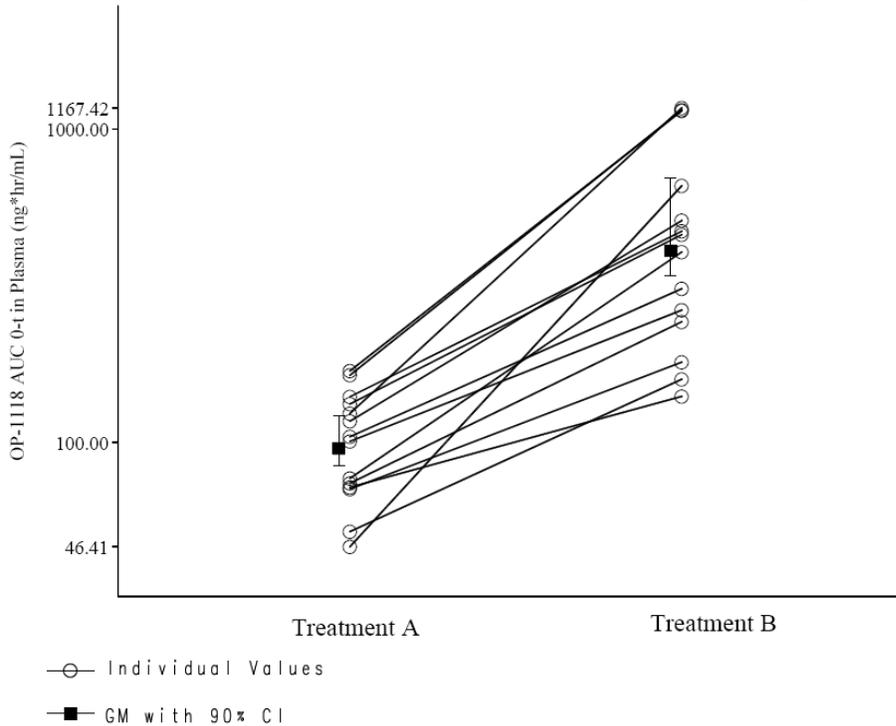
**Figure 4.** Individual and geometric mean with 90% CI for **OP-1118 C<sub>max</sub>** following single 200 mg PO dose of fidaxomicin alone (Treatment A) or with cyclosporine 200 mg (Treatment B) in healthy males



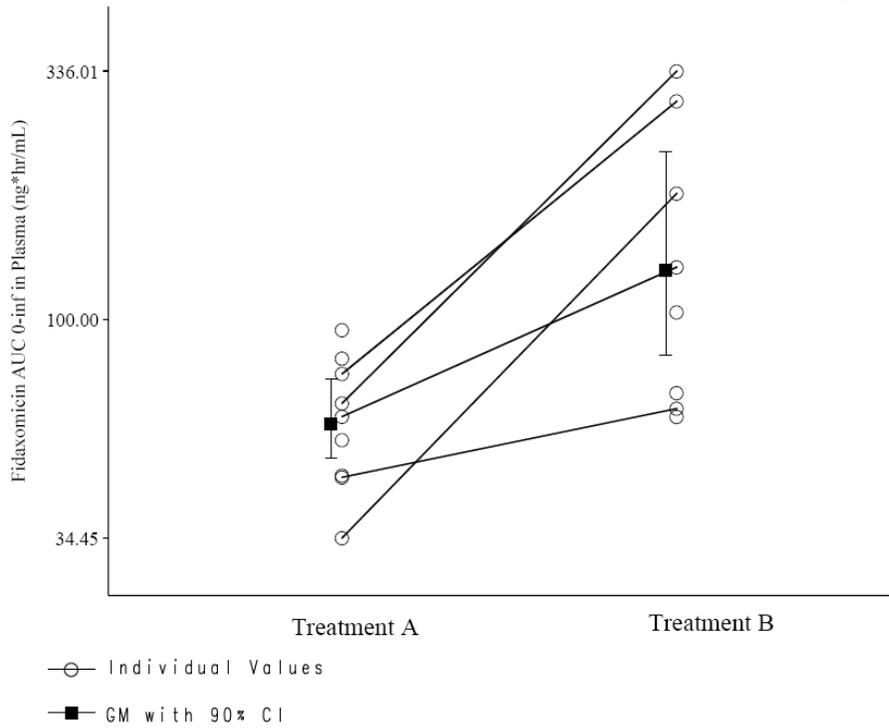
**Figure 5.** Individual and geometric mean with 90% CI for **fidaxomicin AUC<sub>0-t</sub>** following single 200 mg PO dose of fidaxomicin alone (Treatment A) or with cyclosporine 200 mg (Treatment B) in healthy males



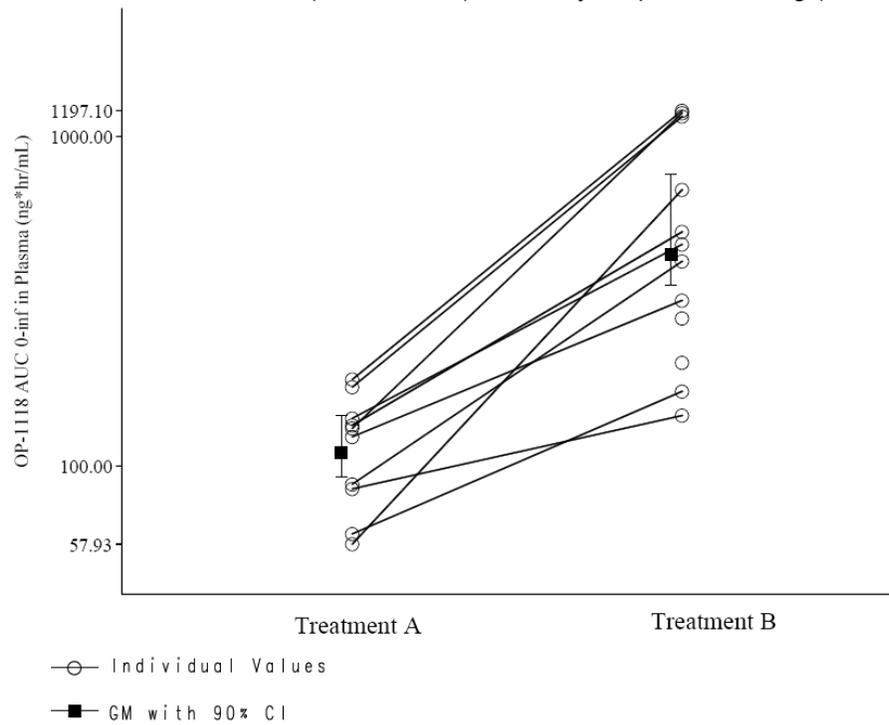
**Figure 6.** Individual and geometric mean with 90% CI for **OP-1118 AUC<sub>0-t</sub>** following single 200 mg PO dose of fidaxomicin alone (Treatment A) or with cyclosporine 200 mg (Treatment B) in healthy males



**Figure 7.** Individual and geometric mean with 90% CI for **fidaxomicin AUC<sub>0-∞</sub>** following single 200 mg PO dose of fidaxomicin alone (Treatment A) or with cyclosporine 200 mg (Treatment B) in healthy males



**Figure 8.** Individual and geometric mean with 90% CI for **OP-1118 AUC<sub>0-∞</sub>** following single 200 mg PO dose of fidaxomicin alone (Treatment A) or with cyclosporine 200 mg (Treatment B) in healthy males



With co-administration of cyclosporine, systemic exposures ( $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ ) of fidaxomicin and OP-1118 were significantly increased, while  $T_{max}$  and  $t_{1/2}$  were largely unaffected (**Table 4**).

**Table 4.** Pharmacokinetic parameters of fidaxomicin and OP-1118 following single 200 mg PO dose of fidaxomicin alone (Treatment A) or with cyclosporine 200 mg (Treatment B) in healthy males

Parameter	Treatment A		Treatment B	
	Fidaxomicin 200 mg		Cyclosporine 200 mg + Fidaxomicin 200 mg <sup>a</sup>	
	N	Mean ± SD	N	Mean ± SD
<b>Fidaxomicin</b>				
$C_{max}$ (ng/mL)	14	5.20 ± 2.81	14	26.9 ± 24
$T_{max}$ <sup>b</sup> (h)	14	2.00 (1.00-5.00) <sup>b</sup>	14	2.32 (1.00-6.00) <sup>b</sup>
$AUC_{0-t}$ (ng*h/mL)	14	48.3 ± 18.4	14	141 ± 110
$AUC_{0-\infty}$ (ng*h/mL)	9	62.9 ± 19.5	8	155 ± 106
$t_{1/2}$ (h)	9	11.7 ± 4.80	8	10.2 ± 2.61
<b>OP-1118</b>				
$C_{max}$ (ng/mL)	14	12.0 ± 6.06	14	132 ± 92.1
$T_{max}$ <sup>b</sup> (h)	14	1.02 (1.00-5.00) <sup>b</sup>	14	2.00 (1.00-3.00) <sup>b</sup>
$AUC_{0-t}$ (ng*h/mL)	14	103 ± 39.4	14	519 ± 374
$AUC_{0-\infty}$ (ng*h/mL)	10	118 ± 43.3	12	561 ± 401
$t_{1/2}$ (h)	10	11.2 ± 3.01	12	10.4 ± 3.93

<sup>a</sup> Staggered administration of cyclosporine dose followed 1 h later by fidaxomicin dose

<sup>b</sup>  $T_{max}$  reported as median (minimum-maximum)

*Reviewer Comment: Unlike Study OPT-80-005, majority of subjects had sufficient concentration-time points (due to more frequent sampling) to allow suitable characterization of the terminal phase, and accordingly, determination of  $AUC_{0-\infty}$  and  $t_{1/2}$ . Pharmacokinetic results following single 200 mg PO dose of fidaxomicin in the fasted state (Treatment A) may be used for labeling purposes in lieu of Study OPT-80-005.*

$C_{max}$  and AUC of fidaxomicin (P-gp substrate) were increased approximately 2-4 fold when co-administered with cyclosporine (inhibitor of multiple transporters, including P-gp) versus when administered alone; while  $C_{max}$  and AUC of OP-1118 (P-gp substrate) were increased approximately 4-9 fold (**Table 5**). For all exposure parameters of fidaxomicin and OP-1118, 90% CI around point estimates were outside the no-effect boundary of 0.80-1.25.

**Table 5.** Statistical analysis of DDI for fidaxomicin and OP-1118 with single 200 mg PO dose of fidaxomicin alone versus with cyclosporine 200 mg in healthy males

Parameter	Treatment B		Treatment A		Point Estimate of Test/Reference (90% CI)
	Cyclosporine 200 mg + Fidaxomicin 200 mg <sup>a</sup>		Fidaxomicin 200 mg		
	N	Least Squares Mean	N	Least Squares Mean	
<b>Fidaxomicin</b>					
$C_{max}$ (ng/mL)	14	19.4	14	4.67	4.15 (3.23-5.32)
$AUC_{0-t}$ (ng*h/mL)	14	111	14	45.3	2.45 (1.96-3.06)
$AUC_{0-\infty}$ (ng*h/mL)	8	114	9	59.5	1.92 (1.39-2.64)
<b>OP-1118</b>					
$C_{max}$ (ng/mL)	14	100	14	10.6	9.51 (6.93-13.05)
$AUC_{0-t}$ (ng*h/mL)	14	408	14	95.6	4.27 (3.41-5.34)
$AUC_{0-\infty}$ (ng*h/mL)	12	438	10	106	4.11 (3.06-5.53)

<sup>a</sup> Staggered administration of cyclosporine dose followed 1 h later by fidaxomicin dose

Pharmacokinetic parameters for cyclosporine were consistent with those reported in the literature using LC-MS methods with plasma.

**Safety:** In total, 6 adverse events were reported by 4/14 (28.6%) subjects; 1 occurred with fidaxomicin alone (Treatment A) and 5 with the combination of fidaxomicin and cyclosporine (Treatment B). All events were mild in severity and included diarrhea (n=2), abdominal discomfort (n=2), chest discomfort (n=1), and pain in extremity (n=1). Three of the reported events, including chest discomfort, occurred within 1 h of fidaxomicin dosing which coincided not with fidaxomicin  $T_{max}$  but cyclosporine  $T_{max}$  (administered 1 h prior to fidaxomicin, such that median  $T_{max}$  of 2 h occurred approximately 1 h following the fidaxomicin dose).

No clinically significant abnormalities in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, or electrocardiogram were observed.

**SPONSOR'S CONCLUSIONS:** Following single PO dose of fidaxomicin 200 mg alone or in combination with cyclosporine 200 mg in healthy males (n=14):

- A statistically significant increase in fidaxomicin and OP-1118 exposure was observed in the presence of cyclosporine.
- Point estimates of fidaxomicin  $C_{max}$  and  $AUC_{0-\infty}$  values were 4.15- and 1.92-fold greater, respectively, when co-administered with cyclosporine compared to fidaxomicin alone.
- Point estimates of OP-1118  $C_{max}$  and  $AUC_{0-\infty}$  values were 9.51- and 4.11-fold greater, respectively, when co-administered with cyclosporine compared to fidaxomicin alone.
- Despite an increase in  $C_{max}$  and AUC, the  $t_{1/2}$  of fidaxomicin and OP-1118 was unaffected by cyclosporine.
- Fidaxomicin was safe and well-tolerated when administered alone or with a single dose of cyclosporine.

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results. There is a statistically significant DDI between fidaxomicin and cyclosporine via gut-mediated P-gp inhibition, and should be labeled accordingly.

For labeling recommendations, dose adjustment based on matching plasma exposures would be inappropriate for fidaxomicin, given that plasma concentrations are poor markers for concentrations at the site of action/infection (i.e., the gut), and reduction of fidaxomicin dose may compromise efficacy. Recommendations for either avoidance or caution of concomitant use with P-gp inhibitors must consider efficacy and safety results of fidaxomicin-treated Phase 3 patients who also received concomitant P-gp inhibitors.

STUDY NO.: OPT-80-008

**A Phase 1, open-label, monosequence crossover study to evaluate the effect of steady-state fidaxomicin (OPT-80) tablets on the single-dose pharmacokinetic profile of digoxin in healthy subjects**

Date(s): 26 May 2010 – 01 Jul 2010

Investigator(s): W Lewis, M.D.

Clinical Site(s): Covance Clinical Research Unit Inc.; Dallas, TX, US

Analytical Site(s): (b) (4)

**OBJECTIVE:**

- To examine the effect on the single-dose pharmacokinetics of digoxin in the presence of steady-state fidaxomicin in healthy subjects
- To compare the safety and tolerability of steady-state fidaxomicin alone and in the presence of a single dose of digoxin in healthy subjects

**METHODS**

**Study Design:** This was an open-label, monosequence, crossover (with 6-day washout), drug-drug interaction (DDI) study of fidaxomicin (P-gp inhibitor) and digoxin (sensitive P-gp substrate) in healthy subjects (n=14) (**Table 1**).

**Table 1.** Dosing scheme of fidaxomicin and digoxin in monosequence crossover design

Period 1		Period 2	Period 3		Discharge
0.5 mg digoxin (single dose)	Washout	200 mg fidaxomicin tablets q12h	0.5 mg digoxin (single dose) and 200 mg fidaxomicin tablets q12h <sup>a</sup>	200 mg fidaxomicin tablets q12h	Subjects discharged from the clinic
Day 1	Days 2 to 7	Days 8 to 12	Day 13	Days 14 to 18	Day 19

<sup>a</sup> A single 0.5-mg oral dose of digoxin was administered 1 hour after the first dose of fidaxomicin tablets of the day.

**Inclusion Criteria:** Males and females (in approximately equal numbers), 18-40 years of age (inclusive), 18.0-30.0 kg/m<sup>2</sup> in body mass index (BMI) (inclusive), and in good health as determined by medical history, physical exam, and laboratory evaluations were enrolled.

**Treatment:** For digoxin and the 1<sup>st</sup> fidaxomicin dose of the day, subjects were administered doses after a 10-h fast followed by a 4-h fast from food post-dose; water was restricted for 1 h pre-dose and 2 h post-dose. For the 2<sup>nd</sup> fidaxomicin dose of the day, food and water were prohibited for 1 h pre-dose and 2 h post-dose. Fidaxomicin was supplied in the to-be-marketed formulation as 200 mg tablets manufactured by (b) (4) (Lot# R0242001). Digoxin (Lanoxin<sup>®</sup>) was provided as commercially-available 0.25 mg tablets.

No drugs or substances known to be strong inducers or inhibitors of CYP450 enzymes or P-gp were permitted from 30 days prior to Check-In. Prescription medications/products were

prohibited from 14 days prior to Check-In, and non-prescription/over-the-counter (OTC) preparations (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) were prohibited from 30 days prior to Check-In. Grapefruit or grapefruit/apple/orange juice were prohibited from 7 days prior to Check-In, while alcohol- or caffeine-containing foods or beverages were prohibited from 48 hours prior to Check-In.

**Sample Collection:** Blood samples were collected and analyzed for pharmacokinetic purposes (Table 2). For therapeutic drug monitoring of digoxin, samples were also obtained at 4, 8, and 24 h post-dose on Day 1 and Day 13.

**Table 2.** Pharmacokinetic sampling scheme for multiple PO doses of fidaxomicin with/without digoxin

<b>Digoxin</b>	Day1: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 h post-dose Day13: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 h post-dose
<b>Fidaxomicin &amp; OP-1118</b>	Day8: 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24 h post-dose (1 <sup>st</sup> dose of day) Day13: 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 36 h post-dose (1 <sup>st</sup> dose of day)

**Analytical Methods:** Pharmacokinetic samples were analyzed for digoxin by validated high-performance liquid chromatography (HPLC) with tandem mass spectrometric (MS/MS) detection in plasma (Table 3). Concentrations below the lower limit of quantification (LLOQ) were set as 0 or missing (when in between two quantifiable concentrations or when following the last quantifiable concentration) for pharmacokinetic analysis.

**Table 3.** Bioanalytical results of digoxin in plasma

<b>Criterion</b>	<b>Digoxin</b>	<b>Comments</b>
	<b>PLASMA</b>	
Range	0.05-10 ng/mL	Satisfactory
LLOQ	0.05 ng/mL	Satisfactory
Linearity	≥0.9935	Satisfactory
Accuracy	± 1.3%	Satisfactory
Precision	5.7% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>• Study Dates: 26 May 2010 – 01 Jul 2010</li> <li>• Analysis Dates: 21 Jul 2010 – 26 Jul 2010</li> <li>• Stability: 252 days at -60 to -80 °C</li> </ul>	Satisfactory

Concentrations of fidaxomicin and OP-1118 were not analyzed as of the date of this study report.

**Pharmacokinetic Assessment:** Pharmacokinetic parameters for digoxin were determined using single-dose data with non-compartmental methods. Parameters included the following:

- $C_{max}$ , peak observed plasma concentration
- $T_{max}$ , time to  $C_{max}$
- $t_{1/2}$ , apparent elimination half-life
- $AUC_{0-3}$ , area under the concentration-time curve from 0 to 3 hours post-dose
- $AUC_{0-24}$ , area under the concentration-time curve from 0 to 24 hours post-dose
- $AUC_{0-t}$ , area under the concentration-time curve from time 0 to last measured concentration
- $AUC_{0-\infty}$ , area under the concentration-time curve from time 0 to infinity

**Statistical Methods:** DDI was examined between staggered administration of digoxin and fidaxomicin (test) and digoxin administered alone (reference). An analysis of variance (ANOVA) with treatment as a fixed effect and subject as a random effect was performed using

natural log-transformed ( $\ln$ )  $C_{\max}$ ,  $AUC_{0-3}$ ,  $AUC_{0-24}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ . The 90% confidence intervals (CI) of the test means relative to the reference means were obtained by taking the antilog of the corresponding 90% CIs for the differences between means on the log scale. DDI was assessed by examining the 90% CI for the ratios of the test means relative to the reference means. Lack of DDI would be concluded if the antilog of 90% CI from  $\ln$ -transformed  $C_{\max}$ ,  $AUC_{0-3}$ ,  $AUC_{0-24}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  were entirely contained within the 0.80-1.25 interval.

## RESULTS

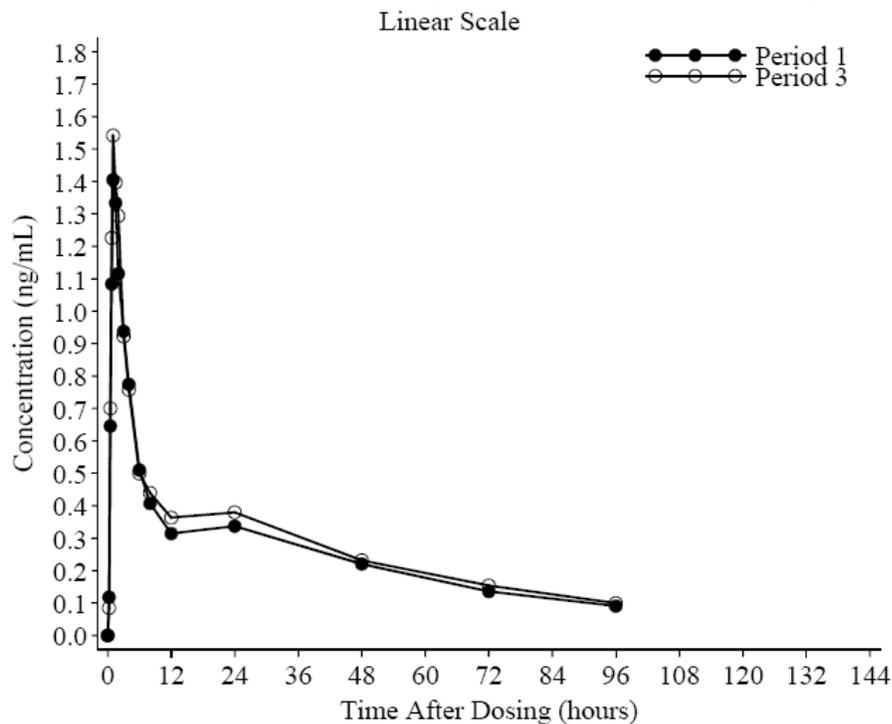
**Study Population:** In total, 14 subjects were enrolled and all completed the study (**Table 4**).

**Table 4.** Demographic characteristics of enrolled subjects

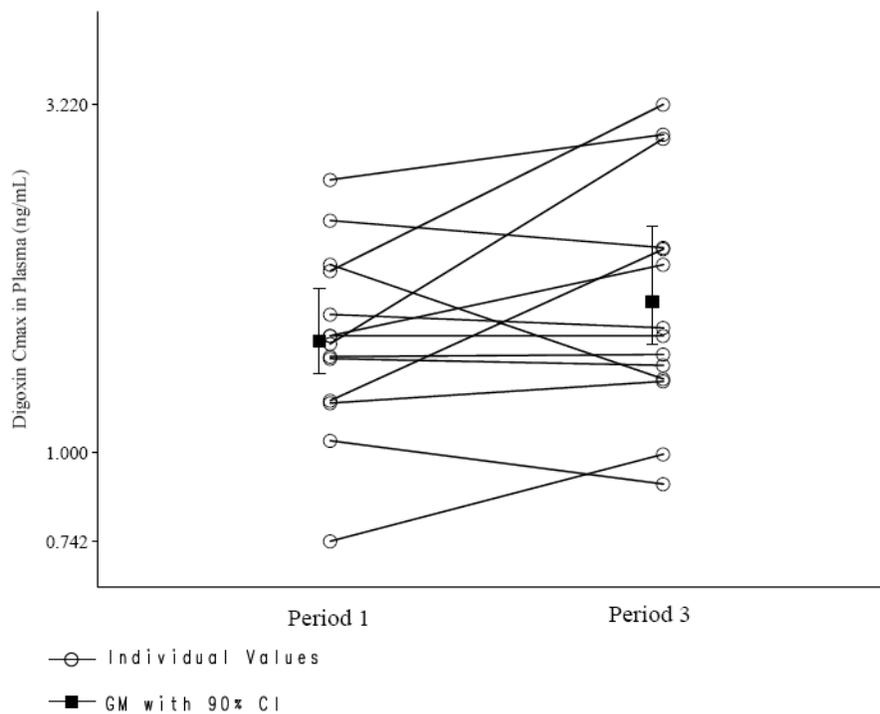
Demographic Variable	
Mean age in years	31 (range 21 to 40 years)
Mean weight in kg	75.0 (range 54.9 to 92.8 kg)
Mean height in cm	170.7 (range 152.6 to 194.4 cm)
BMI in kg/m <sup>2</sup>	25.6 (range 22.3 to 29.5 kg/m <sup>2</sup> )
Gender (n[%])	
Male	7 (50%)
Female	7 (50%)
Ethnicity (n[%])	
Hispanic or Latino	6 (42.9%)
Not Hispanic or Latino	8 (57.1%)
Race (n[%])	
White	7 (50%)
Black or African American	7 (50%)

**Pharmacokinetics:** Geometric mean concentration-time profile of digoxin following a single 0.5 mg dose alone or in combination with fidaxomicin is shown in **Figure 1**. Individual and geometric mean values are further portrayed for digoxin exposure parameters as  $C_{\max}$  (**Figure 2**),  $AUC_{0-t}$  (**Figure 3**), and  $AUC_{0-\infty}$  (**Figure 4**).

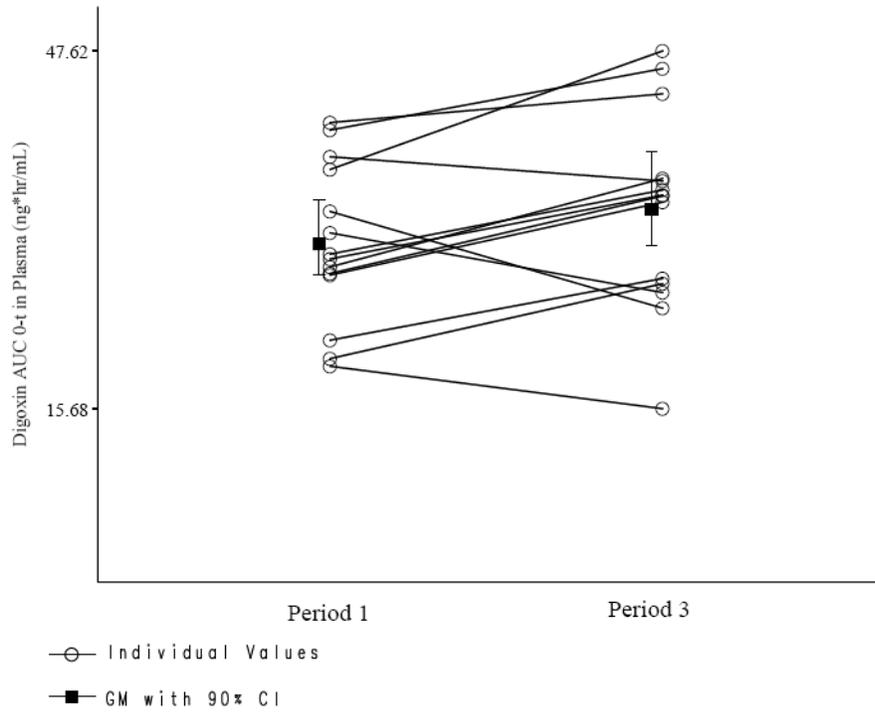
**Figure 1.** Geometric mean plasma concentrations of digoxin following single 0.5 mg PO dose alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy subjects (n=14)



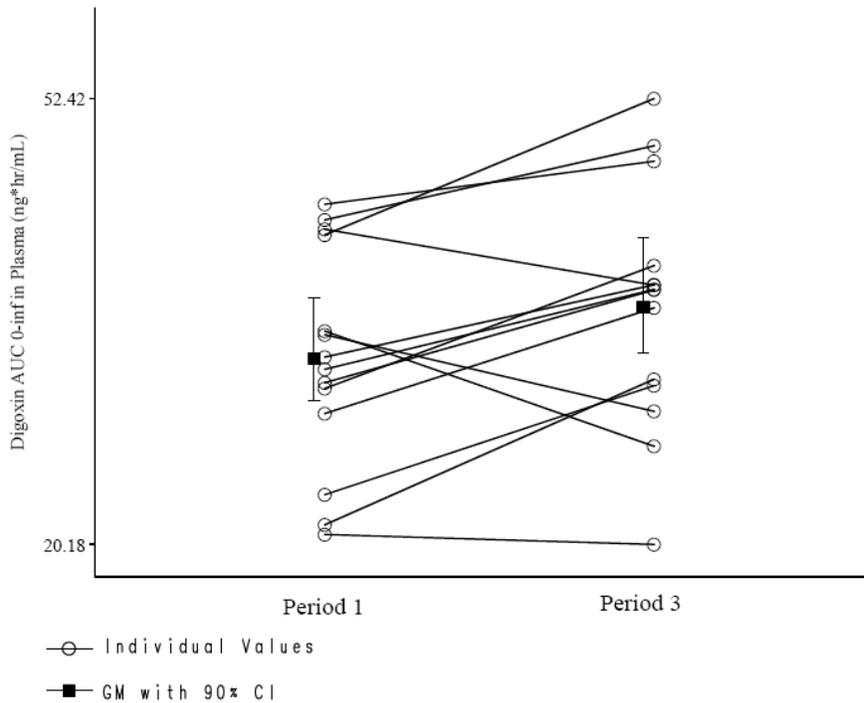
**Figure 2.** Individual and geometric mean with 90% CI for digoxin  $C_{max}$  following single 0.5 mg PO dose alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy subjects



**Figure 3.** Individual and geometric mean with 90% CI for **digoxin AUC<sub>0-t</sub>** following single 0.5 mg PO dose alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy subjects



**Figure 4.** Individual and geometric mean with 90% CI for **digoxin AUC<sub>0-∞</sub>** following single 0.5 mg PO dose alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy subjects



Overall, pharmacokinetic parameters of digoxin were comparable when administered alone versus in combination with fidaxomicin, including  $T_{max}$  and  $t_{1/2}$  (**Table 5**).

**Table 5.** Pharmacokinetic parameters of digoxin following single 0.5 mg PO dose alone or with fidaxomicin 200 mg Q12h in healthy subjects (n=14)

Parameter	Day 1	Day 13
	Digoxin 0.5 mg	Digoxin 0.5 mg + Fidaxomicin 200 mg Q12h <sup>a</sup>
$C_{max}$ (ng/mL)	1.52 ± 0.46	1.79 ± 0.74
$T_{max}^b$ (h)	1.00 (0.75-1.50)	1.00 (0.75-2.00)
$AUC_{0-3}$ (ng*h/mL)	3.09 ± 0.71	3.45 ± 1.18
$AUC_{0-24}$ (ng*h/mL)	11.7 ± 2.75	12.9 ± 3.67
$AUC_{0-t}$ (ng*h/mL)	26.9 ± 6.63	30.4 ± 9.22
$AUC_{0-\infty}$ (ng*h/mL)	30.8 ± 7.14	34.6 ± 8.99
$t_{1/2}$ (h)	38.8 ± 10.9	41.6 ± 9.16

<sup>a</sup> Staggered administration of digoxin dose 1 h after fidaxomicin dose

<sup>b</sup>  $T_{max}$  reported as median (minimum-maximum)

$C_{max}$  and various AUC parameters of digoxin (sensitive P-gp substrate) showed <15% increase with co-administration of fidaxomicin (P-gp inhibitor) versus when administered alone (**Table 6**). For all exposure parameters of digoxin, 90% CI around point estimates were within the no-effect boundary of 0.80-1.25, with the exception of  $C_{max}$ .

**Table 6.** Statistical analysis of DDI for digoxin with single 0.5 mg PO dose alone versus with fidaxomicin 200 mg Q12h in healthy subjects

Parameter	Day 13		Day 1		Point Estimate of Test/Reference (90% CI)
	Digoxin 0.5 mg + Fidaxomicin 200 mg Q12h <sup>a</sup>		Digoxin 0.5 mg		
	N	Least Squares Mean	N	Least Squares Mean	
<b>Digoxin</b>					
$C_{max}$ (ng/mL)	14	1.66	14	1.46	1.14 (0.99-1.31)
$AUC_{0-3}$ (ng*h/mL)	14	3.26	14	3.01	1.08 (0.98-1.20)
$AUC_{0-24}$ (ng*h/mL)	14	12.4	14	11.4	1.09 (1.02-1.16)
$AUC_{0-t}$ (ng*h/mL)	14	29.1	14	26.1	1.11 (1.01-1.23)
$AUC_{0-\infty}$ (ng*h/mL)	14	33.6	14	30.0	1.12 (1.03-1.22)

<sup>a</sup> Staggered administration of digoxin dose 1 h after fidaxomicin dose

*Reviewer Comment: Although deemed statistically significant, the increase in digoxin  $C_{max}$  with co-administration of fidaxomicin is not clinically significant considering (i) results for digoxin AUC indicate no change and (ii) the geometric mean  $C_{max}$  value remained in the desired therapeutic range for digoxin (0.8-2.0 ng/mL). The Sponsor also employed  $AUC_{0-3}$  as an alternative measure to  $C_{max}$  (exposure during the digoxin absorption phase), for which no statistically significant change was observed.*

**Safety:** In total, 28 adverse events were reported by 10/14 (71.4%) subjects; 15 occurred with digoxin alone (Period 1), 12 with fidaxomicin (Period 2), and 1 with the combination of digoxin and fidaxomicin (Period 3). Majority of events (26/28) were mild in severity, with 2 moderate events (dizziness and abdominal pain). Adverse events with the highest reported incidence were headache (n=6) and dizziness (n=4).

No clinically significant abnormalities in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, or electrocardiogram were observed.

**SPONSOR'S CONCLUSIONS:** Following single PO dose of digoxin 0.5 mg alone or in combination with fidaxomicin 200 mg Q12h in healthy subjects (n=14):

- Fidaxomicin 200 mg Q12h has little or no effect on digoxin pharmacokinetics.
- Digoxin  $C_{max}$  increased by 14% when co-administered with fidaxomicin compared to digoxin alone, while there was no statistically significant change in digoxin AUC values.
- Fidaxomicin was safe and well-tolerated when administered alone or with a single dose of digoxin.

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results. There is no clinically significant DDI between fidaxomicin and digoxin via gut-mediated P-gp inhibition and no restrictions regarding concomitant use is warranted for labeling.

**STUDY NO.:** OPT-80-009

**A Phase 1, open-label, monosequence crossover study to evaluate the potential for cytochrome P450-mediated drug interactions with fidaxomicin (OPT-80) in healthy male subjects**

Date(s): 24 May 2010 – 16 Jul 2010

Investigator(s): W Lewis, M.D.

Clinical Site(s): Covance Clinical Research Unit Inc.; Dallas, TX, US

Analytical Site(s): (b) (4)

**OBJECTIVE(S):**

- To examine the effect of steady-state fidaxomicin (OPT-80) on the single-dose pharmacokinetics of a cocktail of 3 drugs, namely, warfarin, omeprazole, and midazolam
- To compare the safety and tolerability of steady-state fidaxomicin alone and in the presence of a cocktail of warfarin, omeprazole, and midazolam in healthy male subjects

**METHODS**

**Study Design:** This was an open-label, monosequence, crossover (with 16-day washout), drug-drug interaction (DDI) study of fidaxomicin (CYP450 inhibitor) and a single-dose cocktail of warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), and midazolam (CYP3A4/5 substrate) in healthy males (n=24) (**Table 1**).

**Table 1.** Dosing scheme of fidaxomicin and CYP450 substrates (warfarin, omeprazole, and midazolam) in monosequence crossover design

Period 1		Period 2	Period 3		Discharge
10 mg warfarin, 40 mg omeprazole, and 5 mg midazolam (single dose)	Washout	200 mg fidaxomicin tablets q12h	10 mg warfarin, 40 mg omeprazole, and 5 mg midazolam (single dose) and 200 mg fidaxomicin tablets q12h	200 mg fidaxomicin tablets q12h	Subjects discharged from the clinic
Day 1	Days 2 to 17	Days 18 to 20	Day 21	Days 22 to 24	Day 34

**Inclusion/Exclusion Criteria:** Males, 18-40 years of age (inclusive), 18.0-30.0 kg/m<sup>2</sup> in body mass index (BMI) (inclusive), and in good health as determined by medical history, physical exam, and laboratory evaluations were enrolled. Poor metabolizers for CYP2C9, CYP2C19, or CYP2D6 (as determined by genotyping) were excluded.

**Treatment:** For CYP450 cocktail and the 1<sup>st</sup> fidaxomicin dose of the day, subjects were administered doses after a 10-h fast followed by a 4-h fast from food post-dose; water was restricted for 1 h pre-dose and 2 h post-dose. For the 2<sup>nd</sup> fidaxomicin dose of the day, food and water were prohibited for 1 h pre-dose and 2 h post-dose. Fidaxomicin was supplied in the to-be-marketed formulation as 200 mg tablets manufactured by (b) (4) (Lot# R0242001). Warfarin (Coumadin<sup>®</sup>) was provided as commercially-available 10 mg tablets, omeprazole (Prilosec OTC<sup>®</sup>) as commercially-available 20 mg tablets, and midazolam (generic Versed<sup>®</sup>) as commercially available 2 mg/mL syrup.

No drugs or substances known to be strong inducers or inhibitors of CYP450 enzymes or P-gp were permitted from 30 days prior to Check-In. Prescription medications/products were prohibited from 14 days prior to Check-In, and non-prescription/over-the-counter (OTC) preparations (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) were prohibited from 30 days prior to Check-In. Grapefruit or grapefruit/apple/orange juice were prohibited from 7 days prior to Check-In, while alcohol- or caffeine-containing foods or beverages were prohibited from 48 hours prior to Check-In.

**Sample Collection:** Blood samples were collected and analyzed for pharmacokinetic purposes (**Table 2**). For monitoring of the pharmacodynamic effects of warfarin, prothrombin time INR was assessed at 24, 48, and 72 h post-dose for Day 1 and Day 21.

**Table 2.** Pharmacokinetic sampling scheme for multiple PO doses of fidaxomicin with/without CYP450 cocktail

<b>R- &amp; S-warfarin</b>	Day1: 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, 144, 168, 216, 264, 312 h Day21: 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, 144, 168, 216, 264, 312 h
<b>Omeprazole &amp; 5-OH-omeprazole</b>	Day1: 0, 0.25, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24 h
<b>Midazolam &amp; 1-OH-midazolam</b>	Day21: 0, 0.25, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24 h
<b>Fidaxomicin &amp; OP-1118</b>	Day18: 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24 h (1 <sup>st</sup> dose of day) Day21: 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 36 h (1 <sup>st</sup> dose of day)

**Analytical Methods:** Pharmacokinetic samples were analyzed for R- and S-warfarin, omeprazole, 5-hydroxyomeprazole, midazolam, and 1-hydroxymidazolam by validated high-performance liquid chromatography (HPLC) with tandem mass spectrometric (MS/MS) detection in plasma (**Table 3**). Concentrations below the lower limit of quantification (LLOQ) were set as 0 or missing (when in between two quantifiable concentrations or when following the last quantifiable concentration) for pharmacokinetic analysis.

**Table 3.** Bioanalytical results of warfarin, omeprazole, and midazolam in plasma

Criterion	R- & S-warfarin	Omeprazole & 5-OH-omeprazole	Midazolam & 1-OH-midazolam	Comments
<b>PLASMA</b>				
Range	5-1500 ng/mL	0.5-1000 ng/mL	0.1-100 ng/mL	Satisfactory <sup>a</sup>
LLOQ	5 ng/mL	0.5 ng/mL	0.1 ng/mL	Satisfactory
Linearity	≥0.9957	≥0.9930	≥0.9944	Satisfactory
Accuracy	± 8.9%	± 7.7%	± 5.7%	Satisfactory
Precision	5.6% CV	8.1% CV	4.7% CV	Satisfactory
Stability	<ul style="list-style-type: none"> <li>• Study Dates: 24 May 2010 – 16 Jul 2010</li> <li>• Analysis Dates: 23 Jun 2010 – 26 Jul 2010</li> </ul>			Satisfactory <sup>b</sup>
	334 days at -10 to -30 °C	Missing	592 days at -10 to -30 °C	

<sup>a</sup> Dilution factor of 10 tested with 3750 ng/mL for omeprazole and 5-OH-omeprazole

<sup>b</sup> Missing stability data for omeprazole and 5-OH-omeprazole found acceptable since reported DDI results will involve the change in concentrations and not the quantified values themselves

Concentrations of fidaxomicin and OP-1118 were not analyzed as of the date of this study report.

**Pharmacokinetic Assessment:** Pharmacokinetic parameters for R- and S-warfarin, omeprazole, 5-hydroxyomeprazole, midazolam, and 1-hydroxymidazolam were determined using single-dose data with non-compartmental methods. Parameters included the following:

- $C_{max}$ , peak observed plasma concentration
- $T_{max}$ , time to  $C_{max}$
- $t_{1/2}$ , apparent elimination half-life
- $AUC_{0-t}$ , area under the concentration-time curve from time 0 to last measured concentration
- $AUC_{0-24}$ , area under the concentration-time curve from 0 to 24 hours post-dose
- $AUC_{0-\infty}$ , area under the concentration-time curve from time 0 to infinity
- M/P Ratio, ratio of metabolite  $AUC_{0-\infty}$  to parent  $AUC_{0-\infty}$

**Statistical Methods:** DDI was examined between co-administration of fidaxomicin and CYP450 cocktail (warfarin, omeprazole, and midazolam) (test) and CYP450 cocktail administered alone (reference). An analysis of variance (ANOVA) with treatment as a fixed effect and subject as a random effect was performed using natural log-transformed ( $\ln$ )  $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-24}$ , and  $AUC_{0-\infty}$ . The 90% confidence intervals (CI) of the test means relative to the reference means were obtained by taking the antilog of the corresponding 90% CIs for the differences between means on the log scale. DDI was assessed by examining the 90% CI for the ratios of the test means relative to the reference means. Lack of DDI would be concluded if the antilog of 90% CI from  $\ln$ -transformed  $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-24}$ , and  $AUC_{0-\infty}$  were entirely contained within the 0.80-1.25 interval.

## RESULTS

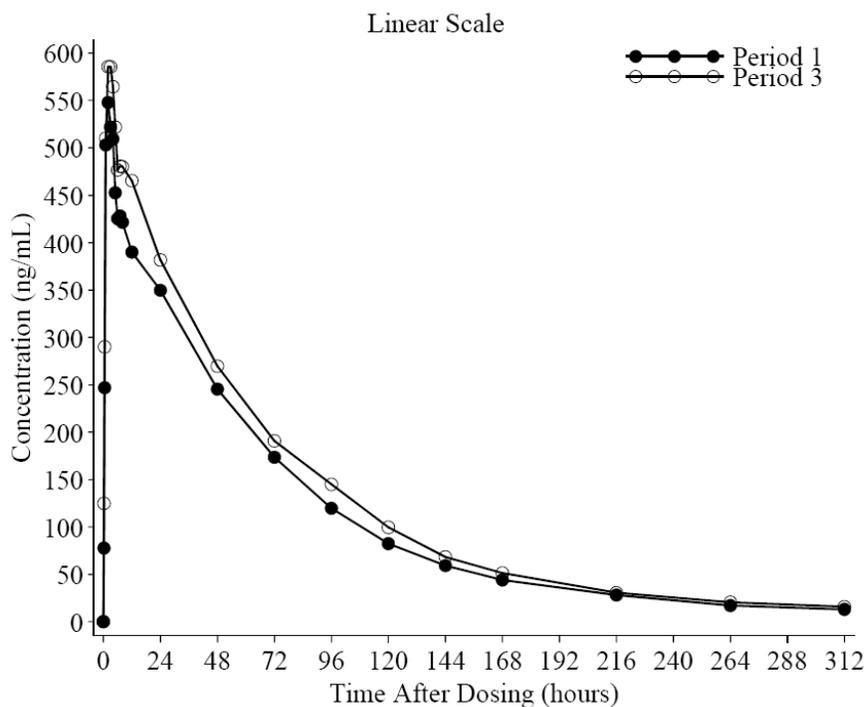
**Study Population:** In total, 24 subjects were enrolled (Table 4). Of these, 22 subjects completed the study: Subject 006 discontinued dosing on Day 20 due to an adverse event of eosinophilia and Subject 009 withdrew from the study on Day 32 by choice.

**Table 4.** Demographic characteristics of enrolled subjects

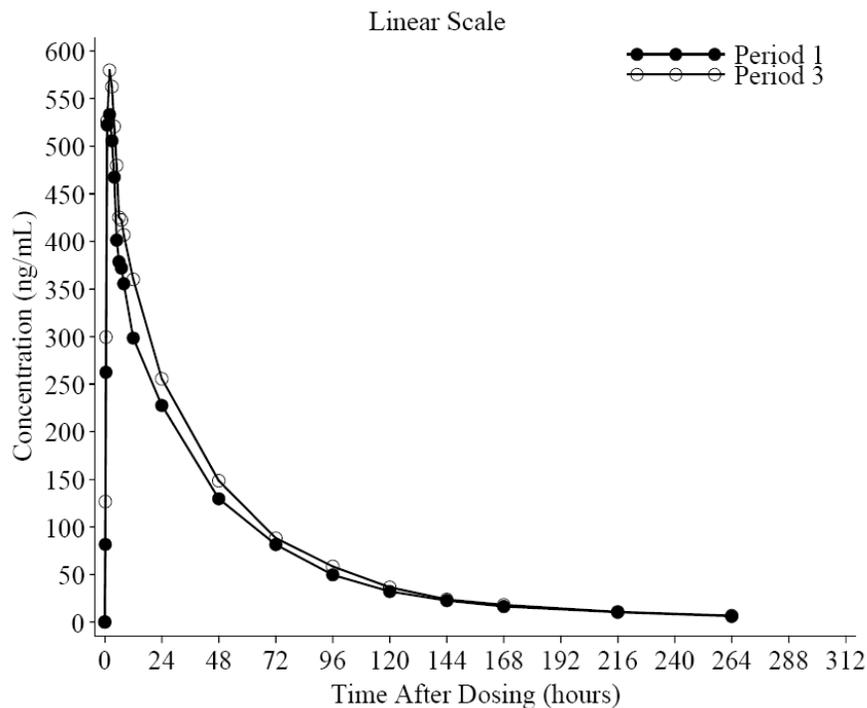
Demographic Variable	
Mean age in years	32 (range 20 to 40 years)
Mean weight in kg	80.7 (range 56.6 to 98.7 kg)
Mean height in cm	176.6 (range 161.5 to 186.5 cm)
BMI in $kg/m^2$	25.8 (range 19.8 to 29.6 $kg/m^2$ )
Gender (n[%])	
Male	24 (100.0%)
Ethnicity (n[%])	
Hispanic or Latino	12 (50.0%)
Not Hispanic or Latino	12 (50.0%)
Race (n[%])	
White	15 (62.5%)
Black or African American	8 (33.3%)
Asian	1 (4.2%)

**Pharmacokinetics:** Geometric mean concentration-time profiles following a single-dose CYP450 cocktail alone or in combination with fidaxomicin are shown in **Figures 1** and **2** for R- and S-enantiomers of warfarin, **Figures 3** and **4** for omeprazole and its metabolite, and **Figures 5** and **6** for midazolam and its metabolite. Concentration-time curves were nearly superimposable, and correspondingly, pharmacokinetic parameters of CYP450 substrates (including  $T_{max}$ ,  $t_{1/2}$ , and M/P Ratio) were comparable with or without fidaxomicin co-administration (**Table 5**).

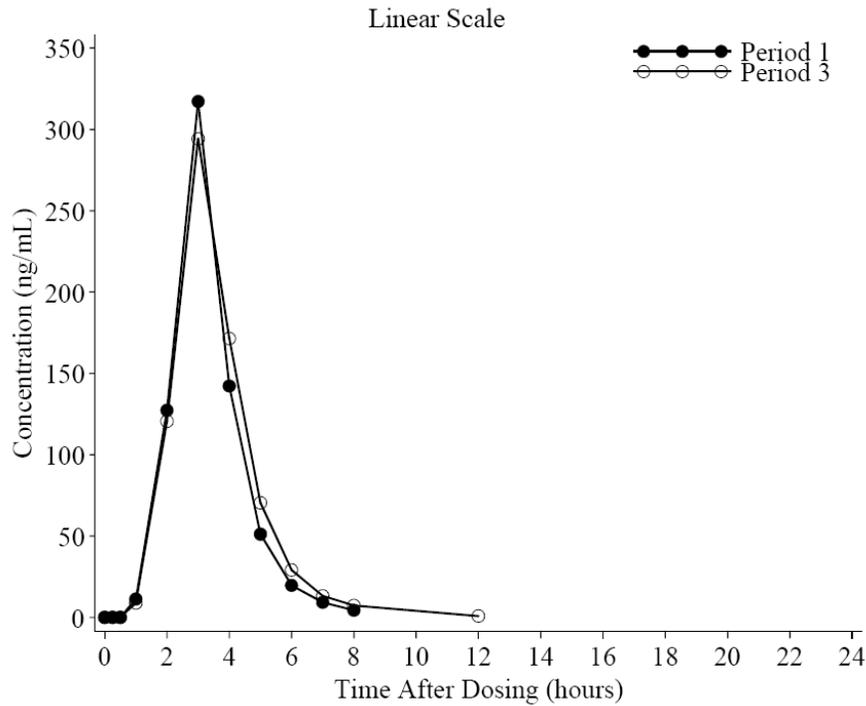
**Figure 1.** Geometric mean plasma concentrations of **R-warfarin** following single 10 mg PO dose (part of CYP450 cocktail) alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy males (n=24)



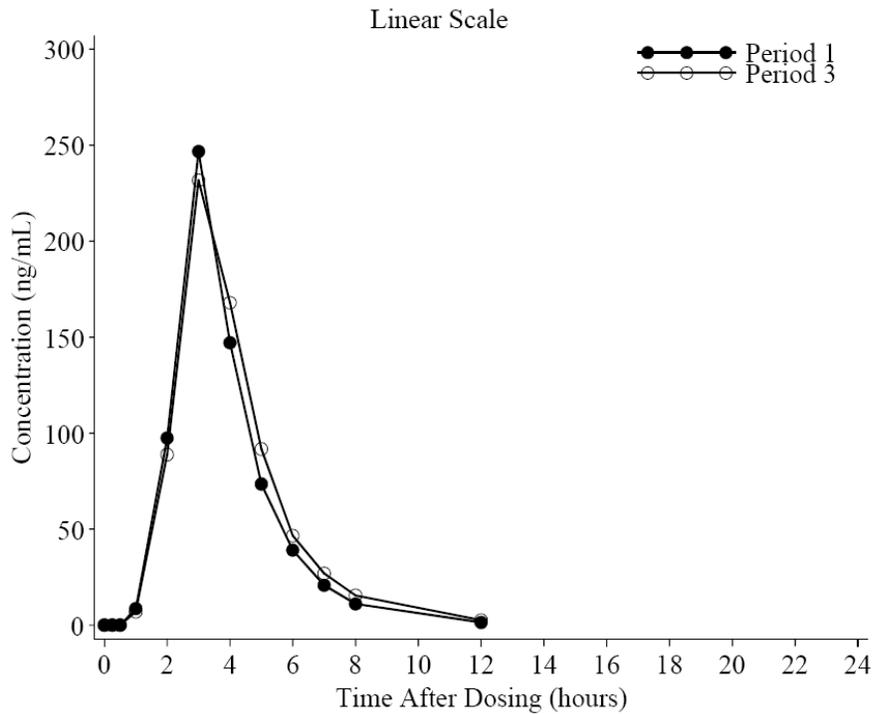
**Figure 2.** Geometric mean plasma concentrations of **S-warfarin** following single 10 mg PO dose (part of CYP450 cocktail) alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy males (n=24)



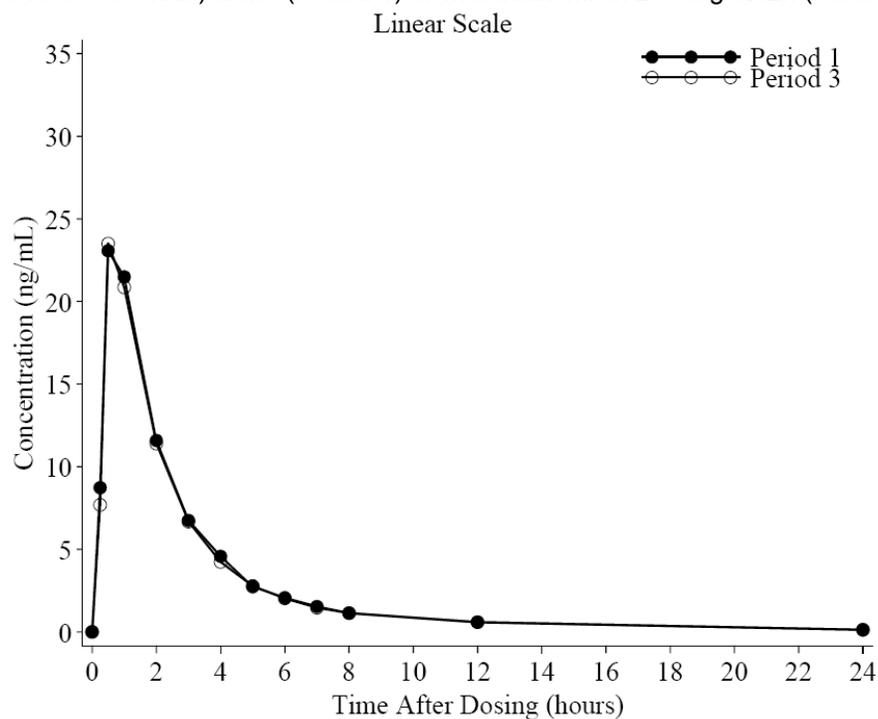
**Figure 3.** Geometric mean plasma concentrations of **omeprazole** following single 40 mg PO dose (part of CYP450 cocktail) alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy males (n=24)



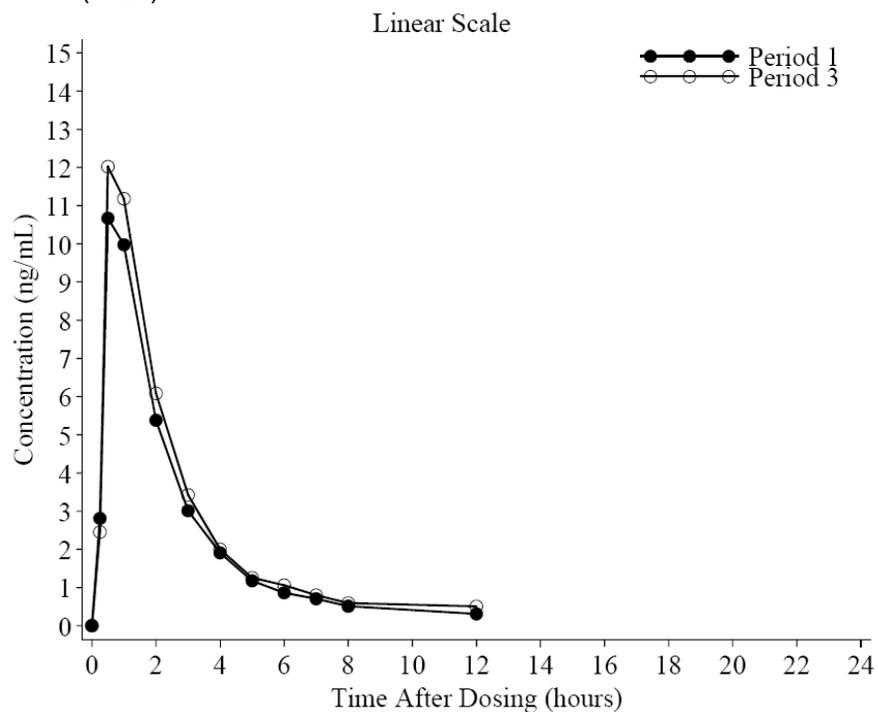
**Figure 4.** Geometric mean plasma concentrations of **5-hydroxyomeprazole** following single 40 mg PO dose (part of CYP450 cocktail) alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy males (n=24)



**Figure 5.** Geometric mean plasma concentrations of **midazolam** following single 5 mg PO dose (part of CYP450 cocktail) alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy males (n=24)



**Figure 6.** Geometric mean plasma concentrations of **1-hydroxymidazolam** following single 5 mg PO dose (part of CYP450 cocktail) alone (Period 1) or with fidaxomicin 200 mg Q12h (Period 3) in healthy males (n=24)



**Table 5.** Pharmacokinetic parameters of warfarin, omeprazole, and midazolam following single PO dose of CYP450 cocktail alone or with fidaxomicin 200 mg Q12h in healthy males (n=24)

Parameter	Day 1	Day 21
	CYP450 Cocktail (Warfarin 10 mg, Omeprazole 40 mg, Midazolam 5 mg)	CYP450 Cocktail (Warfarin 10 mg, Omeprazole 40 mg, Midazolam 5 mg) + Fidaxomicin 200 mg Q12h
<b>R-warfarin</b>		
C <sub>max</sub> (ng/mL)	619 ± 130	676 ± 142
T <sub>max</sub> <sup>a</sup> (h)	2.00 (0.27-4.00)	2.00 (0.30-4.00)
AUC <sub>0-t</sub> (ng*h/mL)	34854 ± 7302	39272 ± 7192
AUC <sub>0-24</sub> (ng*h/mL)	9817 ± 1600	11123 ± 1668
AUC <sub>0-∞</sub> (ng*h/mL)	36606 ± 7817	41920 ± 8032
t <sub>1/2</sub> (h)	87.1 ± 13.1	102 ± 20.3
<b>S-warfarin</b>		
C <sub>max</sub> (ng/mL)	624 ± 133	684 ± 147
T <sub>max</sub> <sup>a</sup> (h)	1.50 (0.50-4.00)	1.00 (0.30-4.00)
AUC <sub>0-t</sub> (ng*h/mL)	20260 ± 5828	23063 ± 7002
AUC <sub>0-24</sub> (ng*h/mL)	7969 ± 1425	9110 ± 1439
AUC <sub>0-∞</sub> (ng*h/mL)	21313 ± 6279	24026 ± 8225
t <sub>1/2</sub> (h)	91.2 ± 24.1	97.3 ± 32.7
<b>Omeprazole</b>		
C <sub>max</sub> (ng/mL)	689 ± 367	661 ± 402
T <sub>max</sub> <sup>a</sup> (h)	2.00 (1.00-4.00)	2.00 (1.00-4.00)
AUC <sub>0-t</sub> (ng*h/mL)	1336 ± 893	1381 ± 965
AUC <sub>0-24</sub> (ng*h/mL)	1340 ± 895	1424 ± 975
AUC <sub>0-∞</sub> (ng*h/mL)	1340 ± 895	1424 ± 975
t <sub>1/2</sub> (h)	1.02 ± 0.12	1.18 ± 0.24
<b>5-hydroxyomeprazole</b>		
C <sub>max</sub> (ng/mL)	390 ± 99.1	382 ± 73.6
T <sub>max</sub> <sup>a</sup> (h)	2.00 (1.00-4.00)	2.00 (1.00-4.00)
AUC <sub>0-t</sub> (ng*h/mL)	908 ± 172	970 ± 179
AUC <sub>0-24</sub> (ng*h/mL)	911 ± 173	976 ± 181
AUC <sub>0-∞</sub> (ng*h/mL)	911 ± 173	976 ± 181
t <sub>1/2</sub> (h)	1.31 ± 0.12	1.47 ± 0.11
M/P Ratio	0.89 ± 0.48	0.93 ± 0.51
<b>Midazolam</b>		
C <sub>max</sub> (ng/mL)	29.5 ± 13.2	26.9 ± 12.6
T <sub>max</sub> <sup>a</sup> (h)	0.50 (0.25-1.00)	0.50 (0.50-1.00)
AUC <sub>0-t</sub> (ng*h/mL)	68.6 ± 27.4	67.8 ± 38.0
AUC <sub>0-24</sub> (ng*h/mL)	69.1 ± 27.5	68.4 ± 37.8
AUC <sub>0-∞</sub> (ng*h/mL)	70.4 ± 28.1	70.0 ± 39.1
t <sub>1/2</sub> (h)	5.16 ± 1.62	5.27 ± 1.52
<b>1-hydroxymidazolam</b>		
C <sub>max</sub> (ng/mL)	15.1 ± 9.72	14.9 ± 7.21
T <sub>max</sub> <sup>a</sup> (h)	0.50 (0.25-1.00)	0.53 (0.50-1.00)
AUC <sub>0-t</sub> (ng*h/mL)	31.7 ± 14.0	35.4 ± 14.8
AUC <sub>0-24</sub> (ng*h/mL)	34.0 ± 13.7	39.1 ± 14.3
AUC <sub>0-∞</sub> (ng*h/mL)	32.2 ± 11.1	40.7 ± 15.4
t <sub>1/2</sub> (h)	6.29 ± 2.88	6.72 ± 2.18
M/P Ratio	0.47 ± 0.16	0.55 ± 0.20

<sup>a</sup> T<sub>max</sub> reported as median (minimum-maximum)

$C_{max}$  and various AUC parameters of warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), and midazolam (CYP3A4/5 substrate) showed <20% difference with co-administration of fidaxomicin (CYP450 inhibitor) versus when administered alone (**Table 6**). For all exposure parameters, 90% CI around point estimates were within the no-effect boundary of 0.80-1.25, with the exception of  $AUC_{0-\infty}$  for 1-hydroxymidazolam. The slight increase in metabolite  $AUC_{0-\infty}$  (by 17%), however, was not accompanied by an increase in the parent midazolam  $AUC_{0-\infty}$ , suggesting that the increase was not mediated by intestinal CYP3A4/5 inhibition.

**Table 6.** Statistical analysis of DDI for warfarin, omeprazole, and midazolam with single PO dose of CYP450 cocktail alone versus with fidaxomicin 200 mg Q12h in healthy males

Parameter	Day 21		Day 1		Point Estimate of Test/Reference (90% CI)
	CYP450 Cocktail (Warfarin 10 mg, Omeprazole 40 mg, Midazolam 5 mg) + Fidaxomicin 200 mg Q12h		CYP450 Cocktail (Warfarin 10 mg, Omeprazole 40 mg, Midazolam 5 mg)		
	N	Least Squares Mean	N	Least Squares Mean	
<b>R-warfarin</b>					
$C_{max}$ (ng/mL)	23	661	24	606	1.09 (1.05-1.14)
$AUC_{0-t}$ (ng*h/mL)	23	38475	24	34202	1.12 (1.09-1.16)
$AUC_{0-24}$ (ng*h/mL)	23	10993	24	9700	1.13 (1.11-1.16)
$AUC_{0-\infty}$ (ng*h/mL)	22	40862	24	35902	1.14 (1.11-1.17)
<b>S-warfarin</b>					
$C_{max}$ (ng/mL)	23	668	24	611	1.09 (1.04-1.15)
$AUC_{0-t}$ (ng*h/mL)	23	21959	24	19515	1.13 (1.10-1.16)
$AUC_{0-24}$ (ng*h/mL)	23	8963	24	7854	1.14 (1.12-1.16)
$AUC_{0-\infty}$ (ng*h/mL)	21	23171	24	20495	1.13 (1.10-1.17)
<b>Omeprazole</b>					
$C_{max}$ (ng/mL)	23	561	24	603	0.93 (0.82-1.06)
$AUC_{0-t}$ (ng*h/mL)	23	1131	24	1097	1.03 (0.94-1.14)
$AUC_{0-24}$ (ng*h/mL)	22	1132	24	1100	1.03 (0.93-1.14)
$AUC_{0-\infty}$ (ng*h/mL)	22	1132	24	1100	1.03 (0.93-1.14)
<b>5-hydroxyomeprazole</b>					
$C_{max}$ (ng/mL)	23	377	24	378	1.00 (0.91-1.09)
$AUC_{0-t}$ (ng*h/mL)	23	955	24	892	1.07 (1.02-1.12)
$AUC_{0-24}$ (ng*h/mL)	23	961	24	895	1.07 (1.03-1.12)
$AUC_{0-\infty}$ (ng*h/mL)	23	961	24	895	1.07 (1.03-1.12)
<b>Midazolam</b>					
$C_{max}$ (ng/mL)	23	25.1	24	27.4	0.92 (0.83-1.02)
$AUC_{0-t}$ (ng*h/mL)	23	61.8	24	64.5	0.96 (0.87-1.05)
$AUC_{0-24}$ (ng*h/mL)	23	62.6	24	65.0	0.96 (0.88-1.05)
$AUC_{0-\infty}$ (ng*h/mL)	23	63.9	24	66.2	0.96 (0.88-1.06)
<b>1-hydroxymidazolam</b>					
$C_{max}$ (ng/mL)	23	13.4	24	13.0	1.03 (0.91-1.16)
$AUC_{0-t}$ (ng*h/mL)	23	32.5	24	29.0	1.12 (1.04-1.21)
$AUC_{0-24}$ (ng*h/mL)	18	34.7	21	31.1	1.12 (1.01-1.23)
$AUC_{0-\infty}$ (ng*h/mL)	18	36.2	19	31.0	1.17 (1.07-1.28)

**Safety:** Of 24 enrolled subjects, 23 received all study doses to completion (i.e., 2 doses of CYP450 cocktail and 14 doses of fidaxomicin). Subject 006 discontinued dosing early on Day 20 due to an adverse event and received just 1 dose of CYP450 cocktail and 6 doses of fidaxomicin. In total, 23 adverse events were reported by 14/24 (58.3%) subjects; 6 occurred with CYP450 cocktail alone (Period 1), 5 with fidaxomicin (Period 2), and 12 with the combination of CYP450 cocktail and fidaxomicin (Period 3). All events were mild in severity, except for 1 moderate event of eosinophilia by Subject 006 which led to study discontinuation although the event was determined unrelated to study drug. Adverse events with the highest reported incidence were dizziness (n=3), chest discomfort (n=2), and diarrhea (n=2).

Subject 006 had clinically significant increases in absolute and percent eosinophil levels on Days 21-34 that were approximately  $4 \times$  ULN (upper limit of normal). Aside from eosinophilia by Subject 006, no clinically significant abnormalities in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, or electrocardiogram were observed.

There was no increase in INR when warfarin was co-administered with fidaxomicin versus warfarin alone, and only slight elevations (1.2-1.7; normal range, 0.9-1.1) were observed in 14/24 (58.3%) subjects over the 72-h monitoring period that followed each dose of warfarin. Of these 14 subjects, 7 had similar elevations after warfarin dosing both with (Period 3) or without (Period 1) fidaxomicin, 6 had elevations only after warfarin was dosed alone, and only 1 had an elevation (to 1.2) in Period 3 with no corresponding elevation in Period 1.

**SPONSOR'S CONCLUSIONS:** Following single PO dose of CYP450 cocktail (warfarin 10 mg, omeprazole 40 mg, and midazolam 5 mg) alone or in combination with fidaxomicin 200 mg Q12h in healthy males (n=24):

- Steady-state administration of fidaxomicin did not alter the drug-metabolizing capacity of CYP2C9, CYP2C19, and CYP3A4/5 to metabolize S-warfarin, omeprazole, or midazolam, respectively.
- Steady-state co-administration of fidaxomicin resulted in slight increase (17%) in 1-hydroxymidazolam  $AUC_{0-\infty}$ ; however, this was not accompanied by an increase in the parent  $AUC_{0-\infty}$ , suggesting that the increase was not due to intestinal CYP3A4/5 inhibition.
- Co-administration of fidaxomicin with warfarin did not cause an increase in INR as compared to warfarin alone.
- Fidaxomicin was safe and well-tolerated when administered alone or with a single dose CYP450 cocktail of warfarin, omeprazole, and midazolam.
- One subject had clinically significant increases in absolute and percent eosinophil levels, which resulted in study discontinuation but was judged to be unlikely related to study drug.

**REVIEWER ASSESSMENT:** The Sponsor's conclusions are appropriate based on study results. There is no clinically significant DDI between fidaxomicin and warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), or midazolam (CYP3A4/5 substrate) via gut-mediated CYP450 inhibition and no restrictions regarding concomitant use is warranted for labeling.

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/s/  
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ARYUN KIM  
04/11/2011

KIMBERLY L BERGMAN  
04/12/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

***General Information About the Submission***

	Information		Information
NDA/BLA Number	201-699	Brand Name	Dificid™ (proposed)
OCP Division (I, II, III, IV, V)	IV	Generic Name	Fidaxomicin
Medical Division	DAIOP	Drug Class	(b) (4)
OCP Reviewer	Aryun Kim, Pharm.D.	Indication(s)	Treatment of <i>Clostridium difficile</i> infection and prevention of recurrences
OCP Team Leader	Kimberly Bergman, Pharm.D.	Dosage Form	Tablet
Pharmacometrics Reviewer	None	Dosing Regimen	200 mg BID for 10 days
Date of Submission	30 Nov 2010	Route of Administration	Oral
Estimated Due Date of OCP Review	30 Apr 2011	Sponsor	Optimer Pharmaceuticals, Inc.
Medical Division Due Date	30 Apr 2011	Priority Classification	Priority
PDUFA Due Date	30 May 2011		

***Clinical Pharmacology and Biopharmaceutics Information***

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:	-			
Isozyme characterization:	X	6		
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	X	6		
<b>Healthy Volunteers-</b>				
single dose:	X	3		
multiple dose:	X	3		
<b>Patients-</b>				
single dose:	-			
multiple dose:	X	3		1 Phase 2A study 2 Phase 3 studies
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:	X	1		

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	X	1		Cyclosporine (P-gp inh bitor)
In-vivo effects of primary drug:	X	2		CYP450 Substrate Cocktail: - Warfarin (2C9) - Omeprazole (2C19) - Midazolam (3A4) Digoxin (P-gp substrate)
In-vitro:	X	4		
<b>Subpopulation studies -</b>				
ethnicity:	-			
gender:	-			Subgroup analysis of Phase 3 studies
pediatrics:	-			
geriatrics:	-			Subgroup analysis of Phase 3 studies
renal impairment:	-			Subgroup analysis of Phase 3 studies
hepatic impairment:	-			Subgroup analysis of Phase 3 studies
<b>PD -</b>				
Phase 2:	X	1		
Phase 3:	X	2		
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	-			
<b>Population Analyses -</b>				
Data rich:	-			
Data sparse:	-			
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>	-			
<b>Relative bioavailability -</b>	-			
solution as reference:	-			
alternate formulation as reference:	-			
<b>Bioequivalence studies -</b>	-			
traditional design; single / multi dose:	-			
replicate design; single / multi dose:	-			
<b>Food-drug interaction studies</b>	X	1		
<b>Bio-waiver request based on BCS</b>	-			
<b>BCS class</b>	X	1		
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>	-			
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>	-			
<b>Chronopharmacokinetics</b>	-			
<b>Pediatric development plan</b>	X			(b) (4)
<b>Literature References</b>	-			
<b>Total Number of Studies</b>		9		6 Phase 1 studies 1 Phase 2A study 2 Phase 3 studies

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The to-be-marketed fidaxomicin tablet formulation was used in pivotal Phase 3 trials. Fidaxomicin tablets were over-encapsulated in Phase 3 studies for blinding purposes. <i>In vitro</i> dissolution studies of over-encapsulated tablets and to-be-marketed tablets (i.e., not over-encapsulated) were performed.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Based on dose-response relationship for efficacy from Phase 2A study.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			PK datasets for Phase 2A/3 studies in PDF form; will request datasets be provided as Excel/SAS transfer files.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Exposure-response analyses could not be performed due to limited and variable systemic exposure.
14	Is there an adequate attempt by the applicant to use exposure-			X	Exposure-response

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				analyses could not be performed due to limited and variable systemic exposure.
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			×	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			×	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	×			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	×			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			×	

### IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

**YES**

If the NDA/BLA is not fileable from the clinical pharmacology 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.

**Aryun Kim, Pharm.D.**

Reviewing Clinical Pharmacologist

**07 Jan 2010**

Date

**Kimberly Bergman, Pharm.D.**

Team Leader/Supervisor

**07 Jan 2010**

Date

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/s/  
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ARYUN KIM  
01/07/2011

KIMBERLY L BERGMAN  
01/07/2011

**BIOPHARMACEUTICS FILLING REVIEW**  
**Office of New Drugs Quality Assessment**

<b>Application No.:</b>	NDA 201-699	<b>Reviewer:</b> Elsbeth Chikhale, PhD	
<b>Submission Date:</b>	November 29, 2010		
<b>Division:</b>	Division of Anti-Infective & Ophthalmology Products	<b>Team Lead:</b> Angelica Dorantes, PhD	
<b>Sponsor:</b>	Optimer Pharmaceuticals. Inc.	<b>Supervisor:</b> Patrick Marroum, PhD	
<b>Trade Name:</b>	Dificid (fidaxomicin) Tablets	<b>Date Assigned:</b>	Nov 24, 2010
<b>Generic Name:</b>	Fidaxomicin	<b>Date of Review:</b>	Dec 23, 2010
<b>Indication:</b>	Treatment of <i>Clostridium difficile</i> infection (CDI) and prevention of recurrences.	<b>Type of Submission:</b> Original New Drug Application	
<b>Formulation/ strengths</b>	Tablet/ 200 mg		
<b>Route of Administration</b>	Oral		

**SUBMISSION:**

This rolling 505(b)(1) New Drug Application is for an immediate release film-coated tablet containing 200 mg of fidaxomicin, indicated for the treatment of *Clostridium difficile* infection (CDI) and prevention of recurrences. Fidaxomicin is a member of a class of antibiotics called macrocycles, with a narrow spectrum antibacterial profile, potent bactericidal activity against *C. difficile*, and very low systemic availability. Low systemic availability is preferred because the infection/site of action is in the GI tract.

**BIOPHARMACEUTICS:**

Four drug product formulations (liquid-filled capsules for phase 1, powder-filled capsules for phase 2, uncoated tablets for the first phase 3 trial, and coated tablets for first and second phase 3 trial) were investigated during the drug product development. The proposed commercial formulation is the coated tablet, which was used in both phase 3 trials. (b) (4)

Clinical Study Number	Dosage Strength and Form	Drug Substance Lot(s)	Drug Product Lot	Site of Manufacture
101.1.C.003	200 mg uncoated tablet (b) (4)	B-0560065	181338	(b) (4)
		B-0660017	183194	
101.1.C.003 101.1.C.004	200 mg film coated tablet (b) (4)	B-0660051	184732	
		B-0660064	R0240001	
		B-0660051 B-0660072	R0242001	
		B-0660051 B-0660064	R0242002	

In addition, the coated tablets were encapsulated for blinding purpose during the clinical trials. The comparator drug product (vancomycin) used in the clinical trials was also encapsulated.

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion for fidaxomicin, and on the evaluation of the comparative dissolution profile data. (b) (4)

(b) (4)

(b) (4)

**RECOMMENDATION:**

The ONDQA/Biopharmaceutics team has reviewed NDA 201-699 for filing purposes. We found this NDA filable from a biopharmaceutics perspective. The sponsor has submitted a reviewable submission. The following information request should be sent to the sponsor:

- Provide the comparative dissolution profile data (*individual, mean, and plot*) for the comparator un-encapsulated vancomycin and the encapsulated vancomycin products used in the clinical studies (101.1.C.003 and 101.1.C.004).

**Elsbeth Chikhale, Ph.D.**

Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Angelica Dorantes, Ph.D.**

Biopharmaceutics Team Leader or Supervisor  
Office of New Drugs Quality Assessment

cc: P. Marroum

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/s/  
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ELSBETH G CHIKHALE  
12/23/2010

ANGELICA DORANTES  
12/23/2010