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Fidaxomicin

Difimicin; Lipiarmycin; OPT 80; OPT-80; PAR 101; PAR-101

Abstract

Fidaxomicin, an RNA polymerase inhibitor, is being developed by Optimer and Par Pharmaceuticals as a narrow-spectrum antibacterial for the treatment of *Clostridium difficile* infections. It is currently in phase III development with promising results so far. This review looks at the development history and scientific profile of this drug to date.

1. Introduction

Fidaxomicin is an oral, narrow-spectrum antibacterial that is being developed by Optimer Pharmaceuticals for the treatment of *Clostridium difficile* infections. The compound was previously being jointly developed by Optimer and Par Pharmaceuticals; the latter had exclusive rights to fidaxomicin in the US and Canada, but this agreement has been terminated. Fidaxomicin, an RNA polymerase inhibitor, is proposed to address the growing clinical problem of *Clostridium difficile*-associated diarrhea (CDAD). It is a naturally occurring 18-membered macrocycle, which is derived from the fermentation of *Dactylosporangium aurantiacum* subspecies *hamdenesis*. The product is undergoing phase III development for CDAD in the US and the EU, and phase I development in the US as prophylaxis for CDAD and vancomycin-resistant enterococcal (VRE) infections.

Antibacterial disturbance of normal anaerobic gut flora allows the overgrowth of toxigenic strains of *C. difficile* and the production of toxins A and B by this strain. Reactions to these toxins can result in lesions and severe damage to the epithelial lining of the colon. *C. difficile* accounts for approximately 20% of cases of antibacterial-associated diarrhea and the majority of cases of antibacterial-associated colitis. The active metabolite of fidaxomicin, OP 1118, selectively targets *C. difficile* to a similar degree as vancomycin, limiting its impact on the normal intestinal flora.

Optimer believes that fidaxomicin may have some advantages relative to established agents for the treatment of *C. difficile* infections, including demonstrated activity against *C. difficile* (including the hypervirulent strain NAP1/027), a low rate of drug resistance in *C. difficile*, minimal systemic exposure, a twice daily dosing regimen and minimal effect on normal gut flora.

Optimer is seeking collaborative partners to commercialize its programs.

1.1 Company Agreements

Par Pharmaceuticals entered into a joint development agreement with Optimer for fidaxomicin (as PAR 101) in May 2005. However, in February 2007, Par returned all marketing rights for the product to Optimer. Optimer paid a termination fee of $US20 million to Par, as it was Optimer's decision to terminate the agreement. Under the terms of the previous collaboration, Par had the exclusive rights to market, sell and distribute the product in the US and Canada. Under the terms of the termination agreement, Par will receive royalties on future global product sales in addition to upfront and milestone payments.[1-4]

Optimer has an arrangement with Biocon for manufacture of the active pharmaceutical ingredient of fidaxomicin tablets.

1.2 Key Development Milestones

1.2.1 Clostridium difficile-Associated Diarrhea (CDAD)

Optimer Pharmaceuticals reported in March 2009 that it was beginning preparations to file a Marketing Authorisation Application (MAA) with the European Medicines Agency for oral administration of fidaxomicin to treat *C. difficile* infection. The filing is based on results of the first phase III trial.[5] Positive results have been reported from the second phase III trial of fidaxomicin and Optimer plans to use data from this trial to support a New Drug Application (NDA) submission in the US in the second half of 2010.[6]

In a multicenter, randomized, double-blind trial (NCT00314951), the efficacy and safety of a 10-day course of oral fidaxomicin (200 mg every 12 h) was compared with that of oral vancomycin (125 mg every 6 h) in 629 patients with *C. difficile* infection. Cured patients were followed up for a subsequent 4-week period to evaluate recurrence. Results from this trial were favorable.[7-11] The trial had been initiated as a phase IIb/III trial in May 2006 in the US; approximately 100 patients with CDAD were enrolled in the initial phase IIb trial. Following a positive recommendation from the Independent Data Safety Monitoring Board (DSMB) and the US FDA's agreement with this decision, Optimer advanced fidaxomicin into the phase III portion of the trial. The company also increased the number of study sites in order to meet the targeted patient enrollment. Enrollment for this first pivotal phase III trial was completed in July 2008. A second pivotal phase III trial (NCT00468728), having an identical design as the first, was initiated in the US and the EU in 2007, and completed patient enrollment in November 2009. This trial enrolled a total of 536 patients. Data reported in February 2010 showed that the trial met its primary endpoint of non-inferiority of fidaxomicin to vancomycin. The drug was well tolerated in the study.[6,12-14]

Fidaxomicin completed proof-of-principle phase IIa trials for CDAD; fast track status has been granted by the FDA for this indication. Preliminary results showed that fidaxomicin appeared to be efficacious in patients with CDAD.[3,15] The FDA also selected fidaxomicin for participation in a Continuous Marketing Applications (CMA) Pilot 2 Program; this was to include continuous FDA feedback that was designed to streamline the development process.

The US National Institute of Allergy and Infectious Diseases (NIAID) is sponsoring an initiative to find a new treatment for CDAD and has awarded Optimer a grant to fund the project. The $US1 million grant is renewable each year until August 2010 to a maximum of $US3 million over a 3-year funding period. The award will allow the examination of the gut flora as a supplementary study to the ongoing fidaxomicin trials, in order to confirm narrow spectrum activity and potency of the agent against hypervirulent epidemic CDAD strains. Funds will also be used to conduct additional toxicology and microbiological studies, as well as a surveillance study of *C. difficile* isolates across North America to compare the activity of fidaxomicin with existing agents. The NIAID previously awarded the company a grant to progress development of the agent in October 2005.[16,17]

During 2005, Optimer secured $US34.2 million in financing, which was to be used for further development of fidaxomicin for this indication in the North American market.[18]

Results from phase Ib and phase IIa studies in CDAD were reported in December 2005. The phase Ib study was designed to evaluate the pharmacokinetics, tolerance and safety of fidaxomicin in healthy volunteers. The phase IIa study was conducted in order to select an appropriate dose for further clinical development.[19]

Optimer Pharmaceuticals is also developing an oral suspension formulation to complement the existing tablet form of fidaxomicin. The suspension formulation is for use in intensive care unit and elderly patients. The oral suspension formulation is in the preclinical stage of development.

1.2.2 CDAD Prophylaxis

Fidaxomicin is being developed for the prevention of CDAD and Optimer is continuing to evaluate the design of a proof-of-concept trial in high-risk populations. Phase I development is ongoing.

1.2.3 Vancomycin-Resistant Enterococcal Infection Prevention

Phase I trials for the prophylaxis (prevention) of VRE infections have been completed. Subject to results of an analysis of the propensity of vancomycin and fidaxomicin to promote VRE colonization in a completed phase III trial in *C. difficile* infection, Optimer will assess whether it will conduct a clinical trial for the prevention of VRE infection.

1.2.4 Other Indications

Optimer is also developing fidaxomicin for the prophylaxis of meticillin-resistant *Staphylococcus aureus* (MRSA) infections. Preclinical development is ongoing in this indication.

1.3 Patent Information

In April 2009, Optimer was issued a US production patent (no. 7 507 564), covering the steps used in the manufacture of fidaxomicin.[20]

In May 2008, Optimer was issued a US patent entitled *Polymorphic Crystalline Forms of Tiacumicin B* (no. 7 378 508). This patent covers the Form A polymorph of the active ingredient in fidaxomicin, as well as all dosage forms and pharmaceutical compositions.[21]

Optimer received a Notice of Allowance on a US patent application in April 2008. The pending patent covers the polymorphic form of the active ingredient and once issued, is expected to provide protection until 2025.[22]

In its Form 10-Q (filed on 5 November 2008), Optimer reported that it has filed several patent applications with the US Patent and Trademark Office, including an application for a composition of matter patent.

2. Scientific Summary

2.1 Pharmacokinetics

2.1.1 Clinical Studies

Results from a phase III study have shown that there was minimal systemic absorption of fidaxomicin in patients with *C. difficile* infection, with all post-dose plasma concentrations being in the nanogram range. At the same time, the average fecal drug concentrations were >5000 times the 90% minimum inhibitory concentration (MIC_{90}) of fidaxomicin against *C. difficile*. These results indicated that fidaxomicin has a favorable pharmacokinetic profile for the treatment of *C. difficile* infections. Plasma samples were collected predose and 3–5 hours postdose at the start and end of therapy (EOT; ~day 10), and stool samples were collected within 24 hours of the last dose. Postdose samples were available for 168 patients on day 1 and 61 patients at EOT. Plasma concentrations of fidaxomicin were <50 ng/mL (i.e. <0.05 μg/mL) in 90% and 87% of patients on day 1 and EOT, respectively. Mean fecal levels were 1225 ± 759 μg/g (range <0.05–4640 μg/g) for fidaxomicin and 809 ± 651 μg/g (range <0.05–4170 μg/g) for the metabolite OP 1118 that is formed in the bowel.[8,23]

Following oral administration in a phase I study, plasma concentrations of fidaxomicin were generally low, with most falling below the limit of quantification. However, there appeared to be dose-related increase in plasma concentrations for fidaxomicin. In the 450 mg dose group, fidaxomicin exhibited a plasma half-life of 0.94–2.77 hours. In the 200 and 300 mg doses of fidaxomicin, high fecal concentrations were observed, with peak levels being between 80 and 435 μg/g. In this single-dose, double-blind, placebo-controlled study, 16 volunteers in two groups were given two different, escalating doses (100/300 mg or 200/450 mg) of fidaxomicin or placebo.[24]

Absorption of fidaxomicin was minimal, with the majority of the drug being eliminated in the feces, after oral administration at a dosage of 150, 300 or 450 mg/day for 10 days. Plasma and urinary concentrations of fidaxomicin were generally ≤5 ng/mL (below the lower limit of quantification) and the mean fecal concentration of fidaxomicin was high at 916 μg/g.[25]

2.1.2 Preclinical Studies

In Sprague-Dawley rats, the 50% lethal dose of intravenous fidaxomicin was approximately 200 mg/kg. Following an intravenous dose of 20 mg/kg, fidaxomicin was cleared from rat plasma within 10 minutes, with the maximum concentration (C_{max}) being between 2 and 7 μg/mL.

Following oral administration of fidaxomicin in monkeys, the C_{max} in plasma after doses of 30 mg/kg and 90 mg/kg was 50–85 ng/mL and 120–420 ng/mL, respectively.[26]

2.2 Adverse Events

2.2.1 CDAD

Phase III: In a pivotal phase III trial involving 629 patients with CDAD, fidaxomicin was well tolerated.[10] The incidence of adverse events (AEs) and serious AEs was similar between the fidaxomicin- and vancomycin-treated groups.[9]

These results were confirmed by review of safety reports from 320 fidaxomicin recipients and 323 vancomycin recipients. Plasma samples from 183 patients were analyzed for levels of fidaxomicin and OP 1118 (major metabolite in the gastrointestinal [GI] tract). There were no significant differences in rates of among AEs and serious AEs between the fidaxomicin and vancomycin arms. Any treatment-emergent AE was reported in 62.3% and 60.4% in the fidaxomicin and vancomycin arms, respectively. In the fidaxomicin and vancomycin arms, GI disorders were the most common (25.0% vs 22.3%) followed by general disorders (fever, chills, edema, fatigue; 15.3% vs 16.7%) and infections (urinary tract, pneumonia; 21.3% vs 19.5%). All-cause mortality was 5.3% with fidaxomicin and 6.5% for vancomycin.[8,27]

2.2.2 Healthy Subjects

Fidaxomicin (150, 300 or 450 mg/day for 10 days) was not associated with any treatment-related AEs in 24 healthy volunteers in a phase Ib double-blinded, placebo-controlled study.[25]

In a phase I study, fidaxomicin was well tolerated after single oral doses of up to 450 mg, with no serious AEs being reported. In this single-dose, double-blind, placebo-controlled study,

Table I. Features and properties

Alternate names	Difimicin; Lipiarmycin; OPT 80; OPT-80; PAR 101; PAR-101
Originator	Optimer Pharmaceuticals
Highest development phase	III (Canada, EU, US)
Active development-indications	*Clostridium* infections, Methicillin-resistant *Staphylococcus aureus* infections, Vancomycin-resistant enterococcal infections
Class	Glycosides
Mechanism of action	DNA-directed RNA polymerase inhibitors
Chemical name	(3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-3-({ [6-deoxy-4-*O*-(3,5-dichloro-2-ethyl-4,6- dihydroxybenzoyl)-2-*O*-methyl-β-D-mannopyranosyl] oxy}methyl)-12-{ [6-deoxy-5-*C*-methyl-4-O-(2-methylpropanoyl)-β-D-lyxo-hexopyranosyl] oxy}-11-ethyl-8-hydroxy-18- [(1*R*)-1-hydroxyethyl] -9,13,15-trimethyloxacyclooctadeca-3,5,9,13,15-pentaen-2-one
Molecular formula	C52 H74 Cl2 O18
CAS registry number	873857-62-6
Route of administration	PO
Pharmacodynamics	Reduces counts of *Clostridium difficile* and has minimal effect on native anaerobic fecal flora *in vivo*
Antimicrobial activity	Active against all Gram-positive organisms, especially clostridia; selectivity for *C. difficile* similar to vancomycin; equally efficacious against hypervirulent and non-hypervirulent strains of *C. difficile*
ATC codes	
WHO ATC code	J01 (antibacterials for systemic use), J01X (other antibacterials)
EphMRA ATC code	J1 (systemic antibacterials), J1X (other antibacterials)
Pharmacokinetics	
Route of elimination	Fecal
t (1/2) beta (h)	0.94–2.77 (Adult)
Adverse events	
Most frequent	Gastrointestinal disorders, infections
Occasional	Signs, symptoms and ill-defined conditions

Table II. History

Date	Comment
10 February 2010	inThought analysis for *Clostridium* infections updated
5 February 2010	Efficacy data from a phase III trial in *Clostridium* infections released by Optimer Pharmaceuticals[6]
31 October 2009	Efficacy data from a phase III trial in *Clostridium* infections presented at the 47th Annual Meeting of the Infectious Diseases Society of America (IDSA-2009)[7,32-34]
15 September 2009	Efficacy, adverse events, pharmacokinetic & antimicrobial activity data from a phase III trial in *Clostridium* infections presented at the 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC-2009)[8,23,27,30,36]
2 June 2009	Efficacy data from a subgroup analysis of a phase III trial in *Clostridium* infections presented at the Digestive Disease Week 2009 (DDW-2009)[37]
17 May 2009	Efficacy and adverse events data from a subgroup analysis of a phase III trial in *Clostridium* infections presented at the 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID-2009)[9]
11 November 2008	Final efficacy and adverse events data from a phase III trial in *Clostridium difficile*-associated diarrhea released by Optimer Pharmaceuticals[10]
24 July 2008	Optimer Pharmaceuticals completes enrollment in the first of its two pivotal phase III trials for *Clostridium* infections
27 June 2008	Antimicrobial data from a phase IIa trial in *Clostridium* infections released by Optimer Pharmaceuticals[15]
27 June 2008	Preclinical trials in *Clostridium* infections in the US (PO, suspension)
8 January 2008	Optimer Pharmaceuticals receives federal grant from the US NIAID for development of difimicin in the treatment of CDAD
21 September 2007	Data presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC-2007) added to the Bacterial Infections antimicrobial activity section[28]
3 May 2007	Optimer Pharmaceuticals initiates enrollment in its second phase III trial for CDAD in North America and Europe
3 May 2007	Phase III clinical trials in *Clostridium* infections in Canada (PO)
3 May 2007	Phase III clinical trials in *Clostridium* infections in Europe (PO)
20 March 2007	Phase I clinical trials in *Clostridium* infections prevention in the US (PO)
14 March 2007	Phase III clinical trials in *Clostridium* infections in the US (PO)
2 March 2007	Par Pharmaceutical returns marketing rights for PAR 101 in the US and Canada
2 March 2007	Preclinical trials in meticillin-resistant *Staphylococcus aureus* infections in the US (PO)
1 May 2006	Par Pharmaceutical has initiated enrollment in a phase IIb trial for *Clostridium difficile*-associated diarrhea
1 May 2006	Phase II/III clinical trials in *Clostridium* infections in the US (PO)
3 February 2006	Data presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC-2005) have been added to the adverse events, pharmacokinetics, pharmacodynamics and bacterial infections therapeutic trials sections[19,25,31]
19 October 2005	Phase I clinical trials in Vancomycin-resistant enterococcal infections prevention in the US (PO)
16 May 2005	Optimer Pharmaceuticals and Par Pharmaceutical have entered into an agreement to co-develop PAR 101 in Canada and the US for *Clostridium* infections
16 May 2005	PAR 101 has received fast track status for *Clostridium* infections in the US
30 November 2004	Phase II clinical trials in *Clostridium* infections in the US (PO)
15 November 2004	Data presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC-2004) have been added to the Adverse events, pharmacokinetics and Viral Infections Antimicrobial Activity sections[24,26,29]
17 March 2004	PAR 101 is available for partnering (http://www.optimerpharma.com)
17 March 2004	Phase I clinical trials in *Clostridium* infections in the US (PO)
29 August 2003	Optimer Pharmaceuticals has filed an IND with the US FDA for the treatment of CDAD
27 November 2002	New profile
27 November 2002	Preclinical trials in *Clostridium* infections in the US (unspecified route)

16 volunteers in two groups were given two different, escalating doses (100/300 mg or 200/450 mg) of fidaxomicin or placebo.[24]

2.2.3 Animal Toxicology

No treatment-related effects were observed when rats were administered an oral dose of

fidaxomicin at ≤1000 mg/kg. In rats and monkeys, repeated oral administration of fidaxomicin, at doses of ≤90 mg/kg, for 28 consecutive days did not result in any drug-related adverse effects.[26]

2.3 Antimicrobial Activity

2.3.1 Bacterial Infections

Fidaxomicin showed no difference in MIC values between BI/NAP1/027 strains and the non-BI/NAP1/027 strains, compared with metronidazole and vancomycin which showed high MIC values (lower *in vitro* efficacy) for the hypervirulent strains.[15]

The major metabolite of fidaxomicin, OP 1118, had selective activity against *C. difficile* in vitro. The study tested OP 1118 against 32 bacteria commonly found in the gastrointestinal tract. OP 1118 showed selectivity for *C. difficile* over the other pathogens similar to vancomycin.[28]

In vitro studies have shown fidaxomicin to be active against all Gram-positive organisms, especially clostridia, where it inhibited *C. difficile* at an MIC value of ≤0.25 μg/mL.[29]

Analysis of fecal specimens from patients enrolled in a phase III trial of fidaxomicin have shown that there was no relationship between the MIC of baseline clinical isolates and clinical outcome. No resistance to either fidaxomicin or vancomycin developed during the study. MIC_{90} values were generally low (0.25 μg/mL for fidaxomicin and 2 μg/mL for vancomycin). Furthermore, two of the *C. difficile* strain typing groups (i.e. BI and K group strains) had lower susceptibilities than other groups to rifaximin and metronidazole, with resistance to rifaximin occurring in 14% of the BI group and 18% in the K group. A 10-day course of oral fidaxomicin (200 mg twice daily) was compared with vancomycin (125 mg four times daily) in 629 adult patients (548 evaluable) with *C. difficile* infection in a phase III randomized, double-blind trial conducted in North America.[8,30]

2.4 Pharmacodynamics

2.4.1 Bacterial Infections

In a phase IIa study, fidaxomicin at dosages of 50, 100, or 200 mg twice daily for 10 days appeared to selectively reduce counts of *C. difficile* without significantly reducing counts of *Bacteroides* (anaerobic fecal flora). This compared favorably in comparison to treatment with vancomycin 125 mg four times daily for 10 days, which severely impaired *Bacteroides* counts.[31]

2.5 Therapeutic Trials

2.5.1 Bacterial Infections

Phase III: A phase III trial met its primary endpoint of non-inferiority, with 91.7% of fidaxomicin recipients achieving clinical cure, compared with 90.6% in vancomycin recipients. Compared with vancomycin, fidaxomicin treatment resulted in lower recurrence rates (12.8% vs 25.3%), and higher global cure rates (79.6% vs 65.5%) [p = 0.002]. The trial enrolled 535 subjects and those with confirmed *C. difficile* infections (CDI) received either fidaxomicin (200 mg every 12 hours) or vancomycin (125 mg every 6 hours) for 10 days.[6]

In a pivotal phase III clinical trial, 92.1% of patients with CDI receiving fidaxomicin achieved clinical cure, compared with 89.8% of patients receiving vancomycin. 13.3% of patients treated with fidaxomicin experienced a recurrence compared with 24.0% with vancomycin; the difference was significant (p = 0.004). Patients receiving fidaxomicin had a global cure rate of 77.7%, compared with 67.1% in patients receiving vancomycin. In this trial, 629 subjects with *C. difficile* infections were randomized to receive either

Table III. Forecasts

InThought Probability of Approval			
Indication	Approval Date Estimate	inThought Approvability Index	Last Update
Clostridium infections	1 Nov 2010	75%	10 Feb 2010
Vancomycin-resistant enterococcal infections		31%	27 Jul 2009

200 mg fidaxomicin orally twice daily or 125 mg vancomycin orally four times daily.[5,10] Analysis of data from this trial (596/629 patients were in the modified intent-to-treat [mITT] population and 548/629 in the per protocol [PP] group), showed the significant correlation between age and albumin with clinical cure (CC), recurrence and global cure (GC) rates ($p \leq 0.09$). Disease severity (leukocytosis/fever) correlated with CC and GC rates but not with the recurrence rate.[32] Fidaxomicin was associated with a faster time to resolution of diarrhea than vancomycin (79 hours vs 105 hours; $p = 0.056$).[7] At 60 hours after start of therapy, more patients in the fidaxomicin group were free of diarrhea than in the vancomycin group (mITT: 63.1% vs 57.6%; $p = 0.052$ and PP: 67.6% vs 61.5%; $p = 0.038$).[33] In this same trial, 20% of subjects with CDI received concomitant antibiotics and analysis of data showed that in this group, those treated with fidaxomicin versus vancomycin had a significantly improved GC rate (72% vs 50%; $p = 0.022$), lower CDI recurrence rate (23% vs 40%; $p = 0.061$), and higher CC rate (87% vs 77%; $p = 0.171$). Concomitant antibiotics during CDI treatment significantly decreased CC and increased recurrence rates.[34]

PP analysis of 432 patients with *C. difficile*-associated diarrhea confirmed these previous data that fidaxomicin was associated with a significantly lower infection recurrence rate than vancomycin (28/211 [13%] vs 53/221 [24%] patients; $p < 0.01$). Fidaxomicin was also associated with a significantly later onset of recurrent infection than vancomycin (3% vs 14% recurrence within 10 days and 9% vs 20% recurrence within 20 days after therapy; both $p < 0.01$). Patients received oral fidaxomicin (200 mg twice daily) or oral vancomycin (125 mg four times daily) for 10 days.[8,35]

Strain typing results from this phase III trial showed that the overall cure rate among patients with hypervirulent BI isolates (also known as NAP1 by PFGE and 027 by PCR ribotyping) was significantly lower than patients with non-BI strains (85.4% vs 95.5%; $p = 0.04$). *C. difficile* was isolated from stools of patients with diarrhea enrolled in the phase III treatment trial of fidaxomicin versus vancomycin. Restriction endonuclease analysis (REA) typing was performed on 184 fidaxomicin and 198 vancomycin isolates from the baseline and recurrence stools of 70% of patients. PP findings were presented; mITT findings were similar. The recurrence rates in the BI/NAP1/027 group (i.e. 36% of the patients analyzed), were similar following treatment with fidaxomicin and vancomycin. In the non-BI/NAP1/027 groups (64% of the patients analyzed), patients treated with fidaxomicin had only a 7.8% (8/103) recurrence rate versus a 25.5% (27/106) recurrence rate for vancomycin-treated patients.[8,36]

In a subgroup analysis from the same trial, fidaxomicin outperformed vancomycin at a recurrence rate endpoint in both outpatient (8.6%, 21.8%) and inpatient (17.9%, 26.1%) settings, as well as in subjects over the age of 65 years (9.5%, 18.6%) and under the age of 65 years (18.8%, 30.1%). Recurrence rates in the strain type BI/NAP1/027 subgroup were similar between agents (25.0%, 24.1%).[9] Additional subgroup analysis showed that there were lower recurrence rates for fidaxomicin recipients than for vancomycin recipients with regard to risk factors such as serum albumin levels, white blood cell (WBC) count and body temperature (BT), and non-BI (NAP1/027) strain types. Recurrence rates by subgroup for fidaxomicin recipients versus vancomycin recipients were: WBC of <15 000 per μL and BT of <38°C, 10.7% versus 22.4% (17/159 vs 35/156); WBC of 15 000–25 000 per μL or BT of 38–39°C, 12.0% versus 20.0% (3/25 vs 6/30); WBC of >25 000 per μL or BT of >39°C, 33.3% vs 40.0% (1/3 vs 2/5); serum albumin levels of ≤25 mg/mL, 22.2% versus 31.5% (8/36 vs 17/54); serum albumin levels of 26–35 mg/mL, 10.0% versus 23.3% (9/90 vs 20/86); strain type non-BI (NAP1/027), 7.8% versus 25.5% (8/103 vs 27/106).[37]

Phase II: In a phase IIa study, fidaxomicin therapy (50, 100 or 200 mg bid for 10 days) successfully treated 41/45 patients (>91% cured overall) with mild-to-moderate CDAD. Two patients transferred to conventional therapy. Of the 41 patients who completed therapy, two patients (5%) experienced recurrent symptoms

within the 6-week follow-up. All of the 16 subjects in the top dosing group (200 mg twice daily) achieved clinical cure.[3,15,25]

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