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APPLICATION NUMBER:

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MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY DRUG PRODUCTS
(HFD-520)

CLINICAL MICROBIOLOGY REVIEW

NDA 201- 699

DATE REVIEW COMPLETED: 29 Mar 11

Date Company Submitted: 29 Nov 10
Date Assigned: 30 Nov 10

Date Received by CDER: 30 Nov 10
Reviewer: Fred Marsik, Ph.D.

NAME AND ADDRESS OF SPONSOR

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DRUG PRODUCT NAME

Proprietary: Dificid™ (formerly PAR-101, OPT-80 or Fidaxomicin)

Established Name: Tiacumicin B

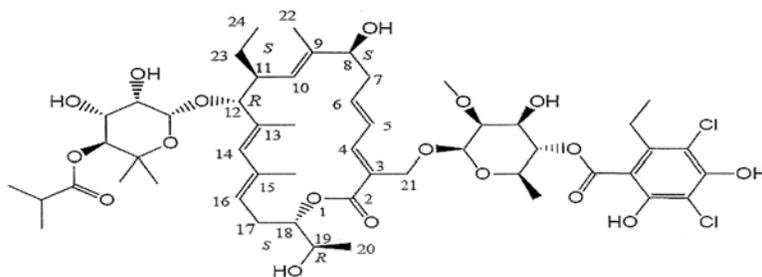
Code name/Number: None

Chemical Name: 3-[[[6Deoxy-4-0-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-oxomethyl-β-L-mannopyranosyl]oxymethyl]-12-[[6-deoxy-5-C-methyl-4-o(2-methyl-1-oxopropyl)-β-D-lyxo-hexopyranosyl]oxy]-11-ethyl-8-hydroxy-18-(1-hydroxyethyl)-9,13,15-trimethylxacyclooctadeca-3,5,9,13,15-pentene-2-one.

Chemical Formula: C₅₂H₇₄Cl₂O₁₈

Structure:

Figure 1: Structure of fidaxomicin



Dificid is being developed as a tablet dosage form for oral administration. All clinical lots of fidaxomicin drug substance and Dificid drug product were prepared under current Good Manufacturing Practices (cGMP).

PROPOSED INDICATION and USAGE

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Treatment of *Clostridium difficile* Infection (CDI) more specifically *Clostridium difficile* Associated Diarrhea (CDAD)

**PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION,
DURATION OF TREATMENT**

Dosage form: Tablet
Strength: 200 mg
Route of administration: Oral
Dosing: 200 mg every 12 hours
Duration of treatment: 10 days

DISPENSED

Rx

RELATED DOCUMENTS

IND 64,435

REMARKS

This submission provides in vitro, in vivo, and data from phase 3 clinical trials for Dificid. The company uses the term *Clostridium difficile* Infection (CDI) to describe the infection for which they have developed Dificid. The Agency has requested that the term *Clostridium difficile* Associated Diarrhea (CDAD) be used because it more specifically describes the indication for Dificid. Therefore the term *Clostridium difficile* Associated Diarrhea (CDAD) used throughout this submission refers to *Clostridium difficile* Infection (CDI).

In this review the words Dificid™, Fidaxomicin, OPT-80 are synonymous.

CONCLUSION

From a Clinical Microbiology perspective Dificid™ shows activity both in vitro and in vivo against *C. difficile*. In vitro testing of Dificid against isolates of *C. difficile* obtained prior to the clinical studies and during the clinical studies showed that the isolates were susceptible to Dificid concentrations (MIC₉₀ 0.25 mcg/mL) that are many fold below the concentration of Dificid that is achieved in stool (5 to 7630 mcg/g of stool) using the dose the company is recommending. Dificid was not inferior to the comparator drug vancomycin in treating *Clostridium Difficile* Associated Diarrhea (CDAD). In relation to recurrence of CDAD after treatment Dificid treated patients had fewer recurrences than did vancomycin treated patients. (b) (4)

There was one

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instance in the Difcid treated population where the *C. difficile* obtained during the recurrence had a higher MIC (16 mcg/mL) then the baseline MIC (0.06 mcg/mL). The isolate with the higher MIC has a single mutation (VAl143Gly) in the beta subunit of RNA polymerase. The company in a laboratory derived *C. difficile* mutant displaying decreased susceptibility to Difcid (Study B10091206A) reported the same mutation. No isolates of *C. difficile* recovered from patients treated with vancomycin had a higher vancomycin MIC (+/- one doubling dilution). It is not possible to determine what Difcid MIC is related to clinical success or failure. The Difcid MIC (16 mcg/mL) of the isolate obtained from the patient with recurrence of CDAD is many fold below the median concentration of Difcid in stool (1210 mcg/g) but it is also above the lowest concentration (5 mcg/g) found in the stool. It is not possible to say that resistance to Difcid will occur at any significant rate after it is introduced to the market. However, the fact that there was an isolate recovered from a case of recurrence during clinical studies with a higher Difcid MIC then the baseline isolate and a *C. difficile* was obtained during laboratory experiments with a higher Difcid MIC then the parent bacteria both with the same single mutation makes surveillance for Difcid resistance after introduction into the market important.

COMMENT

1. Surveillance studies to determine if *C. difficile* isolates are developing decreased susceptibility to Difcid after it introduction to the market place are a post-marketing requirement with the running for a minimum of five years with results reported annually.

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EXECUTIVE SUMMARY**Introduction**

Dificid™ (also known as OPT-80, PAR-101, Fidaxomicin) is an antibiotic characterized by an 18-membered macrocyclic ester structure. It is obtained from the fermentation of *Dactylosporangium aurantiacum* and belongs to a group of compounds known as Tiacumicins (Groups A, B, C, D, E, and F) with Dificid belonging to group B.

Spectrum of Activity of Dificid

Dificid has a narrow in vitro spectrum of activity being primarily active against vegetative *Clostridium* spp. such as *Clostridium difficile*. It has reduced in vitro activity against *Enterobacteriaceae*, *Pseudomonas aeruginosa*, staphylococci, streptococci, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Acinetobacter baumannii*, and *Candida albicans* when compared to its activity against *C. difficile* and *Clostridium perfringens*. While Dificid is active in vitro against the Gram-positive bacterium *Micrococcus luteus* that is comparable to its activity against the *Clostridium* spp. it has minimal activity against other Gram-positive bacteria. The activity of Dificid against *Micrococcus luteus* has no direct relevance for the use of Dificid to treat CDAD. Dificid has no in vitro activity against the spores of clostridia. The Table below shows the 90th percentile of the minimal inhibitory concentration (MIC₉₀) required to inhibit the in vitro growth of vegetative *C. difficile*. This MIC₉₀ value is the same for *C. difficile* isolates collected before clinical trials and those collected during the Phase 3 clinical trials.

Table 1. In vitro susceptibility of *Clostridium difficile* to Dificid

<u>Organism</u>	<u>MIC or Range (mcg/mL)</u>	<u>MIC₅₀ (µg/mL)</u>	<u>MIC₉₀ (µg/mL)</u>
<i>Clostridium difficile</i>	0.12 - 0.25	0.25	0.25

Mechanism of Action

Dificid is bactericidal in vitro against *C. difficile*. It acts via inhibition of ribonucleic acid (RNA) synthesis by RNA bacterial polymerase at a site different from that at which rifamycins act. Antibacterial activity of Dificid is mediated through inhibition of transcriptional initiation. A metabolite of Dificid OP-1118 has activity that is 1/32nd of the parent compound against *C. difficile*.

Post-Antibiotic Effect (PAE) of Dificid

The PAE of Dificid and its metabolite is in the range of 5 to 10 hours.

Mechanism of Decreased Susceptibility to Difcid

In vitro studies indicate a low frequency of spontaneous decreased susceptibility development of *C. difficile* to Difcid. Serial passage studies also confirm a low propensity for decreased susceptibility to Difcid.

A *C. difficile* with decreased susceptibility to Difcid was created in the laboratory and one patient in the phase 3 Difcid clinical trial that had a recurrence of CDAD had a *C. difficile* isolate with an MIC of 16 mcg/mL while the baseline *C. difficile* from this patient had an MIC of 0.06 mcg/mL. The isolate obtained from the recurrence episode had a single mutation (VAl143Gly) in the beta subunit of RNA polymerase. The same mutation existed in the laboratory derived *C. difficile* mutant that had decreased susceptibility to fidaxomicin.

Cross Decreased Susceptibility to Other Antibacterials

No decreased susceptibility to rifampin, azithromycin, ampicillin, metronidazole, vancomycin, and clindamycin has been detected in *C. difficile* with decreased susceptibility to Difcid.

Synergy/Antagonism with Other Antibacterials

No Difcid antagonistic relationship with ampicillin, azithromycin, clindamycin, metronidazole, rifampicin, rifaximin, telithromycin or vancomycin has been demonstrated in vitro. Synergistic interactions for both Difcid and OP-1118 were observed in vitro with rifamycin class of compounds and marginally with ampicillin, clindamycin and metronidazole.

In Vitro Susceptibility Test Method

In vitro anaerobic susceptibility testing of Difcid against anaerobe bacteria can be done by anaerobic standardized methods.

In Vitro Susceptibility Test Method Interpretive Criteria

In vitro susceptibility test interpretive criteria have not been established for Difcid against *C. difficile*. There was no correlation identified between clinical success and the minimal inhibitory concentration of Difcid needed to prevent growth of the *C. difficile* isolated from patients with CDAD (Table 3.2-10).

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Table 3.2-10. Baseline Strain Susceptibilities Versus Outcome for Pooled Phase 3 Studies (mITT Population)

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

Reference: Integrated Summary of Efficacy, Table 14.2.7.3.1

In Vitro Quality Control Parameters for Susceptibility Testing

An in vitro MIC susceptibility test quality control range was developed for Dificid so that laboratories that wish to determine the Dificid MIC of *C. difficile* isolates can determine whether the susceptibility test is performing correctly. The QC range is shown below.

Acceptable Quality Control Ranges for Fidaxomicin

Microorganism	MIC Range (µg/mL)
<i>C. difficile</i> (ATCC 700057)	0.03 – 0.25

Overall Clinical Cure Rates as Determined by Applicant

Table 3.2-1. Summary of Clinical Cure Rates at End of Therapy in the Phase 3 Studies

	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹
PP population	247/268 (92.2)	251/280 (89.6)	2.5 (-2.4,7.3)	199/217 (91.7)	212/234 (90.6)	1.1 (-4.2,6.4)	446/485 (92.0)	463/514 (90.1)	1.9 (-1.7,5.4)
95% CI around PE ¹	(88.2,94.9)	(85.5,92.7)		(87.2,94.7)	(86.1,93.7)		(89.2,94.1)	(87.2,92.4)	
mITT population	255/289 (88.2)	263/307 (85.7)	2.6 (-2.9, 8.0)	222/253 (87.7)	222/256 (86.7)	1.0 (-4.8, 6.8)	477/542 (88.0)	485/563 (86.1)	1.9 (-2.1,5.8)
95% CI around PE ¹	(84.0,91.5)	(81.3,89.2)		(83.1,91.2)	(82.0,90.4)		(85.0,90.5)	(83.0,88.8)	

¹ 2-sided 95% CI using method recommended by Agresti and Caffo, 2000

PE = point estimate

Reference: Integrated Summary of Efficacy, Tables 14.2.1.1.1 and 14.2.1.1.2

Fecal Concentrations of Dificid in Patient Stools

Table 3.2-12. Fecal Fidaxomicin and OP-1118 Concentrations at EOT (µg/g) and Fidaxomicin: MIC Ratios in Pooled Phase 3 Studies (mITT Population)

Statistic	Fidaxomicin	OP-1118	Fidaxomicin/MIC
N	175	172	140
Mean (SD)	1396.88 ± 1018.85	834.14 ± 616.50	27466.51 ± 40046.16
Median	1210.00	699.50	15826.65
Range	5.0, 7630.0	63.4, 4170.0	160.4, 280000.0

Reference: Integrated Summary of Efficacy, Tables 14.2.8.1.1 and 14.2.8.2.1

Clinical Outcome Based on MICs and *C. difficile* Strain

The following table (Table 3.2-11) shows the clinical outcome for Dificid and vancomycin by MIC and strain type. The BI (also known as 027) strain is the hypervirulent *C. difficile* strain while the non-BI are other strains obtained from patients during the Phase 3 studies. As can be seen the BI strain tends to have a slightly higher Dificid MIC and the cure rate is somewhat lower. The cure rate for vancomycin is also lower for patients with the BI strain of *C. difficile*.

As is seen in Table 3.2-12 the Dificid MIC of the *C. difficile* isolates both in the clinical cure and failure groups are well below the Dificid concentration in stool shown in Table 3.2-12.

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Table 3.2-11. Cure Rates by MIC and Strain in Pooled Phase 3 Studies (mITT Population)

Arm, strain	MIC, µg/mL											
	0.007	0.015	0.02	0.03	0.06	0.125	0.25	0.5	1	2	4	8
Fidaxomicin												
BI n/N (%)	0/0	0/0	0/0	3/3 (100)	5/7 (71.4)	40/48 (83.3)	54/69 (78.3)	11/13 (84.6)	1/1 (100)	0/0	0/0	0/0
Non-BI n/N (%)	7/7 (100)	15/16 (93.8)	4/5 (80.0)	24/27 (88.9)	83/89 (93.3)	87/92 (94.6)	16/19 (84.2)	2/2 (100)	0/0	0/0	0/0	0/0
Vancomycin												
BI n/N (%)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	36/45 (80.0)	53/65 (81.5)	22/24 (91.7)	5/8 (62.5)	1/1 (100)
Non-BI n/N (%)	0/0	0/0	0/0	0/0	0/0	0/0	3/3 (100)	67/72 (93.1)	115/129 (89.1)	36/41 (87.8)	5/7 (71.4)	0/0

Reference: Integrated Summary of Efficacy, Table 14.2.7.1.1

Recurrence Rates

The company did attempt to recover *C. difficile* isolates from patients that were determined to be failures. However, there was only limited success. Most likely this was due to the presence of the antibiotic in the specimen which inhibited the growth of *C. difficile* in the specimen. However, in the Dificid-treated subjects with baseline isolates were recovered at failure or recurrence for 16 subjects in study 101.1.C.003, and 13 subjects in study 101.1.C.004. In nearly all cases, the final isolate had the same MIC as the baseline isolate or was within one dilution of the baseline isolate MIC. There was one patient in the 101.1.C.004 study treated with Dificid whose baseline *C. difficile* isolate had a Dificid MIC of 0.06 mcg/mL who was a cure but whose stool was still positive for *C. difficile*. This patient went on to have recurring disease and the *C. difficile* isolate obtained from the stool at this time had a Dificid MIC of 16 mcg/mL. Ribotyping of the original isolate and the isolate from the time of recurrence could not determine if the strains were similar since they both were typed as “non-specified REA type. The company has suggested two scenarios. The one scenario being that the isolate developed resistance during treatment with Dificid. Their alternate explanation is that there was reinfection with a strain having an innately lower susceptibility to Dificid, although an MIC of >2 mcg/mL has not been seen previously in the wild type population. The company provided information that shows that the isolate obtained from the recurrence episode had a single mutation (VAlI43Gly) in the beta subunit of RNA polymerase. The company in a laboratory derived *C. difficile* mutant reported this same mutation with decreased susceptibility to Dificid (Study B10091206A).

In the vancomycin treatment group, Subject 003-011-068 from Study 101.1.C.003 had an MIC increase greater than one dilution difference. The strain identified at recurrence, however, was a different REA group from the day 1 isolate, which suggests that this subject’s recurrence was due to infection by a new strain. The recurrence strain belonged to the hypervirulent group B-1. While the recurrence isolate had a higher vancomycin MIC (see table below) its OPT-80 MIC was one dilution lower than the baseline isolate MIC.

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Subject Number	MIC ($\mu\text{g/mL}$)				REA Grouping
	OPT-80	Vanco	Met	Rifax	
003-011-068 (Day 1 isolate)	0.06	0.5	0.5	0.015	Y group
003-011-068 (Recurrence isolate)	0.03	4	1	257	BI group

In the following table are the recurrence rates for the hyper-virulent *C. difficile* strain (B1) and the non-B1 types. Here it can be seen that recurrence in the Dificid treated group was greater when the patient was infected with the B1 strain.

Table 3.2-8. Outcomes by Strain Type in Studies 101.1.C.003 and 101.1.C.004 (PP Population)

Outcome	Study	Strain type	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Total n/N (%)
Clinical cure					
	101.1.C.003	BI	56/65 (86.2)	61/72 (84.7)	117/137 (85.4)
	101.1.C.003	Non-BI	115/119 (96.6)	119/126 (94.4)	234/245 (95.5)
	101.1.C.004	BI	49/55 (89.1)	45/52 (86.5)	94/107 (87.9)
	101.1.C.004	Non-BI	110/117 (94.0)	103/112 (92.0)	213/229 (93.0)
Recurrence					
	101.1.C.003	BI	11/45 (24.4)	13/55 (23.6)	24/100 (24.0)
	101.1.C.003	Non-BI	8/103 (7.8)	27/106 (25.5)	35/209 (16.7)
	101.1.C.004	BI	10/45 (22.2)	16/38 (42.1)	26/83 (31.3)
	101.1.C.004	Non-BI	9/100 (9.0)	23/90 (25.6)	32/190 (16.8)
Global cure					
	101.1.C.003	BI	40/65 (61.5)	48/72 (66.7)	88/137 (64.2)
	101.1.C.003	Non-BI	103/119 (86.6)	86/126 (68.3)	189/245 (77.1)
	101.1.C.004	BI	38/55 (69.1)	27/52 (51.9)	65/107 (60.7)
	101.1.C.004	Non-BI	100/117 (85.5)	74/112 (66.1)	174/229 (76.0)

Reference: 101.1.C.003 CSR, Table 14.2.1.5, Table 14.2.2.11, and Table 14.2.4.1.2; 101.1.C.004 CSR, Table 14.2.1.5, Table 14.2.2.11, and Table 14.2.4.1.2.

Table 3.2-9. Outcomes by Strain Type in Studies 101.1.C.003 and 101.1.C.004 (mITT Population)

Outcome	Study	Strain type	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Total n/N (%)
Clinical cure					
	101.1.C.003	BI	59/75 (78.7)	67/83 (80.7)	126/158 (79.7)
	101.1.C.003	Non-BI	117/125 (93.6)	121/132 (91.7)	238/257 (92.6)
	101.1.C.004	BI	54/65 (83.1)	47/57 (82.5)	101/122 (82.8)
	101.1.C.004	Non-BI	120/131 (91.6)	108/123 (87.8)	228/254 (89.8)
Recurrence					
	101.1.C.003	BI	16/59 (27.1)	14/67 (20.9)	30/126 (23.8)
	101.1.C.003	Non-BI	12/117 (10.3)	34/121 (28.1)	46/238 (19.3)
	101.1.C.004	BI	12/54 (22.2)	18/47 (38.3)	30/101 (29.7)
	101.1.C.004	Non-BI	11/120 (9.2)	30/108 (27.8)	41/228 (18.0)
Global cure					
	101.1.C.003	BI	43/75 (57.3)	53/83 (63.9)	96/158 (60.8)
	101.1.C.003	Non-BI	105/125 (84.0)	87/132 (65.9)	192/257 (74.7)
	101.1.C.004	BI	42/65 (64.6)	29/57 (50.9)	71/122 (58.2)
	101.1.C.004	Non-BI	109/131 (83.2)	78/123 (63.4)	187/254 (73.6)

Reference: 101.1.C.003 CSR, Table 14.2.1.3, Table 14.2.2.9, and Table 14.2.4.1.1; 101.1.C.004 CSR, Table 14.2.1.3, Table 14.2.2.9, and Table 14.2.4.1.1

Time to recurrence was also evaluated and it was found that the Dificid treated group had a longer period to recurrence then did the vancomycin treated group.

CONCLUSION

From a Clinical Microbiology perspective Dificid shows activity both in vitro and in vivo against *C. difficile*. In vitro testing of Dificid against isolates of *C. difficile* obtained prior to the clinical studies and during the clinical studies showed that the isolates were susceptible to Dificid concentrations (MIC₉₀ 0.25 mcg/mL) that are many fold below the concentration of Dificid that is achieved in the stool (5 to 7630 mcg/g of stool) using the

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dose the company is recommending. Dificid was not inferior to the comparator drug vancomycin in treating *Clostridium Difficile* Associated Diarrhea (CDAD). In relation to recurrence of CDAD after treatment Dificid treated patients had fewer recurrences of then did vancomycin treated patients with the difference being statistically significant. There was one instance in the Dificid treated population where the *C. difficile* obtained during the recurrence had a higher MIC (16 mcg/mL) then the baseline MIC (0.06 mcg/mL). The isolate with the higher MIC has a single mutation (Vall43Gly) in the beta subunit of RNA polymerase. The company in a laboratory derived *C. difficile* mutant displaying decreased susceptibility to Dificid (Study B10091206A) reported the same mutation. No isolates of *C. difficile* recovered from patients treated with vancomycin had a higher vancomycin MIC (+/- one doubling dilution). It is not possible to determine what Dificid MIC is related to clinical success or failure. The Dificid MIC (16 mcg/mL) of the isolate obtained from the patient with recurrence of CDAD is many fold below the median concentration of Dificid in stool (1210 mcg/g) but it is also above the lowest concentration (5 mcg/g) found in the stool. While it is not possible to say that resistance to Dificid will occur at any significant rate after it is introduced to the market the fact that there was an isolate recovered from a case of recurrence during clinical studies with a higher Dificid MIC then the baseline isolate and a *C. difficile* was obtained during laboratory experiments with a higher Dificid MIC then the parent bacteria and both had the same mutation makes surveillance for Dificid resistance after introduction into the market important.

COMMENTS

1. Surveillance studies to determine if *C. difficile* isolates are developing decreased susceptibility to Dificid after it introduction to the market place are a post-marketing requirement with the running for a minimum of five years with results reported annually.

AGENCY PROPOSED MICROBIOLOGY SUBSECTION OF THE DIFICID™
PACKAGE INSERT

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

INTRODUCTION:

Clostridium difficile associated diarrhea (CDAD) also referred to as either *C. difficile* associated disease (CDAD) or *C. difficile* Infection (CDI) is a disease that is commonly associated with taking broad-spectrum antimicrobials and certain cancer chemotherapy drugs (1). *Clostridium difficile* is a spore-forming, anaerobic, Gram-positive bacillus. CDAD is the most common cause of nosocomial diarrhea in industrialized nations (2). The disease is diagnosed in approximately 20% of hospitalized patients who develop diarrhea after treatment with antimicrobials or cancer chemotherapy drugs (3). These drugs unbalance the ecosystem of the colon causing *C. difficile* to become the predominant part of the microflora. *Clostridium difficile* causes diarrhea and colitis by the elaboration of one or more toxins. *C. difficile* may cause a variety of complications, including pseudomembranous colitis, toxic megacolon, perforations in the colon, sepsis, and in some cases death. The mortality rate from CDAD is 2 to 5% but increases to 10 to 20% among elderly debilitated patients, and is even greater in patients who develop severe colitis or systemic toxicity (4,5,6). While typically associated with hospitals and long-care facilities, CDAD has now spread into the community. While not as common as hospital-acquired CDAD, community-acquired CDAD is afflicting healthy individuals with no recent history of hospital admission or antibiotic use (7,8). In addition, there is also growing concern that CDAD is developing into a more serious disease as a result of the emergence of a hypervirulent strain referred to as B1 (9,10,11).

Patients are currently treated for CDAD by discontinuance of the offending medication and given supportive therapy. Antimicrobial therapy is required if these steps do not eliminate the infection. The more commonly used antimicrobial therapies are vancomycin or metronidazole (12). Patients treated with these antimicrobials may suffer relapse after initial therapy or do not respond to treatment with either of these antimicrobials (13). Both vancomycin and metronidazole are also known to cause CDAD (12).

Dificid is an 18-membered macrolide antibiotic that belongs to the Tiacumicin family. The Tiacumicin family of macrolides is unsaturated 18-membered macrocycles. The applicant indicates that Dificid has activity in vitro against *Clostridium difficile* and has the potential to be used to treat CDAD. Dificid is a classical fermentation product. Tiacumicins were first reported by Hochlowski et al. (14) who isolated a series of six compounds, known as Tiacumicins (A, B, C, D, E, and F) from the fermentation broth of *Dactylosporangium aurantiacum*. Dificid is Tiacumicin B.

INCIDENCE OF STRAINS OF *CLOSTRIDIUM DIFFICILE* IN WESTERN EUROPE AND NORTH AMERICA

As seen in Table 7 the incidence of various strains of *C. difficile* as determined by ribotyping shows variation in the types seen in various Western countries. Strain 027 (also known as B1) seems to be a strain that is common throughout the Western Europe

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countries and North America while strain 001 is seen among a majority of countries including North America.

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Table 7: Comparison of Incidence of *C. difficile* Strains in North America and Europe

Country	Major Ribotypes by region (% or no. of ribotype/total no. of isolates)														SE21*
	001	002	012	014+020	017	020	023	027	031	053	054	057	078	106	
Germany (REF 1-3)	55%	-	-	-	-	-	44 cases	-	-	-	-	-	7%	-	
Sweden (REF 6-9)	7%	7%	20%	-	-	7.5%	Isolated cases	-	-	-	-	-	-	9.4%	
UK-England (REF 5 and 11)	7.8%	-	-	-	-	-	41%	-	-	-	-	-	2.3%	20%	
UK-Scotland (REF 10)	21%	-	-	-	-	-	5.7%	-	-	-	-	-	-	55%	
UK-Northern Ireland (REF 2 and 10)	35%	-	-	-	-	-	55 cases in an outbreak	-	-	-	-	-	8.3%	11%	
Other EU Countries															
Belgium (REF 2 and 11)	-	-	-	-	-	-	17.6%	5.6%	-	-	-	-	6.3%	-	
France (REF 3)	-	-	-	-	-	-	17.4%	-	-	-	-	-	-	-	
Netherlands (REF 12-13)	17.8%	-	-	7.2%	-	-	25.3%	-	-	-	-	-	10.6%	-	
Spain (REF 9)	-	-	-	-	-	-	4/388	-	-	-	-	-	-	-	
Diffid Phase 2A Trial	8% (3/38)	13% (5/38)	-	8% (3/38)	-	-	42% (16/38)	-	-	-	3% (1/38)	-	-	-	
Diffid Phase 3 trial [#] (US and Canada)	7.2% (30/444)	6.8% (30/444)	-	7.4% (32/444)	0.9% (4/444)	-	38.3% (170/444)	-	4.9% (22/444)	0.7% or (4/444)	0.23% (1/444)	0.5% (2/444)	0.5% (2/444)	-	
Diffid Phase 3 trial [#] (Europe)	8% (5/62)	14.5% (9/62)	-	14.5% (9/62)	-	-	14.5% (9/62)	-	-	-	-	14.5% (5/62)	-	-	
North America Published reports (REF 4, 10)	7-10%	-	-	5-11%	-	-	38-58%	-	7%	5%	-	1.3%	-	-	

*SE21 ribotype has not been translated to commonly used ribotyping classification developed by [Stubbs, 1999].

[#] Microtyping analysis still in progress for these studies

REF1: Borgmann, 2008; REF2: Rupnik, 2008; REF3: Zaib, 2007; REF4: Kleinkauf, 2007; REF 5: Kuijper, 2008; REF6: Noren, 2004; REF 7: Aspevall, 2006; REF8: Noren, 2008; REF9: Akerlund, 2008; REF 10: Brazier, 2008; REF11: Joseph, 2005; REF12: Goorhuis, 2007; REF13: Goorhuis, 2008; REF14: Chekris, 2008; REF15: Citron, 2008; REF16: Jhung, 2008

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IN VITRO

Spectrum of Activity of Dificid

Table 1 is an abbreviated summary of information the Applicant provided in a previous submission (IND 64,435, 20 Aug 03) on the activity of OPT-80 (Dificid) against a variety of bacteria. The data for the activity of OPT-80 against the 15 isolates of *C. difficile* in Table 1 was from the paper by Swanson et al. (15). Swanson et al. determined the MICs by agar dilution using Wilkins-Chalgrin agar. The in vitro susceptibility testing of the facultative anaerobes and anaerobes in the following tables were done according to the National Committee for Clinical Laboratories Standards [NCCLS now the Clinical and Laboratory Standards Institute (CLSI)] methods (16,17). As noted in Table 1 OPT-80 has reduced in vitro activity against *Enterobacteriaceae*, *Pseudomonas aeruginosa*, staphylococci, streptococci, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Acinetobacter baumannii*, and *Candida albicans* when compared to its activity against *C. difficile* and *Clostridium perfringens*. OPT-80 does have activity against *Micrococcus luteus* that is comparable to its activity against the *Clostridium* spp. Additional information on the in vitro activity of OPT-80 can be seen in Tables 2 (18), 3 (19) and 6 (20). All of the quality control results were within the NCCLS recommended ranges (16,17). The Applicant in a previous submission (IND 64,435, 20 Aug 03) provided evidence to show that Dificid (OPT-80) is bactericidal against *C. difficile*.

Table 1. In vitro susceptibility of *Clostridium difficile* and other bacteria to OPT-80

<u>Organism (# of isolates)</u>	<u>MIC or Range (mcg/mL)</u>	<u>MIC₅₀ (µg/mL)</u>	<u>MIC₉₀ (µg/mL)</u>
<i>Clostridium difficile</i> (15)	0.12 - 0.25	0.25	0.25
<i>C. difficile</i> ATCC 43255 (1)	MIC = 0.25		
<i>C. difficile</i> ATCC 9689 (1)	MIC = 0.062		
<i>C. difficile</i> ATCC 17857 (1)	MIC = 0.031		
<i>Clostridium perfringens</i> ATCC 13124 (1)	MIC = ≤0.0156		
<i>Enterococcus faecium</i>			

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ATCC 19434 (1)	4
<i>E. faecium</i> ATCC 49032 (1)	4
<i>E. faecium</i> vancomycin- resistant ATCC 700221(1)	4
<i>Micrococcus luteus</i> ATCC 4698 (1)	≤0.06
<i>Staphylococcus aureus</i> methicillin-resistant ATCC 33591(1)	8
<i>S. aureus</i> ATCC 29213 (1)	8
<i>Staphylococcus</i> <i>epidermidis</i> ATCC 12228 (1)	1
<i>Streptococcus pyogenes</i> ATCC 19615 (1)	16
<i>Streptococcus</i> <i>pneumoniae</i> ATCC 49619 (1)	>32
<i>Escherichia coli</i> ATCC 25922 (1)	>32
<i>Enterobacter cloacae</i> ATCC 23355 (1)	>32
<i>Klebsiella pneumoniae</i> ATCC 13883 (1)	>32
<i>Salmonella typhimurium</i> ATCC 14028 (1)	>32
<i>Serratia marcescens</i> ATCC 8100 (1)	>32

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<i>Pseudomonas aeruginosa</i> ATCC 27853 (1)	>32		
<i>Haemophilus influenzae</i> ATCC 49247 (1)	>32		
<i>Neisseria gonorrhoeae</i> ATCC 49226 (1)	32		
<i>Bacteroides fragilis</i> (69 isolates tested)		>128	>128
<i>Prevotella</i> spp. (35 isolates tested)		>128	>128
<i>Eubacterium</i> spp. (2 isolates tested)		>32	>128

Table 2 (18)

TABLE 2. MICs for antimicrobial agents tested against 110 toxigenic clinical *C. difficile* isolates

Antimicrobial agent	MIC (µg/ml)			
	Range	MIC ₅₀	MIC ₉₀	Geometric mean
Rifaximin	0.0038->16	0.0075	0.015	0.009
Rifalazil	0.0019->16	0.0075	0.03	0.0067
Tizoxanide	0.015-0.5	0.06	0.125	0.0652
Nitazoxanide	0.03-0.5	0.06	0.125	0.076
OPT-80	0.015-0.25	0.125	0.125	0.081
Tigecycline	0.06-1.0	0.125	0.25	0.142
Metronidazole	0.025-0.5	0.125	0.25	0.149
Tinidazole	0.03-1.0	0.125	0.25	0.165
Ramoplanin	0.06-0.5	0.25	0.5	0.291
Vancomycin	0.06-4.0	1.0	1.0	0.801
Doripenem	0.5-4.0	1.0	2.0	1.19
Meropenem	1.0-4.0	2.0	2.0	1.87
Gatifloxacin	0.5-64	1.0	16	1.752
Moxifloxacin	0.5-32	1.0	16	1.90
Levofloxacin	2.0-64	4.0	32	5.801

Table 3 (19)

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Clostridium difficile (23)

Amoxicillin-clavulanate	2	4	0.5-8
Ciprofloxacin	8	32	1.0-64
Clindamycin	2	>128	0.5->128
Linezolid	4	32	1.0-32
Metronidazole	0.25	0.5	0.25-1
Optimer-80	0.12	0.25	0.06-2
Tobramycin	512	>1,024	64->1,024
Vancomycin	1	2	0.5-4

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This in vitro susceptibility information supports an OPT-80 (Dificid) MIC₉₀ of 0.25 mcg/mL.

Table 6: MIC Values for Fidaxomicin, Metronidazole and Vancomycin

Test drug	MIC values (µg/mL)						
	<i>C. difficile</i>		Gram-negative organisms		Gram-positive organisms		
	>110 distinct genotypes	NAP1/027 strain ^a	Aerobic	Facultative and Aerobic	Aerobic cocci	Aerobic nonspore-forming rods	Facultative and Aerobic ^b
Fidaxomicin	0.125	0.25	>128	>128	2	32	4-8 (<i>Staphylococcus</i>) 2-4 (<i>Enterococcus</i>) 32 (<i>Streptococcus</i>)
Metronidazole	0.25	1	4	>128	1	>128	≥128
Vancomycin	1	2	>128	>128	1	2	1-16 (<i>Staphylococcus</i>) 1->64 (<i>Enterococcus</i>) 1 (<i>Streptococcus</i>)

^a MIC data from Phase 3 Dificid trial (171 NAP1/027 strains from a total of 515 clinical isolates, analysis still in progress)

^b MIC₉₀ values for *Staphylococcus* and *Enterococcus* were obtained from a study by (b) (4)
Other references includes Finegold, 2004; Credito, 2004; Hecht, 2007

In order to determine if the *C. difficile* isolates obtained from outside the US would have similar MICs to those in the US the Applicant provided the data seen in Table 8. This information was requested because clinical trials were to be conducted outside the US. As can be seen the MICs for OPT-80 as well as other drugs commonly used to treat CDAD were similar in the various regions from which isolates were obtained.

Table 8. Comparison of Antimicrobial Susceptibility Profile of *C. difficile* Strains in North America and Europe (MIC = mcg/mL)

Region (number of strains)	OPT-80			Vancomycin			Metronidazole		
	MIC ₅₀	MIC ₉₀	MIC Range	MIC ₅₀	MIC ₉₀	MIC Range	MIC ₅₀	MIC ₉₀	MIC Range
US and Canada (515)	0.125	0.25	0.003-0.5	1	2	0.25-4	0.5	1	0.02-4
Europe (72)	0.06	0.25	0.003-0.5	1	2	0.25-4	0.5	1	0.02-4
Germany (11)	0.06	-	0.007-0.125	1	-	1-4	0.5	-	0.125-2
Sweden (8)	0.125	-	0.015-0.25	1	-	1-4	0.5	-	0.25-4
UK (34)	0.125	0.25	0.003-0.5	1	2	0.25-4	0.5	1	0.02-4

Activity of OPT-80 against Yeast

Study report BIO080803A suggests that OPT-80 had no activity against the yeast *Candida albicans*. However, only one isolate of *C. albicans* was tested therefore no definitive statement can be made about the activity of OPT-80 against yeast.

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Activity of Metabolite (OP-1118) of OPT-80 against *C. difficile*

The Applicant provided data to show that a metabolite OP-1118 of OPT-80 had decreased activity compared to OPT-80. This information can be found in the report titled "In vitro activity of OPT-1118 against *Clostridium difficile*" (Report Study No. Citron 012910). The conclusion from the report shows the MIC₉₀ for OPT-80 against a collection of 135 isolates of *C. difficile* to be 0.25 mcg/mL while the OP-1118 MIC₉₀ against the same 135 isolates was 8 mcg/mL. Thus the OPT-80 metabolite may have some clinical activity against *C. difficile* but it is reduced relative to the parent compound OPT-80.

OPT-80 Related Substance Profiling Against Facultative Bacteria and *C. difficile*

OPT-80 drug substance contains, in addition to the primary component (OPT-80) at least 11 related substances. These related substances were profiled against *C. difficile* and a panel of facultative bacteria, including *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Staphylococcus epidermidis*, *Neisseria gonorrhoeae*, *Enterococcus faecalis*, and vancomycin-resistant *Enterococcus faecium* (VRE). None of the related substances had the same activity as the parent compound against *C. difficile*; however, one substance (OP-1405) had MICs against the various bacteria that were within 1-4 dilutions of OPT-80. The other compounds had less activity than OP-1405 (Study report BIO053006A).

Interaction of All Excipients in the Drug Product with the Active Component OPT-80 and its Metabolite OP-1118

For all excipients comprising the drug product, fidaxomicin and OP-1118 MICs in the presence of the excipient were the same or within one dilution of MICs in the absence of excipient, indicating lack of drug-excipient interaction as measured by *C. difficile* antimicrobial susceptibility.

MECHANISM OF ACTION

OPT-80 inhibits RNA synthesis in *Escherichia coli* and *Bacillus subtilis* from the DNA template (transcription) by inhibiting the action of *E. coli* and *Bacillus subtilis* RNA polymerases. Inhibition of *Bacillus* enzyme occurs at a concentration (0.5 μM), two orders of magnitude lower than that for *E. coli* (10-50 μM), possibly explaining the significant species variation of OPT-80 activity. The Applicant states that they have verified that OPT-80 is a RNA polymerase inhibitor, with an IC₅₀ for the *E. coli* enzyme on the order of 25 μM (Study reports BIO012204A and BIO090203A). Order of addition experiments indicate that OPT-80 binds prior to the formation of transcriptionally active, fully melted open complex, and this is supported by the observation that OPT-80 does not destabilize the open complex (Study report Artsimovitch 2010). Additional results suggest that bacterial RNA polymerase (RNAP) is the target of OPT-80 and its

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metabolite OP-1118 and suggests that the RNAP RNA exit-channel and switch region (where Asp237 resides) may be involved in inhibition (Study report BIO042010A). The mode of action of OPT-80 is distinct from macrolide antimicrobials in that OPT-80 interferes with transcription by inhibiting RNA polymerase while macrolides interfere with translation by acting at the ribosomal level of protein synthesis.

MECHANISM(S) OF RESISTANCE

The Applicant in a previous submission (IND 64,435, 20 Aug 03) speculated (no data provided) that resistance to OPT-80 may be caused by an efflux pump mechanism but note that organisms (*Staphylococcus* and *Streptococcus*) containing the macrolide efflux pumps *mefA* and *msrA* showed no increase in MIC versus the wild type organism. Studies on target modifications done by the Applicant did not explain the wide gap in MIC between resistant and wild-type organisms (>250 fold), which suggests that resistance to OPT-80 is caused by an alternate mechanism.

The Applicant provided the results of a study done with an isolate of *C. difficile* from a patient who had CDI recurrence after completion of a ten day course of fidaxomicin. In this study the genes making up the RNA polymerase core (*rpoA*, *rpoB*, and *rpoC*) were sequenced and analyzed for amino acid mutations. The conclusion from this study was that the *rpoB* Val1143Gly mutation, located within the RNAP exit channel and switch region, may interfere with fidaxomicin binding or allow RNAP to circumvent altered RNAP conformation transitions induced by fidaxomicin (Study report BIO060910A).

The Applicant in a previous submission (IND 64,435, 20 Aug 03) also provided information on resistance development to OPT-80. They indicated that resistance developed in two ATCC strains of *C. difficile* (9689 and 43255) at a rate of $<2.3 \times 10^8$ and $<1.5 \times 10^8$ respectively. The Applicant noted in a previous submission (IND 64,435, 20 Aug 03) that that the spontaneous rate of resistance for five clinical isolates of *C. difficile* were $<3 \times 10^8$.

The Applicant in a previous submission indicated (IND 64,435, 20 Aug 03) that after 13 serial passages of *C. difficile* ATCC 43255 in one half the initial MIC of the strain (0.0625 $\mu\text{g/mL}$), the MIC increased to 2 $\mu\text{g/mL}$. The Applicant noted that the MIC did not decrease after subculture of the organism several times to media not containing OPT-80.

Cross Resistance

The Applicant provided information on cross-resistance. In these studies an OPT-80 resistant isolate of *C. difficile* was produced in the laboratory by serially passing it against steadily increasing concentrations of OPT-80. An isolate with an OPT-80 MIC of 32 mcg/mL was produced after 20 passages. When this OPT-80 resistant *C. difficile* was tested against rifampin, azithromycin, ampicillin, metronidazole, vancomycin and

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clindamycin the MICs for these drugs were similar (+/- one dilution) to the parent isolate of the OPT-80 resistant *C. difficile*.

INTRACELLULAR CONCENTRATION AND POST LEUKOCYTE EFFECT (PALE)

The Applicant on the intracellular activity of OPT-80 or any of its metabolites provides no information.

POST ANTIBIOTIC EFFECT (PAE)

Data on the PAE of OPT-80 was submitted in a previous submission (IND 64,435, 20 Aug 03). The PAE of OPT-80 was measured versus a laboratory isolate of *C. difficile*, ATCC 43255, as well as a human clinical isolate (LC3). Following a one hour exposure of the organism to four times the MIC in broth, the antibiotic was removed and the bacterial titer was measured at various time points. The PAE was measured as the length of time required for the titer to increase by one log. It was noted that the PAE lasted for more than 24 hours. In a later report (BIO101609A) the 24 hour PAE was called incorrect by the Applicant because they felt it was due to residual drug. The PAE for *C. difficile* ranges from 5.5 to 12.5 depending on the *C. difficile* isolate used in the experiments. For OP-1118 the metabolite of OPT-80 the PAE was approximately 3 hours.

INTERACTION WITH OTHER DRUGS

Using the checkerboard method for determining the interaction of OPT-80 with other drugs and the excipient used in the formulation of fidaxomicin the Applicant found OPT-80 to be synergistic with rifampin against *C. difficile* ATCC 43255. Slight synergy was found with ampicillin. OPT-80 was not synergistic or antagonistic with azithromycin, telithromycin, ciprofloxacin, metronidazole, vancomycin or Labrasol. Labrasol is the excipient used in the OPT-80 drug product (study report BIO081903A). Interaction of the OPT-80 metabolite OP-1118 with other drugs was also studied using the checkerboard method. No antagonism was demonstrated with ampicillin, azithromycin, clindamycin, metronidazole, rifampicin, rifaximin, telithromycin, and vancomycin. Synergistic activity was found with rifampicin, and rifaximin while marginal synergy was demonstrated with ampicillin, and metronidazole. Interactions with the macrolide azithromycin and the ketolide telithromycin were borderline between synergy and indifference. ampicillin, clindamycin and metronidazole. Interactions with ciprofloxacin and vancomycin with OP-1118 were indifferent (Study report BIO021109A).

SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE

The Applicant at the beginning of the development of OPT-80 indicated that all susceptibility testing would be done by National Committee for Clinical Laboratory

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Standards (NCCLS) methods. This was agreeable to this reviewer. Since that time NCCLS has changed it is name to Clinical and Laboratory Standards Institute (CLSI).

Effect of Different Factors on Results of In Vito Susceptibility Testing

Because a variety of factors and conditions can effect the outcome of in vitro susceptibility tests the Applicant has provided information on a variety of those factors in relation to the in vitro susceptibility testing of Difcid against *C. difficile*. The information provided indicates that by using the CLSI method of susceptibility testing of anaerobes (22) that the results would be appropriate.

Factor 1: pH

Growth of *C. difficile* at a pH of 5 in the micro-broth system was poor with growth improving with increasing pH. The MICs of OPT-80 also increased in the micro-broth method with increasing pH. Above pH 6.5 the log of the MIC values increased in a roughly linear fashion with the pH.

Factor 2: Calcium and magnesium

The susceptibility of *C. difficile* was found to be unaffected by calcium or magnesium cation concentration.

Factor 3: Inoculum density

An inoculum density ranging from 10^5 to 10^8 CFU/mL (10^2 - 10^5 CFU/spot) was used in susceptibility tests and it was found that the MIC of PAR-101 was unaffected while the MIC of vancomycin increased progressively with increasing inoculum concentration.

QUALITY CONTROL FOR IN VITRO SUSCEPCTIBILITY TESTING OF ISOLATES

The Sponsor in a previous submission (20 Jul 04, pg. 253) had provided preliminary quality control strains and MIC ranges for the proposed quality control bacteria.

The choice of QC organisms was done using the method described in CLSI document M-23 (21). The company had a study conducted (Study # BIO091306) to determine what organism would best serve as a quality control organism when determining the susceptibility of *C. difficile* isolates to OPT-80. It was decided that *C. difficile* ATCC 700057 would be that organism. In a study to determine the OPT-80 quality control range as recommended in CLSI publication M-23 (21) that for *C. difficile* ATCC 700057 the range is 0.06 – 0.25 mcg/mL. After a review of the data this Reviewer agrees with the organism choice and QC range.

IN VIVO

Pharmacokinetics

Animal models

The Sponsor in a previous submission (IND 64,435, 20 Aug 03) referenced a paper by Swanson et al (15) that looked at the pharmacokinetics of OPT-80 in hamsters. This paper noted that a single oral dose of 25 mg/kg produced no detectable plasma levels, while the levels of OPT-80 in cecal contents reached a peak of 248 µg/gram six hours after administration. At 24 hours, cecal drug level was 58 µg/gram. The authors found that OPT-80 protected the hamsters from fatal colitis at a dose as low as 0.2 mg/kg/day while vancomycin failed at a dose of 5 mg/kg/day.

The Sponsor also provided in a previous submission (IND 64,435, 20 Aug 03, Vol. 2, pg. 423) information on pharmacokinetics in a rat. The Sponsor stated “at all time points following a single oral dose of 5.0 mg/kg, there was no detectable drug in the plasma or fecal contents of the small intestines or gastrointestinal tissues (small intestine, cecum, and colon). At eight hours after dosing cecal and colon contents were also below the LLOQ until the 24-hour samples, with the exception of one male at four and eight hours (cecum contents exhibited low levels of OPT-80). Trace amounts of OPT-80 were detected in the 24 and 48 hour fecal samples.”

Animal Models of Infection

The Sponsor in a previous submission (IND 64,435, 20 Aug 03) stated that the CDAD hamster model is a well-studied, reproducible model of fatal *C. difficile* disease that is suitable for evaluation of antimicrobial therapy (11,15). The Sponsor used this model to study the efficacy of OPT-80 to treat CDAD. In their previous submission (IND 64,435, 20 Aug 03, Vol. 2, pg. 420), the Sponsor provided data from two studies (E001, E002).

In studies E001 and E002, CDAD was induced in hamsters by a single intraperitoneal injection of 100 mg/kg of clindamycin 24 hours prior to oral administration of a toxigenic strain of *C. difficile*. In vivo efficacy of antibiotics was determined using two models of the disease, differing in the time at which therapy was started. In the standard “Early Therapy” CDAD disease model (E001 and E002) treatment was initiated eight hours post-infection.

The preferred formulation and efficacy of OPT-80 were identified in studies with the “Early Therapy Model” of disease (E001). Hamsters, in groups of five, were orally infected with a toxigenic strain of *C. difficile* (ATCC 43255-01). Immediately thereafter, three formulations, xanthan gum (a suspension), lecithin (an emulsion) and Labrasol® (a solution – caprylocaproyl macrogol-8 glycerides) were administered as a single dose of 2.5 mg/kg per day for five days. The hamsters were monitored for an additional 14 days.

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No animals treated with the Labrasol formulation died. However, animals treated with xanthan gum and lecithin formulations and those infected but untreated all died, albeit at various times before the end of the 15 day observation period. The Applicant noted that a *C. difficile* toxin test was not performed in this study.

The Labrasol formulation of OPT-80 was used in a dose response study (E002) to compare the efficacy of OPT-80 at 0.3, 0.8, and 2.5 mg/kg in the "Early Therapy Model". The data showed that all animals in the treatment groups (same groups as in E001, five animals/group) survived, indicating that the ED₅₀ of OPT-80 in the Labrasol formulation was <0.3 mg/kg in this model. From this data the Applicant concluded that Labrasol is the most effective excipient for OPT-80.

The Applicant in a previous submission (IND 64,435, 20 Aug 03) indicated that they were in the process of doing an evaluation of the efficacy and relapse potential in (E003) using animals infected with a toxigenic *C. difficile* strain (TTU 614). The strain of *C. difficile* to be used in this experiment was considered to be more virulent and produce a more reliable and consistent infection in the hamster CDAD model than *C. difficile* ATCC 43255-A01 used in previous experiments (IND 64,435, 20 Aug 03, Vol. 2, pg. 422). The animals were to be treated with varying doses of the Labrasol OPT-80 formulation and other antimicrobials eight hours post-infection. Antimicrobial administration was to be once daily for seven days and the animals monitored for 30 days following the final treatment. The assessments to be made were 1) survival rate of hamsters, 2) quality and frequency of animal stools, 3) evaluation of gastrointestinal microflora prior to start of experiment, 4) examination of bacterial content of feces to follow bacterial recolonization of the gastrointestinal tract, 5) examination for effects of potential for relapse, and 6) evaluation of feces for the presence of detectable *C. difficile* toxins A and B using a commercially available immunoassay kit. A summary of these experiments was provided in this submission and indicated that these experiments confirmed the ED₅₀ previously determined and showed fidaxomicin at 0.8 or 2.5 mg/kg to be as effective as vancomycin (5 mg/kg) or metronidazole (100 mg/kg) in rescuing animals from other wise fatal CDI.

In studies done by Swanson et al. (15) OPT-80 was used in an "Early Therapy Model" of CDAD in hamsters. In these studies, treatment started eight hours following inoculation of *C. difficile* ATCC 9689 and consisted of a single daily oral dose of OPT-80 (0.2 mg/kg/day) or vancomycin (5 mg/kg/day) for five days followed monitoring for a total of 35 days. No animals in the OPT-80 treated group died during administration of the drug or after 35 days. Animals in the vancomycin group did not die during administration of vancomycin but 60% died within the 35 days after treatment.

Human Studies

The Applicant in a previous submission (20 Jul 04) provided information from a Phase 1B, multiple dose-escalating safety study of OPT-80 in 24 healthy volunteers. The doses

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of OPT-80 evaluated (in three groups of eight subjects each) were 150, 300, and 450 mg administered orally after a morning breakfast for 10 consecutive days. At each dose level, six volunteers were randomized to receive active drug and two received placebo. Serial blood, urine, and fecal samples were collected at various time points/intervals during the multiple dosing periods. Plasma, urine and fecal concentrations of OPT-80 were determined for pharmacokinetic analysis. After multiple dose oral administration, plasma concentrations of OPT-80 were mostly below the limit of quantification across the dose range. Detectable plasma concentrations were found in 12 samples from six subjects. Of the 12 detectable concentrations, only two were significantly above the lower limit of quantification (LLOQ, 5 ng/mL), while others barely exceeded it. The two significant plasma levels, 11.1 and 48.0 ng/mL, were observed in subject 021 on day one, hour one and just prior to the tenth dose on day 10, respectively. The Applicant states that OPT-80 was well tolerated after multiple doses up to 450 mg daily for 10 days and there were no serious adverse events.

The Applicant indicated in their summary statement that normalized to the 150 mg dose, fecal OPT-80 averaged 9160 µg/g (138.4 – 2768.9 µg/g). This concentration of OPT-80 in the stool of healthy subjects is well above the MIC₉₀ (0.25 µg/mL) of *C. difficile* isolates tested to date. For a complete analysis of the data from studies conducted by the Applicant the reader is referred to Agency reviews done by biopharmacists and toxicologists. From a microbiology perspective, the information provided suggests that a concentration of OPT-80 can be achieved in the stool using the dosing regimen proposed by the Applicant that would be sufficient to kill *C. difficile* vegetative organisms in the intestines.

Data from a Phase 2A study (An Open-Label, Dose ranging, Randomized Clinical evaluation of OPT-80 in Patients with *Clostridium difficile*-associated Diarrhea) can be seen in Table 25. This study was done with 40 patients who received 100 mg (50 mg q12) or 200 mg (100mg q12 or 400 mg (200 mg q12) of OPT-80 for 10 days.

Table 25: Relief of Symptoms of CDI (Modified Intention-to-Treat [mITT] Population) (Study OPT-80 Phase 2A)

	Fidaxomicin 100mg/Day		Fidaxomicin 200mg/Day		Fidaxomicin 400mg/Day	
	n	%	n	%	n	%
Relief	6	(37.5)	8	(50.0)	13	(86.7)
No Relief	9	(56.3)	6	(37.5)	2	(13.3)
Unknown	1	(6.3)	2	(12.5)	0	(0.0)

Relief of symptoms of CDAD was defined as ≤3 bowel movements per day without other associated signs and symptoms such as fever, abdominal pain and elevated white blood cells (WBC) by Day 10 of the study. Subjects with any of these symptoms remaining by Day 10 were considered No Relief.

In relation to the proportion of patients cured following fidaxomicin treatment the number of patients cured increased with increasing dose: 14/16 (87.5%) subjects in the

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100 mg/day group, 14/16 (87.4%) of subjects in the 200 mg/day group and 15/15 (100%) of patients in the 400 mg/day group.

Fecal concentrations of fidaxomicin and OP1118 (metabolite of OPT-80) obtained on day 10 exhibited dose-related increase (Table 27). Subjects with the highest fecal concentrations (greater than 100 mcg/g) reported no AEs. The concentrations achieved in the stool are many times higher than the fidaxomicin MIC₉₀ (0.25 mcg/mL) needed to inhibit the growth of *C. difficile*.

Table 27: Fidaxomicin and OP-1118 Mean (Range) Fecal Concentrations, µg/g (Study OPT-80 Phase 2A)

Sample	Analyte	100mg/day	200mg/day	400mg/day
Day 10, µ/g	fidaxomicin	255.6 (81.9-558.3)	441.7 (11.7-786.7)	1433.3 (389-3974.8)
Day 10, µ/g	OP-1118	382.9 (140.8-1050.6)	430.1 (16.3-937.8)	759.5 (211.0-1535.2)

Microbiology studies

During the studies fecal samples for microbiological testing were obtained at the screening/enrollment and early termination visits. If an early termination assessment was not performed and the subject was deemed a failure on study day 10 or 11, the fecal sample was to have been obtained at the EOT visit. A fecal sample was collected at the recurrence visit from subjects who met the criteria for diarrhea and who were considered recurrences.

Fecal specimens were tested for the presence of *C. difficile* toxins A and B primarily using enzyme-linked immunoabsorbent assays. While these tests are not as sensitive as PCR they are specific and represent a more easily available method of detecting the toxins for clinical laboratories.

Fecal samples (at entry and for treatment failures and recurrence subjects) were cultured and *C. difficile* isolates were tested for their susceptibility to study drugs plus other drugs that might be used to treat CDAD by Clinical and Laboratory Standards (CLSI) methods (22). Isolates were also subjected to REA typing (23).

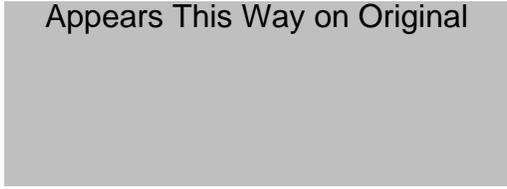
Fecal samples from subjects who failed treatment or who experienced recurrence were to have undergone the original diagnostic test for toxin. If the test was negative by a rapid screening test, a confirmatory test using a non-rapid assay was permitted to consider such stools negative. These samples were also cultured for isolation of *C. difficile*, and isolates of *C. difficile* were tested for their susceptibility to fidaxomicin and other antimicrobials. Isolates were also subjected to REA typing.

Phase 3 Studies

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Table 2.3-1 provides a description of the Phase 3 studies.

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Table 2.3-1. Description of Phase 3 Clinical Studies

Study ID	Number of Study Centers Enrolling subjects (Locations)	Study Start, Enrollment Status, Date, Total Enrollment/ Enrollment goal	Design Control Type	Study and Control Drugs Dose, Regimen, Route	Study Objective	# Subjects by Arm Treated/ Completed	Duration of treatment	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint
101.1. C.003	68 sites (52 USA, 16 Canada)	09 May 06 Completed 21 Aug 08 629/664	Randomized, double-blind, comparative study Vancomycin	Fidaxomicin 200 mg q12h Vancomycin 125 mg q6h Oral	To investigate the safety and efficacy of fidaxomicin versus vancomycin in subjects with CDI	Fidaxomicin 300/280 Vancomycin 323/295	10 days	263/333 Age 63 (18 to 94)	Male or non-pregnant female, ≥16 years old, with CDI and no more than 24 hours of pretreatment with vancomycin or metronidazole	Clinical cure
101.1. C.004	86 sites (30 USA, 12 Belgium, 11 Canada, 6 France, 8 Germany, 3 Italy, 5 Spain, 2 Sweden, 9 UK)	19 April 07 Completed 11 Dec 09 535/664	Randomized, double-blind, comparative study Vancomycin	Fidaxomicin 200 mg q12h Vancomycin 125 mg q6h Oral	To investigate the safety and efficacy of fidaxomicin versus vancomycin in subjects with CDI	Fidaxomicin 264/233 Vancomycin 260/234	10 days	199/310 Age 66 (18 to 94)	Male or non-pregnant female, ≥16 ¹ years old, with CDI and no more than 24 hours of pretreatment with vancomycin or metronidazole	Clinical cure

¹ ≥ 18 years old in Germany only

Cure Rates at the End of Therapy (EOT) in the mITT and PP Populations

Table 3.2-1 provides the Applicant’s overall summary of the efficacy results in each of the studies by per protocol (PP) and modified intent to treat (mITT) populations.

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Table 3.2-1. Summary of Clinical Cure Rates at End of Therapy in the Phase 3 Studies

	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹
PP population	247/268 (92.2)	251/280 (89.6)	2.5 (-2.4,7.3)	199/217 (91.7)	212/234 (90.6)	1.1 (-4.2,6.4)	446/485 (92.0)	463/514 (90.1)	1.9 (-1.7,5.4)
95% CI around PE ¹	(88.2,94.9)	(85.5,92.7)		(87.2,94.7)	(86.1,93.7)		(89.2,94.1)	(87.2,92.4)	
mITT population	255/289 (88.2)	263/307 (85.7)	2.6 (-2.9, 8.0)	222/253 (87.7)	222/256 (86.7)	1.0 (-4.8, 6.8)	477/542 (88.0)	485/563 (86.1)	1.9 (-2.1,5.8)
95% CI around PE ¹	(84.0,91.5)	(81.3,89.2)		(83.1,91.2)	(82.0,90.4)		(85.0,90.5)	(83.0,88.8)	

¹ 2-sided 95% CI using method recommended by Agresti and Caffo, 2000

PE = point estimate

Reference: Integrated Summary of Efficacy, Tables 14.2.1.1.1 and 14.2.1.1.2

The primary endpoint of both studies was the clinical cure at the End of Therapy (EOT) visit. The secondary and exploratory endpoints were rate of recurrence, global cure rate, and time to resolution of diarrhea.

Global Cure Rates

“Global Cure” is defined as achieving cure at the EOT visit and not having a recurrence any time up to the post-study visit (28 days post therapy). Table 6.3-1 shows the “Global Cure Rates” by various subgroup variables. The “Global Cure Rates” are shown for the mITT population only because the results were similar for the PP population. Overall the “Global Cure Rates” for Dificid were higher then for vancomycin. There were particular factors that decreased the cure rates for both Dificid and vancomycin such as increased age, metronidazole failure prior to study drug, use of systemic antibiotics during treatment period for CDAD.

6.3 Global Cure Rate

A number of subgroup variables showed an association with global cure rate in the mITT population for the pooled analysis (Table 6.3-1), with similar results being seen in the PP population (Integrated Summary of Efficacy, Tables 14.2.3.2.2 to 14.2.3.12.2, 14.2.3.2.4, and 14.2.3.9.5.2). These variables were stratum (lower global cure rate for subjects with a prior episode); use of CDI therapy within 24 hours of first dose of study treatment (users had a lower global cure rate); subject status (inpatients had a lower global cure rate than

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outpatients); disease severity at baseline (subjects with severe disease had a lower global cure rate than those with non-severe disease); BI strain versus non-BI strain (lower global cure rate for BI strain); use of systemic anti-infectives, both during the treatment and follow-up periods (users had a lower global cure rate); and use of concomitant antibiotics that were considered to have a potential impact on intestinal microflora (users had a lower global cure rate). In addition, a decrease in global cure rates were seen in both treatment groups with increasing age, related to the decrease in clinical cure rate and the increase in recurrence rates with increasing age, as noted previously. For the majority of the subgroup variables, the global cure rate for the fidaxomicin group was higher than that of the associated vancomycin group. For the variables where this difference was not seen, only a small number of subjects were included in the subgroups, so no meaningful conclusions can be drawn.

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Table 6.3-1. Summary of Global Cure Rates at End of Therapy by Subgroups in the Phase 3 Studies (mITT Population)

Subgroup	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95% CI ¹ p-value ²	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95% CI ¹ p-value ²	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95% CI ¹ p-value ²
mITT for all subjects	215/289 (74.4)	197/307 (64.2)	10.2 (2.8,17.5) p=0.007	194/253 (76.7)	162/256 (63.3)	13.4 (5.4, 21.1) p=0.001	409/542 (75.5)	359/563 (63.8)	11.7 (6.3,17.0) p<0.001
Age Group									
< 65	132/166 (79.5)	106/156 (67.9)	11.6 (1.9,20.9) p=0.018	89/111 (80.2)	84/125 (67.2)	13.0 (1.7,23.7) p=0.025	221/277 (79.8)	190/281 (67.6)	12.2 (4.9,19.3) p=0.001
65-74	37/48 (77.1)	43/65 (66.2)	10.9 (-5.9, 26.6) p=0.207	44/55 (80.0)	26/44 (59.1)	20.9 (2.7, 37.8) p=0.023	81/103 (78.6)	69/109 (63.3)	15.3 (3.1, 26.9) p=0.014
≥ 75	46/75 (61.3)	48/86 (55.8)	5.5 (-9.6, 20.3) p=0.479	61/87 (70.1)	52/87 (59.8)	10.3 (-3.8, 24.0) p=0.153	107/162 (66.0)	100/173 (57.8)	8.2 (-2.1, 18.4) p=0.121
Sex									
Male	90/125 (72.0)	88/138 (63.8)	8.2 (-3.1, 19.2) p=0.154	79/104 (76.0)	56/95 (58.9)	17.0 (4.0, 29.4) p=0.010	169/229 (73.8)	144/233 (61.8)	12.0 (3.5, 20.3) p=0.006
Female	125/164 (76.2)	109/169 (64.5)	11.7 (1.9, 21.2) p=0.019	115/149 (77.2)	106/161 (65.8)	11.3 (1.3, 21.1) p=0.027	240/313 (76.7)	215/330 (65.2)	11.5 (4.5, 18.4) p=0.001
Race									
White	189/254 (74.4)	166/265 (62.6)	11.8 (3.8, 19.6) p=0.004	177/233 (76.0)	148/237 (62.4)	13.5 (5.2, 21.6) p=0.002	366/487 (75.2)	314/502 (62.5)	12.6 (6.8, 18.3) p<0.001
Black	22/30 (73.3)	24/33 (72.7)	0.6 (-20.8,21.7) p=0.957	14/17 (82.4)	12/17 (70.6)	11.8 (-16.6,37.6) p=0.419	36/47 (76.6)	36/50 (72.0)	4.6 (-12.7,21.4) p=0.605
Asian	4/4 (100.0)	6/7 (85.7)	14.3 (-32.2,43.3) p=0.428	2/2 (100.0)	1/1 (100.0)	0.0 (-51.5,68.1)	6/6 (100.0)	7/8 (87.5)	12.5 (-24.5,39.5) p=0.369
American Indian/Alaska Native	0/1 (0.0)	1/2 (50.0)	-50.0 (-80.3,47.0) p=0.387	1/1 (100.0)	1/1 (100.0)	0.0 (-65.3,65.3)	1/2 (50.0)	2/3 (66.7)	-16.7 (-68.8,48.8) p=0.709

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Subgroup	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹ p-value ²	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹ p-value ²	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹ p-value ²
Country									
Canada	99/124 (79.8)	83/121 (68.6)	11.2 (0.3, 21.9) p=0.044	58/79 (73.4)	51/82 (62.2)	11.2 (-3.2, 25.1) p=0.128	157/203 (77.3)	134/203 (66.0)	11.3 (2.6, 19.9) p=0.011
USA	116/165 (70.3)	114/186 (61.3)	9.0 (-0.9, 18.7) p=0.076	55/74 (74.3)	48/76 (63.2)	11.2 (-3.6, 25.4) p=0.141	171/239 (71.5)	162/262 (61.8)	9.7 (1.5, 17.8) p=0.021
Belgium	NA	NA	NA	19/22 (86.4)	11/20 (55.0)	31.4 (3.7, 53.8) p=0.025	19/22 (86.4)	11/20 (55.0)	31.4 (3.7, 53.8) p=0.025
Germany	NA	NA	NA	14/18 (77.8)	13/19 (68.4)	9.4 (-18.7, 35.4) p=0.522	14/18 (77.8)	13/19 (68.4)	9.4 (-18.7, 35.4) p=0.522
Spain	NA	NA	NA	2/5 (40.0)	2/4 (50.0)	-10.0 (-57.6, 43.3) p=0.764	2/5 (40.0)	2/4 (50.0)	-10.0 (-57.6, 43.3) p=0.764
France	NA	NA	NA	9/11 (81.8)	6/8 (75.0)	6.8 (-28.0, 41.9) p=0.719	9/11 (81.8)	6/8 (75.0)	6.8 (-28.0, 41.9) p=0.719
UK	NA	NA	NA	21/26 (80.8)	15/27 (55.6)	25.2 (0.2, 46.6) p=0.049	21/26 (80.8)	15/27 (55.6)	25.2 (0.2, 46.6) p=0.049
Italy	NA	NA	NA	14/14 (100.0)	11/13 (84.6)	15.4 (-9.0, 36.5) p=0.127	14/14 (100.0)	11/13 (84.6)	15.4 (-9.0, 36.5) p=0.127
Sweden	NA	NA	NA	2/4 (50.0)	5/7 (71.4)	-21.4 (-63.8, 30.5) p=0.477	2/4 (50.0)	5/7 (71.4)	-21.4 (-63.8, 30.5) p=0.477
Stratum									
No Prior Episode	182/241 (75.5)	164/253 (64.8)	10.7 (2.6, 18.6) p=0.010	164/213 (77.0)	141/220 (64.1)	12.9 (4.3, 21.2) p=0.003	346/454 (76.2)	305/473 (64.5)	11.7 (5.9, 17.5) p<0.001
Single Prior Episode	33/48 (68.8)	33/54 (61.1)	7.6 (-10.7, 25.3) p=0.420	30/40 (75.0)	21/36 (58.3)	16.7 (-4.4, 36.2) p=0.123	63/88 (71.6)	54/90 (60.0)	11.6 (-2.3, 25.0) p=0.103
CDI Antibiotic 24 Hours Prior to Study									
Yes	73/112 (65.2)	71/122 (58.2)	7.0 (-5.4, 19.1) p=0.273	70/98 (71.4)	55/97 (56.7)	14.7 (1.3, 27.6) p=0.032	143/210 (68.1)	126/219 (57.5)	10.6 (1.4, 19.5) p=0.024
No	141/176 (80.1)	126/185 (68.1)	12.0 (3.0, 20.8) p=0.009	124/155 (80.0)	107/159 (67.3)	12.7 (3.0, 22.1) p=0.011	265/331 (80.1)	233/344 (67.7)	12.3 (5.7, 18.8) p<0.001
Metronidazole Failure Prior to Study									
Yes	11/13 (84.6)	13/17 (76.5)	8.1 (-21.2, 33.8) p=0.581	11/12 (91.7)	7/9 (77.8)	13.9 (-17.8, 43.8) p=0.368	22/25 (88.0)	20/26 (76.9)	11.1 (-10.3, 30.7) p=0.300
No	204/276 (73.9)	184/290 (63.4)	10.5 (2.8, 17.9) p=0.007	183/241 (75.9)	155/247 (62.8)	13.2 (5.0, 21.1) p=0.002	387/517 (74.9)	339/537 (63.1)	11.7 (6.2, 17.2) p<0.001
Anti-Infectives For Systemic Use During Treatment Period									
Yes	55/85 (64.7)	49/92 (53.3)	11.4 (-3.0, 25.3) p=0.122	49/70 (70.0)	40/70 (57.1)	12.9 (-3.0, 28.0) p=0.114	104/155 (67.1)	89/162 (54.9)	12.2 (1.4, 22.6) p=0.027
No	160/204 (78.4)	148/215 (68.8)	9.6 (1.1, 17.8) p=0.026	145/183 (79.2)	122/186 (65.6)	13.6 (4.5, 22.5) p=0.003	305/387 (78.8)	270/401 (67.3)	11.5 (5.3, 17.5) p<0.001

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Fidaxomicin Tablet
Integrated Summary of Efficacy

Optimer Pharmaceuticals, Inc.
Original Application

Subgroup	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹ p-value ²	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹ p-value ²	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹ p-value ²
Anti-Infectives For Systemic Use During Follow-up Period									
Yes	30/50 (60.0)	38/72 (52.8)	7.2 (-10.5, 24.3) p=0.430	46/67 (68.7)	41/64 (64.1)	4.6 (-11.4, 20.3) p=0.578	76/117 (65.0)	79/136 (58.1)	6.9 (-5.1, 18.6) p=0.264
No	185/239 (77.4)	159/235 (67.7)	9.7 (1.7, 17.6) p=0.017	148/186 (79.6)	121/192 (63.0)	16.5 (7.5, 25.3) p<0.001	333/425 (78.4)	280/427 (65.6)	12.8 (6.8, 18.7) p<0.001
Anti-Infectives For Systemic Use During Treatment or Follow-up Period									
Yes	67/101 (66.3)	65/113 (57.5)	8.8 (-4.2, 21.4) p=0.186	71/101 (70.3)	61/100 (61.0)	9.3 (-3.8, 22.0) p=0.165	138/202 (68.3)	126/213 (59.2)	9.2 (-0.1, 18.2) p=0.053
No	148/188 (78.7)	132/194 (68.0)	10.7 (1.8, 19.3) p=0.018	123/152 (80.9)	101/156 (64.7)	16.2 (6.3, 25.7) p=0.001	271/340 (79.7)	233/350 (66.6)	13.1 (6.5, 19.6) p<0.001
Anti-Infectives For Systemic Use During Treatment and Follow-up Period									
Yes	18/34 (52.9)	22/51 (43.1)	9.8 (-11.4, 30.2) p=0.375	24/36 (66.7)	20/34 (58.8)	7.8 (-14.3, 29.2) p=0.497	42/70 (60.0)	42/85 (49.4)	10.6 (-5.1, 25.6) p=0.188
No	197/255 (77.3)	175/256 (68.4)	8.9 (1.2, 16.5) p=0.024	170/217 (78.3)	142/222 (64.0)	14.4 (5.9, 22.6) p<0.001	367/472 (77.8)	317/478 (66.3)	11.4 (5.7, 17.0) p<0.001
Baseline Disease Severity									
Severe	45/74 (60.8)	45/81 (55.6)	5.3 (-10.1, 20.3) p=0.508	44/63 (69.8)	29/61 (47.5)	22.3 (5.1, 38.2) p=0.012	89/137 (65.0)	74/142 (52.1)	12.9 (1.3, 24.0) p=0.030
Non-severe	170/215 (79.1)	152/226 (67.3)	11.8 (3.5, 19.8) p=0.005	150/190 (78.9)	133/195 (68.2)	10.7 (1.9, 19.3) p=0.017	320/405 (79.0)	285/421 (67.7)	11.3 (5.3, 17.2) p<0.001
Subject Status									
Inpatient	112/168 (66.7)	106/186 (57.0)	9.7 (-0.4, 19.6) p=0.062	132/175 (75.4)	106/172 (61.6)	13.8 (4.0, 23.3) p=0.006	244/343 (71.1)	212/358 (59.2)	11.9 (4.9, 18.8) p<0.001
Outpatient	103/121 (85.1)	91/121 (75.2)	9.9 (-0.2, 19.7) p=0.053	62/78 (79.5)	56/84 (66.7)	12.8 (-0.9, 25.8) p=0.067	165/199 (82.9)	147/205 (71.7)	11.2 (3.0, 19.2) p=0.007
Initial Strain of CDI³									
BI	44/76 (57.9)	52/82 (63.4)	-5.5 (-20.4, 9.6) p=0.478	42/65 (64.6)	31/60 (51.7)	12.9 (-4.2, 29.4) p=0.142	86/141 (61.0)	83/142 (58.5)	2.5 (-8.8, 13.8) p=0.663
Non-BI	105/126 (83.3)	87/131 (66.4)	16.9 (6.3, 27.0) p=0.002	109/131 (83.2)	77/121 (63.6)	19.6 (8.7, 29.9) p<0.001	214/257 (83.3)	164/252 (65.1)	18.2 (10.6, 25.5) p<0.001
Age Group³									
< 65	132/166 (79.5)	106/156 (67.9)	11.6 (1.9, 20.9) p=0.018	89/111 (80.2)	84/125 (67.2)	13.0 (1.7, 23.7) p=0.025	221/277 (79.8)	190/281 (67.6)	12.2 (4.9, 19.3) p=0.001
≥ 65	83/123 (67.5)	91/151 (60.3)	7.2 (-4.2, 18.3) p=0.217	105/142 (73.9)	78/131 (59.5)	14.4 (3.2, 25.2) p=0.011	188/265 (70.9)	169/282 (59.9)	11.0 (3.1, 18.8) p=0.007
Concomitant Antibacterials Considered to have Potential Impact on Intestinal Microflora³									
Yes	47/73 (64.4)	53/98 (54.1)	10.3 (-4.5, 24.5) p=0.176	61/83 (73.5)	43/69 (62.3)	11.2 (-3.7, 25.6) p=0.140	108/156 (69.2)	96/167 (57.5)	11.7 (1.2, 21.9) p=0.029
No	168/216 (77.8)	144/209 (68.9)	8.9 (0.5, 17.1) p=0.038	133/170 (78.2)	119/187 (63.6)	14.6 (5.2, 23.6) p=0.003	301/386 (78.0)	263/396 (66.4)	11.6 (5.3, 17.7) p<0.001

¹ 2-sided 95% CI using method recommended by Agresti and Caffo, 2000

² p-value using Pearson's exact chi-square test

³ Added as post-hoc analyses

Reference: Integrated Summary of Efficacy, Tables 14.2.3.2.1 to 14.2.3.12.1, 14.2.3.2.3 and 14.2.3.9.5.1

In Vitro Susceptibility of Initial Bacterial Stool Pathogens

The susceptibility of each initial isolate of *C. difficile* is summarized in Table 3.2-6 by presenting the geometric mean, minimum inhibitory concentration (MIC), the 50th percentile (MIC₅₀) and the 90th percentile (MIC₉₀).

The MIC information in Table 3.2-6 shows that the Difcid MIC₉₀ is 0.25 mcg/mL for studies 0.003 and 0.004. Table 3.2-7 indicates that of the various ribotypes of *C. difficile* obtained during the studies that those belonging to ribotype 27 (BI) tend to have a higher Difcid MIC (0.25 mcg/mL versus 0.125 mcg/mL) then do isolates belonging to the other ribotypes. The vancomycin MIC tends to be consistent across the various biotypes at 1 mcg/mL. The MIC of 0.25 mcg/mL for metronidazole also tends to be consistent across the majority of isolates. Rifaximin has the lowest MICs for the various ribotypes. The fidaxomicin MIC₉₀ of 0.25 mcg/mL seen for the study isolates is similar to the fidaxomicin MIC₉₀ seen for surveillance isolates obtained prior to the clinical studies.

Table 3.2-6. Susceptibilities of Baseline Strains (in µg/mL) Towards Fidaxomicin, Vancomycin, Metronidazole, and Rifaximin

Study (n)	Antibiotic	Geometric mean	Range	MIC ₅₀	MIC ₉₀
Phase 3 101.1.C.003 (n=415 mITT)	Fidaxomicin	0.10	0.003-0.5	0.125	0.25
	Vancomycin	0.80	0.25-4	1	2
	Metronidazole	0.47	0.02-4	0.5	1
	Rifaximin	0.03	0.003 -> 256	0.015	0.125
Phase 3 101.1.C.004 (n=376 mITT)	Fidaxomicin	0.11	0.007-1	0.125	0.25
	Vancomycin	1.23	0.25-8	1	2
	Metronidazole	0.50	0.05-4	0.5	1
	Rifaximin	0.02	0.003 -> 256	0.015	0.03

Reference: 101.1.C.003 CSR, Table 14.2.6.1; 101.1.C.004 CSR, Table 14.2.6.1.

Despite the differing geographic locations of these trials (101.1.C.003 was conducted in North America only but 101.1.C.004 was conducted in North America and Europe), the susceptibility profiles are quite similar for all antibiotics tested (with the exception of the rifaximin MIC₉₀). Thus, from a susceptibility standpoint, there is little to differentiate strains from different geographic locations.

Additionally the Applicant provides a summary of susceptibility by BI strain type (an epidemic hypervirulent *C. difficile* strain) versus non-B1 strain type, treatment group and clinical cure and failure (Table 3.2-7). BI and Non-BI types (Table 3.2-11) also provided the unique MIC distribution and associated cure rates. In Table 3.2-11 it can be seen that there were greater fidaxomicin and vancomycin success rate in patients who had *C. difficile* ribotype non-B1 then those who had B-1. However, the significance of this difference can not be determined due to the small numbers. The majority of the base-line *C. difficile* from patients who had recurrence had fidaxomicin MICs of less then 0.25 mcg/mL.

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Table 3.2-7. Strain Types Represented in Pooled Phase 3 Studies and their Susceptibilities (mITT population: MIC values in µg/mL)

REA Group	N	Antibiotic	Geometric Mean	Range (min-max)	MIC ₅₀	MIC ₉₀
BI Group (ribotype 027)	283	Fidaxomicin	0.18	0.015-1.0	0.25	0.5
		Vancomycin	1.03	0.5-8.0	1.0	2.0
		Metronidazole	0.87	0.125-4.0	1.0	2.0
		Rifaximin	0.05	0.003-257.0	0.015	257.0
BK Group (ribotype 078)	15	Fidaxomicin	0.09	0.03-0.25	0.125	0.125
		Vancomycin	1.10	0.5-2.0	1.0	2.0
		Metronidazole	0.44	0.25-2.0	0.5	1.0
		Rifaximin	0.02	0.003-257.0	0.015	0.015
CF Group	9	Fidaxomicin	0.09	0.015-0.25	0.125	0.25
		Vancomycin	0.86	0.5-2.0	1.0	2.0
		Metronidazole	0.31	0.05-1.0	0.5	1.0
		Rifaximin	0.04	0.008-257.0	0.015	257.0
DH Group	6	Fidaxomicin	0.22	0.125-0.25	0.25	0.25
		Vancomycin	1.00	1.0-1.0	1.0	1.0
		Metronidazole	0.50	0.25-1.0	0.5	1.0
		Rifaximin	0.01	0.003-0.015	0.009	0.015
G Group	58	Fidaxomicin	0.09	0.015-0.25	0.125	0.25
		Vancomycin	0.96	0.5-2.0	1.0	2.0
		Metronidazole	0.32	0.05-1.0	0.25	0.5
		Rifaximin	0.01	0.003-0.125	0.008	0.015
J Group (ribotype 001)	47	Fidaxomicin	0.02	0.007-0.125	0.02	0.125
		Vancomycin	1.05	0.5-4.0	1.0	4.0
		Metronidazole	0.44	0.05-2.0	0.5	1.0
		Rifaximin	0.02	0.003-257.0	0.008	0.06
K Group	17	Fidaxomicin	0.07	0.015-0.25	0.06	0.125
		Vancomycin	1.09	0.5-4.0	1.0	2.0
		Metronidazole	0.69	0.125-4.0	0.5	4.0
		Rifaximin	0.09	0.004-257.0	0.015	257.0
L Group	1	Fidaxomicin	0.13	0.125-0.125	0.125	0.125
		Vancomycin	0.50	0.5-0.5	0.5	0.5
		Metronidazole	0.50	0.5-0.5	0.5	0.5
		Rifaximin	0.13	0.125-0.125	0.125	0.125

REA Group	N	Antibiotic	Geometric Mean	Range (min-max)	MIC ₅₀	MIC ₉₀
Non-Sp REA	277	Fidaxomicin	0.08	0.003-0.5	0.06	0.125
		Vancomycin	0.94	0.25-4.0	1.0	2.0
		Metronidazole	0.33	0.02-2.0	0.25	0.5
		Rifaximin	0.02	0.003-257.0	0.008	0.125
Y Group	79	Fidaxomicin	0.10	0.015-0.5	0.125	0.25
		Vancomycin	0.84	0.25-2.0	1.0	2.0
		Metronidazole	0.37	0.06-2.0	0.25	1.0
		Rifaximin	0.01	0.003-0.125	0.008	0.015
All strains	792	Fidaxomicin	0.10	0.003-1.0	0.125	0.25
		Vancomycin	0.97	0.25-8.0	1.0	2.0
		Metronidazole	0.49	0.02-4.0	0.5	1.0
		Rifaximin	0.03	0.003-257.0	0.015	0.125

Reference: Integrated Summary of Efficacy, Table 14.2.7.2.1

Table 3.2-11. Cure Rates by MIC and Strain in Pooled Phase 3 Studies (mITT Population)

Arm, strain	MIC, µg/mL											
	0.007	0.015	0.02	0.03	0.06	0.125	0.25	0.5	1	2	4	8
Fidaxomicin												
BI n/N (%)	0/0	0/0	0/0	3/3 (100)	5/7 (71.4)	40/48 (83.3)	54/69 (78.3)	11/13 (84.6)	1/1 (100)	0/0	0/0	0/0
Non-BI n/N (%)	7/7 (100)	15/16 (93.8)	4/5 (80.0)	24/27 (88.9)	83/89 (93.3)	87/92 (94.6)	16/19 (84.2)	2/2 (100)	0/0	0/0	0/0	0/0
Vancomycin												
BI n/N (%)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	36/45 (80.0)	53/65 (81.5)	22/24 (91.7)	5/8 (62.5)	1/1 (100)
Non-BI n/N (%)	0/0	0/0	0/0	0/0	0/0	0/0	3/3 (100)	67/72 (93.1)	115/129 (89.1)	36/41 (87.8)	5/7 (71.4)	0/0

Reference: Integrated Summary of Efficacy, Table 14.2.7.1.1

Fecal Fidaxomicin and OP-1118 Concentrations at EOT (mcg/g) and Fidaxomicin: MIC Ratios in Pooled Phase 3 Studies (mITT Population)

The company made an effort to collect fecal specimens at the EOT in order to determine the fecal concentration of fidaxomicin and its metabolite OPT-1118. Table 3.2-12 presents summaries of fidaxomicin and its main metabolite OPT-1118 as well as fecal concentrations/MIC of the infecting *C. difficile* as a pharmacodynamic metric, for all subjects in the mITT population that provided both a fecal PK sample and had a *C. difficile* isolate. Since very few subjects experiencing a clinical failure in either trial had both a baseline isolate and an EOT fecal PK sample, and since the standard deviation for the fecal concentrations are very wide, it is not possible to correlate fecal concentration with clinical outcome.

Table 3.2-12. Fecal Fidaxomicin and OP-1118 Concentrations at EOT (µg/g) and Fidaxomicin: MIC Ratios in Pooled Phase 3 Studies (mITT Population)

Statistic	Fidaxomicin	OP-1118	Fidaxomicin/MIC
N	175	172	140
Mean (SD)	1396.88 ± 1018.85	834.14 ± 616.50	27466.51 ± 40046.16
Median	1210.00	699.50	15826.65
Range	5.0, 7630.0	63.4, 4170.0	160.4, 280000.0

Reference: Integrated Summary of Efficacy, Tables 14.2.8.1.1 and 14.2.8.2.1

Recurrence of Diarrhea

The definition of recurrence was the re-establishment of diarrhea to an extent (frequency of passed unformed stools) that was greater than that noted on the last day of study medication, with the demonstration of either toxin A or B or both of *C. difficile* and, in the investigator's opinion would require retreatment with CDI anti-infective therapy. For

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subjects who achieved cure, the recurrence rate of CDI of the treatment groups up to the post-study visit were compared in the mITT and PP populations.

Table 3.2-3 shows the recurrence data for both studies and the combined study results for the mITT and PP populations. As seen the recurrence rate for fidaxomicin in both the 003 and 004 groups and in both the mITT and PP populations was lower then for the vancomycin treated patients.

TABLE 3.2-3

3.2.3 Secondary Efficacy Parameters

CLINICAL RECURRENCE

In the pooled analysis and in each of the individual studies, the recurrence rate was consistently higher in the vancomycin groups compared to the fidaxomicin groups (Table 3.2-3). Similar results were seen in the PP and mITT populations. In all of the analyses the 95% CIs did not contain the value of zero, indicating a robust superiority of fidaxomicin over vancomycin in the risk of recurrence. The corresponding p-values show the superiority of fidaxomicin, proving a statistical significance favoring fidaxomicin, with these differences also being clinically meaningful.

Table 3.2-3. Summary of CDI Recurrence Rates in the Phase 3 Studies

	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹ p-value ²	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹ p-value ²	Fidaxo- micin n/N (%)	Vanco- mycin n/N (%)	Difference 95% CI ¹ p-value ²
mITT population	40/255 (15.7)	66/263 (25.1)	-9.4 (-16.2, -2.5) p=0.008	28/222 (12.6)	60/222 (27.0)	-14.4 (-21.6, -7.0) p<0.001	68/477 (14.3)	126/485 (26.0)	-11.7 (-16.7, -6.7) p<0.001
95% CI around PE ¹	(11.7,20.7)	(20.2,30.7)		(8.9, 17.7)	(21.6,33.3)		(11.4, 17.7)	(22.3, 30.1)	
PP population	28/213 (13.1)	53/219 (24.2)	-11.1 (-18.2, -3.7) p=0.003	23/181 (12.7)	46/181 (25.4)	-12.7 (-20.6, -4.6) p=0.002	51/394 (12.9)	99/400 (24.8)	-11.8 (-17.1, -6.4) p<0.001
95% CI around PE ¹	(9.2,18.4)	(19.0,30.3)		(8.6,18.4)	(19.6,32.3)		(10.0, 16.7)	(20.8,29.2)	

¹ 2-sided 95% CI using method recommended by Agresti and Caffo, 2000

² p-value using Pearson's exact chi-square test

Reference: Integrated Summary of Efficacy, Tables 14.2.2.1.1 and 14.2.2.1.2

Time to recurrence was also evaluated and showed that subjects treated with fidaxomicin experienced recurrence of CDI later than subjects treated with vancomycin (Figure 3.2-1). The results were statistically significant using both the log-rank test and the Wilcoxon-Gehan test in both the mITT and PP populations (Integrated Summary of Efficacy, Tables 14.2.4.1 and 14.2.4.2). Graphical representations of the time to recurrence, both for the pooled data and in the individual studies, are shown in Integrated Summary of Efficacy, Figure 14.2.4.1 for the mITT population, and in Integrated Summary of Efficacy, Figure 14.2.4.2 for the PP population.

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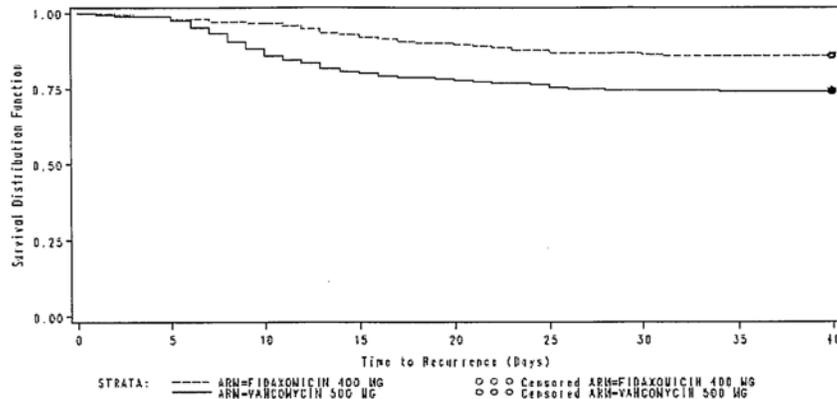


Figure 3.2-1. Time to Recurrence in Pooled Phase 3 Studies (mITT population)

Reference: Integrated Summary of Efficacy, Figure 14.2.4.1

Since both drugs may remain in the large bowel for several days, it is postulated that the early reduction in recurrence represents prevention of relapse from germination of the resident *C. difficile* spores, and within this time frame fidaxomicin was clearly more effective than vancomycin. However, CDI recurrence after 14 days, when both antibiotics have been cleared from the gut, more likely represents new infection from environmental sources, and indeed the rates of recurrence after 14 days were similar for both drugs.

The relation of the recurrence to strain type in both studies and for each population is shown in Tables 3.2-8 and 3.2-9. The hypervirulent strain designated as B-1 was associated more often with recurrence in the fidaxomicin treated population. However in the vancomycin treated populations this same differentiation is not that clear.

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Table 3.2-8. Outcomes by Strain Type in Studies 101.1.C.003 and 101.1.C.004 (PP Population)

Outcome	Study	Strain type	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Total n/N (%)
Clinical cure					
	101.1.C.003	BI	56/65 (86.2)	61/72 (84.7)	117/137 (85.4)
	101.1.C.003	Non-BI	115/119 (96.6)	119/126 (94.4)	234/245 (95.5)
	101.1.C.004	BI	49/55 (89.1)	45/52 (86.5)	94/107 (87.9)
	101.1.C.004	Non-BI	110/117 (94.0)	103/112 (92.0)	213/229 (93.0)
Recurrence					
	101.1.C.003	BI	11/45 (24.4)	13/55 (23.6)	24/100 (24.0)
	101.1.C.003	Non-BI	8/103 (7.8)	27/106 (25.5)	35/209 (16.7)
	101.1.C.004	BI	10/45 (22.2)	16/38 (42.1)	26/83 (31.3)
	101.1.C.004	Non-BI	9/100 (9.0)	23/90 (25.6)	32/190 (16.8)
Global cure					
	101.1.C.003	BI	40/65 (61.5)	48/72 (66.7)	88/137 (64.2)
	101.1.C.003	Non-BI	103/119 (86.6)	86/126 (68.3)	189/245 (77.1)
	101.1.C.004	BI	38/55 (69.1)	27/52 (51.9)	65/107 (60.7)
	101.1.C.004	Non-BI	100/117 (85.5)	74/112 (66.1)	174/229 (76.0)

Reference: 101.1.C.003 CSR, Table 14.2.1.5, Table 14.2.2.11, and Table 14.2.4.1.2; 101.1.C.004 CSR, Table 14.2.1.5, Table 14.2.2.11, and Table 14.2.4.1.2.

Table 3.2-9. Outcomes by Strain Type in Studies 101.1.C.003 and 101.1.C.004 (mITT Population)

Outcome	Study	Strain type	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Total n/N (%)
Clinical cure					
	101.1.C.003	BI	59/75 (78.7)	67/83 (80.7)	126/158 (79.7)
	101.1.C.003	Non-BI	117/125 (93.6)	121/132 (91.7)	238/257 (92.6)
	101.1.C.004	BI	54/65 (83.1)	47/57 (82.5)	101/122 (82.8)
	101.1.C.004	Non-BI	120/131 (91.6)	108/123 (87.8)	228/254 (89.8)
Recurrence					
	101.1.C.003	BI	16/59 (27.1)	14/67 (20.9)	30/126 (23.8)
	101.1.C.003	Non-BI	12/117 (10.3)	34/121 (28.1)	46/238 (19.3)
	101.1.C.004	BI	12/54 (22.2)	18/47 (38.3)	30/101 (29.7)
	101.1.C.004	Non-BI	11/120 (9.2)	30/108 (27.8)	41/228 (18.0)
Global cure					
	101.1.C.003	BI	43/75 (57.3)	53/83 (63.9)	96/158 (60.8)
	101.1.C.003	Non-BI	105/125 (84.0)	87/132 (65.9)	192/257 (74.7)
	101.1.C.004	BI	42/65 (64.6)	29/57 (50.9)	71/122 (58.2)
	101.1.C.004	Non-BI	109/131 (83.2)	78/123 (63.4)	187/254 (73.6)

Reference: 101.1.C.003 CSR, Table 14.2.1.3, Table 14.2.2.9, and Table 14.2.4.1.1; 101.1.C.004 CSR, Table 14.2.1.3, Table 14.2.2.9, and Table 14.2.4.1.1

Relationship of *C. difficile* Baseline MIC to Failure

Table 3.2-10 shows the fidaxomicin as well as vancomycin MIC for the base line *C. difficile* isolates for those patients that were determined to be cures and those that were determined to be failures.

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Table 3.2-10. Baseline Strain Susceptibilities Versus Outcome for Pooled Phase 3 Studies (mITT Population)

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

Reference: Integrated Summary of Efficacy, Table 14.2.7.3.1

Susceptibility of *C. difficile* Isolates at Baseline and Recurrence

The company did attempt to recover *C. difficile* isolates from patients that were determined to be failures. However, there was only limited success. Most likely this was due to the presence of the antibiotic in the specimen which inhibited the growth of the bacteria. However, in the fidaxomicin-treated subjects with baseline isolates, isolates were recovered at failure or recurrence for 16 subjects in study 101.1.C.003, and 13 subjects in study 101.1.C.004. In nearly all cases, the final isolate had the same MIC as the baseline isolate or was within one dilution of the baseline isolate MIC. There was one patient in the 101.1.C.004 study treated with fidaxomicin whose baseline *C. difficile* isolate had a fidaxomicin MIC of 0.06 mcg/mL who was a cure but whose stool was still positive for *C. difficile*. This patient went on to have recurring disease and the *C. difficile* isolate obtained from the stool at this time had a fidaxomicin MIC of 16 mcg/mL. Ribotyping of the original isolate and the isolate from the time of recurrence could not determine if the strains were similar since they both were typed as “non-specified REA type). The company has suggested two scenarios. The one scenario being that the isolate developed resistance during treatment with fidaxomicin. Their alternate explanation is that there was reinfection with a strain having an innately lower susceptibility to fidaxomicin, although an MIC of >2 mcg/mL has not been seen previously in the wild type population. The company provided information that shows that the isolate obtained

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from the recurrence episode had a single mutation (VAl143Gly) in the beta subunit of RNA polymerase. The company in a laboratory derived *C. difficile* mutant displaying decreased susceptibility to fidaxomicin (Study B10091206A) reported this same mutation.

The company reported that in the vancomycin group, Subject 003-011-068 from Study 101.1.c.003 had an MIC increase greater than the expected on dilution difference. The strain identified at recurrence, however, was a different REA group from the Day 1 isolate, which suggests that this subject's recurrence was due to infection by a new strain. This information is in the following table.

Subject Number	MIC (µg/mL)				REA Grouping
	OPT-80	Vanco	Met	Rifax	
003-011-068 (Day 1 isolate)	0.06	0.5	0.5	0.015	Y group
003-011-068 (Recurrence isolate)	0.03	4	1	257	BI group

CONCLUSION and COMMENTS

See page 2.

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