Antimicrobial Activities of Fidaxomicin

Ellie J. C. Goldstein,[1,2] Farah Babakhani,[3] and Diane M. Citron[1]

[1]RM Alden Research Laboratory, Culver City, [2]David Geffen School of Medicine, University of California, Los Angeles, and [3]Optimer Pharmaceuticals, Inc., San Diego, California

Fidaxomicin is bactericidal against *Clostridium difficile*. The combined results of 8 in vitro studies of 1323 *C. difficile* isolates showed the minimum inhibitory concentration (MIC) range of fidaxomicin to be ≤0.001–1 μg/mL, with a maximum MIC for inhibition of 90% of organisms (MIC_{90}) of 0.5 μg/mL. Isolates from 2 phase III clinical trials demonstrated that fidaxomicin MICs of baseline isolates did not predict clinical cure, failure, or recurrence of *C. difficile* infections. No resistance to fidaxomicin developed during treatment in either study, although a single strain recovered from a cured patient had an elevated MIC of 16 μg/mL at the time of recurrence. For 135 strains, OP-1118, a major metabolite, had an MIC for inhibition of 50% of organisms of 4 μg/mL and an MIC_{90} of 8 μg/mL. Changes in inoculum size (10^2–10^5 colony-forming units/spot) or cation concentrations of calcium or magnesium appeared to have no effect on fidaxomicin MICs. Fidaxomicin has little or no activity against gram-negative aerobes and anaerobes or yeast.

In 1991, Swanson et al [1] evaluated the in vitro activity of tiacumicin B (now fidaxomicin) isolated from the fermentation broth of *Dactylosporangium aurantiacum* subspecies *hamdenensis* [2] against *Clostridium difficile*. Fidaxomicin (formerly designated OPT-80 and PAR-101) has been developed for the treatment of *C. difficile*–associated diarrhea and is a potent new macrocyclic antibiotic that targets RNA polymerase. Fidaxomicin has a narrow spectrum of activity, with little or no activity against gram-negative aerobic and anaerobic bacteria, but demonstrates high activity against *C. difficile* (Table 1) [3]. Fidaxomicin reaches a high concentration in the gut with minimal systemic absorption. This article reviews and provides original data for the antimicrobial activity of fidaxomicin, including variations of test conditions and activity of its metabolite OPT-1118, as well as its kill kinetics and pharmacodynamics as related to *C. difficile*.

Correspondence: Ellie J. C. Goldstein, MD, 2021 Santa Monica Blvd, Ste #740 East, Santa Monica, CA 90404 (ejcgmd@aol.com).

Clinical Infectious Diseases 2012;55(S2):S143–8

DOI: 10.1093/cid/cis339

Comparative In Vitro Studies

Eight studies performed on strains isolated between 1983 and 2010 have reported the comparative in vitro activity of fidaxomicin against *C. difficile* [1, 4–10] (Table 2). A combined total of 1323 isolates were reported with a minimum inhibitory concentration (MIC) range of ≤0.001–1 μg/mL and a maximum MIC for inhibition of 90% of organisms (MIC_{90}) of 0.5 μg/mL, which are far below the fidaxomicin levels found in feces after treatment.

Hecht et al [6] reported on the in vitro activity of fidaxomicin against 110 toxigenic *C. difficile* clinical isolates collected during 1983–2004 in the United States, South America, and Europe. With the use of the Clinical and Laboratory Standards Institute (CLSI) [11] supplemented Brucella agar dilution method, the fidaxomicin geometric mean MIC was 0.081 μg/mL, with a maximum MIC of 0.25 μg/mL and an MIC_{90} of 0.125 μg/mL. They did not note any variation of MIC related to year of isolation or restriction endonuclease analysis (REA) BI group status. A German study [4] that used the Wilkins-Chalgren broth microdilution method on isolates collected between 1986 and 2002 showed that all *C. difficile* strains were susceptible to ≤0.06 μg/mL of fidaxomicin and confirmed low MICs by agar dilution for a subset of isolates. A Manitoba, Canada, study [8] that used the CLSI agar dilution method on isolates collected between January and

Table 1. Antimicrobial Profile of Fidaxomicin for Various Aerobic and Anaerobic Bacteria and Yeast

Gram-Negative Bacteria			Gram-Positive Bacteria			Yeast		
Strain	ATCC No.	FDX MIC	Strain	ATCC No.	FDX MIC	Strain	ATCC No.	FDX MIC
Acinetobacter baumannii	19606	>32	*Bacillus cereus*	11778	1	Yeast		
Acinetobacter calcoaceticus	23055	1	*B. cereus*	14579	1	*Candida albicans*	24433	>64
Bacteroides distasonis	8503	>32	*Clostridium difficile*	43255	0.125	*C. albicans*	90028	>64
Bacteroides fragilis	23745	>32	*C. difficile*	9689	0.06	*C. albicans*	14053	>64
B. fragilis	25285	>32	*C. difficile*	17857	0.031	*Candida krusei*	6258	>64
Bacteroides ovatus	8483	>32	*Clostridium perfringens*	13124	≤0.015	*Candida glabrata*	2001	>64
Bacteroides uniformis	8492	>32	*Enterococcus faecalis*	19433	4	*Candida lusitaniae*	66035	>64
Campylobacter jejuni	29428	64	*Enterococcus faecium*	19434	4	*Candida parapsilosis*	22019	>64
C. jejuni	33291	>64	*E. faecium*	49032	4	*Candida tropicalis*	750	>64
C. jejuni	49943	64	*E. faecium*	700221	4			
Citrobacter braakii	43162	>64	*Lactobacillus acidophilus*	4356	>32			
Citrobacter freundii	43864	>64	*Lactobacillus casei*	393	1			
Enterobacter aerogenes	35028	>64	*Lactobacillus rhamnosus*	7469	16			
E. aerogenes	13048	>64	*Micrococcus luteus*	381	≤0.125			
Enterobacter cloacae	49141	>64	*M. luteus*	49732	≤0.125			
E. cloacae	23355	>32	*M. luteus*	533	≤0.125			
Escherichia coli	25922	>32	*M. luteus*	4698	≤0.06			
Fusobacterium nucleatum	25586	>32	*Peptostreptococcus anaerobius*	27337	≤0.06			
Haemophilus influenzae	49247	>32	*Peptostreptococcus (Peptoniphilus) asaccharolyticus*	29743	1			
Helicobacter pylori	43504	>32	*Peptococcus (Finegoldia) magna*	29328	0.5			
Klebsiella oxytoca	43165	>64	*Peptococcus (Micromonas) micros*	33270	0.125			
K. oxytoca	49131	>64	*Propionibacterium acnes*	11827	8			
Klebsiella pneumoniae	33495	>64	*P. acnes*	6919	8			
K. pneumoniae	27736	>64	*Staphylococcus aureus*	33591	8			
K. pneumoniae	13883	>32	*S. aureus*	25923	16			
Moraxella catarrhalis	25238	2	*S. aureus*	29213	8			
M. catarrhalis	49143	1	*Staphylococcus epidermidis*	12228	1			
Neisseria meningitidis	13077	64	*S. epidermidis*	14990	1			
Neisseria gonorrhoeae	19424	8	*Staphylococcus intermedius*	29663	4			
N. gonorrhoeae	49226	32	*Streptococcus agalactiae*	12386	16			
Neisseria lactamica	23970	32	*S. agalactiae*	13813	32			
Porphyromonas asaccharolytica	25260	32	*Streptococcus pyogenes*	19615	16			
Prevotella loescheii	15930	>32	*Streptococcus pneumoniae*	49619	>32			
Proteus mirabilis	25933	>64	*Streptococcus sanguinis*	10556	32			

Table 1 continued.

Gram-Negative Bacteria			Gram-Positive Bacteria			Yeast		
Strain	ATCC No.	FDX MIC	Strain	ATCC No.	FDX MIC	Strain	ATCC No.	FDX MIC
P. mirabilis	29245	>64						
Proteus penneri	33519	>64						
Proteus vulgaris	33420	>64						
Pseudomonas aeruginosa	27853	>32						
Salmonella choleraesuis	19585	>64						
S. choleraesuis	14028	>32						
Serratia marcescens	43861	>64						
S. marcescens	8100	>32						
Veillonella parvula	10790	32						

Data are from [3].

Abbreviations: ATCC, American Type Culture Collection; FDX, fidaxomicin; MIC, minimum inhibitory concentration.

April 2007 showed that all *C. difficile* strains were susceptible to ≤1.0 μg/mL of fidaxomicin, with an MIC_{90} of 0.5 μg/mL.

Clinical Trial In Vitro Susceptibilities

Citron et al [9] reported the activity of fidaxomicin by REA type on *C. difficile* isolates recovered from the fidaxomicin phase II clinical trial for *C. difficile* infection. Thirty-eight of 49 enrolled subjects (78%) had a *C. difficile* organism isolated at baseline. Four subjects grew multiple colony types, with 1 of these subjects having 2 different REA-type strains. Fidaxomicin showed an MIC range of ≤0.008–0.125 μg/mL, with an MIC_{90} of 0.125 μg/mL. Samples from only 2 subjects who had a recurrence within 6 weeks of treatment yielded isolates with MICs within a dilution of those recovered at baseline. It was noted that the REA BI isolates had metronidazole and vancomycin, but not fidaxomicin, MIC_{90} values that were 2 dilutions higher than that for the non-BI strains.

Goldstein et al [10] reported the activity of fidaxomicin by REA type on 716 *C. difficile* isolates from 2 fidaxomicin phase III studies (Table 3). For all pretreatment isolates, the fidaxomicin MIC range was ≤0.004–1.0 μg/mL, with an MIC for inhibition of 50% of organisms (MIC_{50}) of 0.125 μg/mL and an MIC_{90} of 0.25 μg/mL. Analyzed by REA type, 244 of 718 isolates (35%) were from the BI group, with MICs generally higher for all 4 drugs tested (MIC_{90}: fidaxomicin, 0.5; vancomycin, 2.0; metronidazole, 2.0; and rifaximin >256 μg/mL) than for the other REA types. Fidaxomicin susceptibility of baseline isolates did not predict clinical cure, failure, or recurrence for fidaxomicin (baseline MIC_{90}, 0.25 μg/mL [range, ≤0.008–1 μg/mL]). No resistance to fidaxomicin developed during treatment in either phase III study, although a single strain isolated from a cured patient had an elevated fidaxomicin MIC of 16 μg/mL at the time of recurrence.

Results of studies by Ackermann et al [4] and Credito and Applebaum [7] showing more potent activity of fidaxomicin against *C. difficile* than those of Karlowsky et al [8], Hecht et al [6], and Finegold et al [5] may have been related to the inclusion of higher numbers of clones with lower MICs. Although Credito and Applebaum [7] showed an MIC_{90} of 0.125 μg/mL, the MIC_{90} reported by Ackermann et al [4] was exceptionally low (0.008 μg/mL), which could alternatively be attributed to lower viability of cells when dimethyl sulfoxide (DMSO) was used as diluent and/or to use of an anaerobic environment with a higher carbon dioxide concentration (15% vs the CLSI-recommended 4%–7%), because carbon dioxide can acidify media.

Effect of Diluent, pH, Inoculum, and Cations on Susceptibility

Babakhani et al [12] found that variations in pH affected MICs. With use of both Brucella agar dilution and broth dilution methods, fidaxomicin MICs were unchanged between pH values of 6.2 and 7.0 but increased in a linear fashion and were 8-fold

Table 2. In Vitro Activity of Fidaxomicin, Compared With Vancomycin and Metronidazole, Against *Clostridium difficile* Isolates From 8 Published Studies

Drug	No. of isolates	MIC (μg/mL)			[Ref] Year/sites
		Range	MIC_{50}	MIC_{90}	
Fidaxomicin	16	0.12–0.25	0.25	0.25	[1] 1991/US
Vancomycin		0.5–1	0.5	1	
Metronidazole		0.12–0.5	0.25	0.5	
Fidaxomicin	207	≤0.001–0.625	0.002	0.008	[4] 2004/Europe
Vancomycin		0.016–0.5	0.5	0.5	
Metronidazole		0.004–0.5	0.06	0.06	
Fidaxomicin	23	0.06–2	0.12	0.25	[5] 2004/US
Vancomycin		0.5–4	1	2	
Metronidazole		0.25–1	0.12	0.25	
Fidaxomicin	208	0.06–1	0.25	0.5	[8] 2008/Canada
Vancomycin		0.5–4	0.5	1	
Metronidazole		0.25–4	0.5	1	
Fidaxomicin	110	0.015–0.25	0.125	0.125	[6] 1983–2004/US
Vancomycin		0.06–4	1	1	
Metronidazole		0.025–0.5	0.125	0.25	
Fidaxomicin	21	≤0.016–0.25	0.016	0.12	[7] 2004/US
Vancomycin		0.5–2	1	2	
Metronidazole		≤0.125–0.5	0.25	0.5	
Fidaxomicin	38	≤0.008–0.25	…	0.125	[9] 2004–2005/US
Vancomycin		0.25–2	…	1	
Metronidazole		0.25–2	…	1	
Fidaxomicin	716	≤0.008–1	0.125	0.5	[10] 2005–2010/US & Europe
Vancomycin		0.5–8	1	2	
Metronidazole		0.02–4	0.5	1	

Abbreviations: MIC_{50}, minimum inhibitory concentration for inhibition of 50% of organisms; MIC_{90}, minimum inhibitory concentration for inhibition of 90% of organisms; US, United States.

higher at pH values of 7.9–8.0. The organism was shown to grow poorly at a pH of 5.0. With use of the Wilkins-Chalgren broth microdilution method, Swanson et al [1] reported that the MICs of tiacumicin B against *C. difficile* American Type Culture Collection (ATCC) 9689 at pH values of 6.5 and 8.0 were unchanged or only 2-fold different from MICs determined at a pH of 7.3.

The effects of inoculum concentrations of 10^2–10^5 colony-forming units/spot and of cation concentrations of calcium (at 33, 45, and 75 mg/L) or magnesium (21, 30, and 57 mg/L) were also studied [12]. Neither inoculum size nor cation concentration had an effect on fidaxomicin MICs for 2 reference *C. difficile* strains (ATCC 9689 and ATCC 700057) [12]. In contrast, as stated by the investigators, "vancomycin MICs increased progressively with increasing inoculum concentrations" [12, 2674–5]. Additionally, the investigators studied the effect of various commercial lots of media on MICs and reported no fidaxomicin MIC variation when tested with 3 different lots of commercially prepared supplemented Brucella agar media.

In Vitro Studies Against Enteric Flora

Ackermann et al [4] studied the activity of fidaxomicin against a limited number of eubacteria (26 isolates), lactobacilli (8), *Propionibacterium acnes* (16), *Prevotella* species (35), and *Bacteroides fragilis* (69) and found them generally not susceptible. MIC_{50} and MIC_{90} values were >128 μg/mL and >128 μg/mL, respectively, for *B. fragilis* and *Prevotella* species. Finegold et al [5] performed a more extensive study involving 453 intestinal bacteria and reported that streptococci, aerobic and facultative gram-negative rods, anaerobic gram-negative rods, and *Clostridium ramosum* were resistant, which might potentially be less disruptive to normal fecal flora. Against 50 isolates of the *B. fragilis* group, MIC_{50} was 256 μg/mL and MIC_{90} was >1024 μg/mL. They noted that fidaxomicin had activity against most clostridia, staphylococci, and enterococci.

Clinical results in support of these in vitro studies were seen in the fidaxomicin phase IIA dose-ranging trial, in which 30 patient stool samples cultured for normal flora [13] showed

Table 3. Fidaxomicin-Susceptibility Profiles, by Restriction Endonuclease Analysis Group, for 716 *Clostridium difficile* Strains Isolated at Baseline (per protocol population) From 2 Phase III Trials

REA Group	No. of Patients	Geometric Mean (Range)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
BI	244	0.18 (0.015–1)	0.25	0.5
BK	12	0.09 (0.03–0.25)	0.06	0.125
CF	7	0.09 (0.015–0.25)	0.125	0.25
DH	4	0.25 (0.25–0.25)	0.25	0.25
G	54	0.08 (0.015–0.25)	0.06	0.125
J	43	0.02 (≤0.008–0.12)	0.02	0.125
Nonspecific REA	260	0.08 (≤0.004–0.5)	0.06	0.125
K	15	0.07 (0.015–0.25)	0.06	0.125
Y	77	0.10 (0.015–0.5)	0.125	0.25
All strains	716	0.10 (≤0.004–1)	0.125	0.25

Abbreviations: MIC_{50}, minimum inhibitory concentration for inhibition of 50% of organisms; MIC_{90}, minimum inhibitory concentration for inhibition of 90% of organisms; REA, restriction endonuclease analysis.

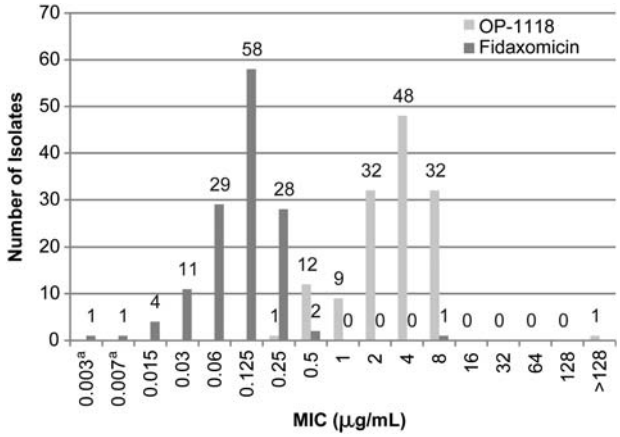

Figure 1. Minimum inhibitory concentration distribution of fidaxomicin and OPT-1118 against 135 *Clostridium difficile* clinical isolates from the FDX-004 [14]. [a]Refers to ≤0.004 μg/mL (for 0.003) and ≤0.008 μg/mL (for 0.007). Abbreviation: MIC, minimum inhibitory concentration.

that *B. fragilis* group counts were not affected by increasing fidaxomicin dosages.

OP-1118 In Vitro Activity

OP-1118 is a major metabolite of fidaxomicin that also exhibits a narrow spectrum of activity. Tested in vitro by using CLSI susceptibility testing methods against 32 strains belonging to the commensal gastrointestinal flora, OP-1118 demonstrated activity against only some gram-positive organisms, with MICs 4–16-fold greater than those of fidaxomicin [14]. Similar to the parent compound, OP-1118 was not active against gram-negative bacteria.

We now report previously unpublished data regarding the in vitro activity of fidaxomicin and OP-1118 against 135 clinical strains of *C. difficile* isolated from patients in the 004 study who were compared by using the CLSI agar dilution method in M11-A7 [11]. An inoculum of 10^5 colony-forming units/mL of *C. difficile* ATCC 700057 was included as a quality control strain. OP-1118 was dissolved and diluted in DMSO to achieve final study concentrations that ranged from 0.004 to 128 μg/mL. The MIC_{50} and MIC_{90} for OP-1118 were 4 and 8 μg/mL, compared with 0.125 and 0.25 μg/mL, respectively, for fidaxomicin (Figure 1).

Low Fecal-Binding Properties

The fecal-binding properties of fidaxomicin and OP-1118 were compared with those of vancomycin by testing their antibacterial activity in the presence or absence of 5% fecal material, using a microbroth dilution method. Similar to vancomycin, both fidaxomicin and OP-1118 demonstrated low fecal-binding properties, and their MICs against *C. difficile* increased only 4–8-fold in the presence of feces: the MIC of fidaxomicin increased from 0.25 to 2 μg/mL, and the MIC of OP-1118 increased from 1 to 4 μg/mL, with both increases much lower than the expected gut-level concentrations following oral administration of 400 mg/day of fidaxomicin [14].

Killing Kinetics

Fidaxomicin and its major metabolite, OP-1118, both demonstrate bactericidal activity against *C. difficile* strains, including the hypervirulent REA BI group strains. Exposure of *C. difficile* strains to fidaxomicin or OP-1118 at ≥4 times the MIC of each agent led to a ≥3 log decrease in colony-forming units in 48 hours, indicating time-dependent bactericidal activity [15]. Interestingly, fidaxomicin has been shown to be bactericidal against laboratory-generated mutant strains with reduced fidaxomicin susceptibility, indicating that with fecal concentrations that reach milligram-per-gram amounts, even mutant strains with increased fidaxomicin MICs are likely to be killed during therapy [15].

Susceptibility Breakpoints/Resistance

Results from fidaxomicin clinical trials have not demonstrated a correlation between MIC and clinical outcome [10, 16]. Although the MIC_{90} was shown to be 0.25 μg/mL in these trials, the highest reported MIC for wild-type isolates is 1 μg/mL. The only clinical isolate with reduced susceptibility was obtained from a subject with recurrence of disease 6 days following cure with fidaxomicin. The isolate at day 1 and the end of treatment had an MIC of 0.06 μg/mL, but the recurrence isolate demonstrated reduced susceptibility, with an MIC

of 16 μg/mL, which is still less than gut-level concentrations of the drug (mean fidaxomicin and OP-1118 concentrations were reported as 1433 and 760 μg/g, respectively) [16]. The strain with reduced susceptibility has been analyzed further, and a single mutation in the β subunit of the RNA polymerase has been identified in only the isolate associated with recurrence (unpublished data). Similar mutations in the homologous positions in other bacterial species that demonstrate reduced susceptibility to lipiarmycin, a related macrocycle compound, have been reported [17, 18]. However, the functional significance of such mutations needs to be elucidated further because laboratory-generated isolates with similar mutations are rapidly killed by fidaxomicin at 4 times the MICs [15].

CONCLUSION

Fidaxomicin has excellent in vitro activity against *C. difficile* isolates of all REA types, including the epidemic BI strain. Resistance has not developed during therapy in clinical trials. Its lack of activity against enteric gram-negative flora should help maintain colonization resistance.

Notes

Acknowledgments. We thank Judee H. Knight and Alice E. Goldstein for various forms of assistance.

Supplement sponsorship. This article was published as part of a supplement entitled "Fidaxomicin and the Evolving Approach to the Treatment of *Clostridium difficile* Infection," sponsored by Optimer Pharmaceuticals, Inc.

Potential conflicts of interest. E. J. C. G. serves on the advisory boards of Merck, Optimer, Bayer Pharmaceuticals, Theravance, BioK+, and Viropharma, Kindred Healthcare; is on the speakers bureau of Bayer, Merck, Sanofi Pasteur, and Forest Labs; and has received research grants from Merck, Schering-Plough Pharmaceuticals, Optimer Pharmaceuticals, Theravance, Cubist, Pfizer, Astellas, Cerexa, Impex Pharmaceuticals, Novexel, Novartis, Clinical Microbiology Institute, Genzyme, Nanopacific Holdings, Romark Laboratories, Viroxis, Warner Chilcott, Avidbiotics, GLSynthesis, Immunome, Toltec Pharma, and Salix Pharmaceuticals, GSK. F. B. is an employee of Optimer Pharmaceuticals. D. M. C. certifies no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Swanson RN, Hardy DJ, Shipkowitz NL, et al. In vitro and in vivo evaluation of tiacumicins B and C against *Clostridium difficile*. Antimicrob Agents Chemother **1991**; 35:1108–11.
2. Theriault RJ, Karwowski JP, Jackson M, et al. Tiacumicins, a novel complex of 18-membered macrolide antibiotics. I. Taxonomy, fermentation and antibacterial activity. J Antibiot **1987**; 40:567–74.
3. Babakhani FK, Robert N, Shangle S, et al. Antimicrobial activity and post-antibiotic effect of OPT-89, a new macrocyclic compound, against *Clostridium difficile* [abstract]. Presented at: 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 30 October–2 November 2004, Washington, DC.
4. Ackermann G, Löffler B, Adler D, Rodloff AC. In vitro activity of OPT-80 against *Clostridium difficile*. Antimicrob Agents Chemother **2004**; 48:2280–2.
5. Finegold SM, Molitoris D, Vaisanen ML, Song Y, Liu C, Bolaños M. In vitro activities of OPT-80 and comparator drugs against anaerobic bacteria. Antimicrob Agents Chemother **2004**; 48:4898–902.
6. Hecht DW, Galang MA, Sambol SP, Osmolski JR, Johnson S, Gerding DN. In vitro activities of 15 antimicrobial agents against 110 toxigenic *Clostridium difficile* clinical isolates collected from 1983 to 2004. Antimicrob Agents Chemother **2007**; 51:2716–9.
7. Credito KL, Applebaum PC. Activity of OPT-80, a novel macrocycle, compared with those of eight other agents against selected anaerobic species. Antimicrob Agents Chemother **2004**; 48:4430–4.
8. Karlowsky JA, Laing NM, Zhanel GG. In vitro activity of OPT-80 tested against clinical isolates of toxin-producing *Clostridium difficile*. Antimicrob Agents Chemother **2008**; 52:4163–5.
9. Citron DM, Babakhani F, Goldstein EJ, et al. Typing and susceptibility of bacterial isolates from the fidaxomicin (OPT-80) phase II study for *C. difficile* infection. Anaerobe **2009**; 15:234–6.
10. Goldstein EJ, Citron DM, Sears P, Babakhani F, Sambol SP, Gerding DN. Comparative susceptibilities of fidaxomicin (OPT-80) of isolates collected at baseline, recurrence, and failure from patients in two fidaxomicin phase III trials of *C. difficile* infection. Antimicrob Agents Chemother **2011**; 55:5194–9.
11. Clinical and Laboratory Standards Institute. Methods for antimicrobial susceptibility testing of anaerobic bacteria. 7th ed. CLSI document M11-A7. Wayne, PA: CLSI, **2007**.
12. Babakhani F, Seddon J, Robert N, Shue YK, Sears P. Effects of inoculum, pH, and cations on the in vitro activity of fidaxomicin (OPT-80, PAR-101) against *Clostridium difficile*. Antimicrob Agents Chemother **2010**; 54:2674–6.
13. Louie TJ, Emery J, Krulicki W, Bryne B, Mah M. OPT-80 eliminates *Clostridium difficile* and is sparing of *Bacteroides* species during treatment of *C. difficile* infection. Antimicrob Agents Chemother **2009**; 53:261–3.
14. Babakhani FK, Seddon J, Robert N, et al. Narrow spectrum activity and low fecal binding of OPT-80 and its major hydrolysis metabolite (OP-1118) [abstract E-2076]. Presented at: 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, 17–20 September 2007, Chicago, Illinois.
15. Babakhani F, Gomez A, Robert N, Sears P. Killing kinetics of fidaxomicin and its major metabolite, OP-1118, against *Clostridium difficile*. J Med Microbiol **2011**; 60:1213–7.
16. Louie T, Miller M, Donskey C, Mullane K, Goldstein EJ. Clinical outcomes, safety, and pharmacokinetics of OPT-80 in a phase 2 trial with patients with *Clostridium difficile* infection. Antimicrob Agents Chemother **2009**; 53:223–8.
17. Gultieri M, Tupin A, Brodolin K, Leonetti JP. Frequency and characterization of spontaneous lipiarmycin-resistant *Enterococcus faecalis* mutants selected in vitro. Int J Antimicrobial Agents **2009**; 34: 605–16.
18. Kurabachew M, Lu S, Krastel P, et al. Lipiarmycin targets RNA polymerase and has good activity against multidrug-resistant strains of *Mycobacterium tuberculosis*. J Antimicrob Chemother **2008**; 62: 713–9.