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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)  
ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (AIDAC)

Tuesday, April 5, 2011

8:00 a.m. to 2:00 p.m.

Hilton Washington DC/Silver Spring  
8727 Colesville Road  
Silver Spring, Maryland



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1                   P R O C E E D I N G S

2                   (8:00 a.m.)

3                   **Call to Order and**

4                   **Introduction of Committee Members**

5                   DR. GOETZ: Good morning. If everybody  
6 could please take their seats, we can get started.  
7 I would like to remind everyone present to please  
8 silence their cell phones, BlackBerrys, and other  
9 devices if you have not already done so. We'll get  
10 started by going around the table and introducing  
11 ourselves.

12                   So if we can go to my far right.

13                   DR. REX: Good morning. My name is John  
14 Rex. I'm a board-certified physician in internal  
15 medicine and infectious diseases, formerly  
16 professor of medicine in ID at the University of  
17 Texas Medical School at Houston. I'm currently  
18 vice president for clinical infection at  
19 AstraZeneca Pharmaceuticals.

20                   As Dr. Minh Doan will note, my role on the  
21 committee today is that of the nonvoting industry  
22 representative. In this role, I represent

1 regulated industry as a whole rather than  
2 AstraZeneca Pharmaceuticals or any specific  
3 sponsor.

4 DR. SURAWICZ: I'm Christa Surawicz. I'm  
5 from the University of Washington. I'm a  
6 gastroenterologist.

7 DR. SHYR: My name is Yu Shyr. I'm the  
8 biostatistician, serve as a professor at Vanderbilt  
9 University, biostatistical department.

10 MR. MAKOWKA: I'm Ken Makowka. I'm the  
11 patient representative on the panel.

12 DR. HASLER: Yes. I'm Bill Hasler,  
13 professor, Division of Gastroenterology, University  
14 of Michigan.

15 MS. YOUNG: Kathy Young, executive director  
16 of the Alliance for Prudent Use of Antibiotics. My  
17 background is public health and public policy, and  
18 I'm consumer representative, voting member.

19 DR. HILTON: Joan Hilton, professor of  
20 biostatistics, UCSF.

21 DR. KAPLAN: I'm Shelly Kaplan, pediatric  
22 infectious disease person at Baylor College of

1 Medicine and Texas Children's Hospital in Houston.

2 DR. SEPKOWITZ: I'm Kent Sepkowitz. I'm an  
3 infectious disease specialist in New York City at  
4 Memorial Sloan-Kettering, and a professor of  
5 medicine at Cornell.

6 DR. GOETZ: Matthew Goetz, infectious  
7 diseases, VA Greater Los Angeles Healthcare System  
8 and UCLA.

9 DR. DOAN: Minh Doan, Designated Federal  
10 Officer of AIDAC.

11 DR. CHATTERJEE: Archana Chatterjee,  
12 professor of pediatrics. I'm a pediatric  
13 infectious disease specialist at Creighton  
14 University School of Medicine.

15 DR. AUWAERTER: Good morning. Paul  
16 Auwaerter, clinical director in the Division of  
17 Infectious Diseases at Johns Hopkins.

18 DR. FOLLMAN: I'm Dean Follman, head of  
19 biostatistics at the National Institutes of Allergy  
20 and Infectious Diseases.

21 DR. SOLGA: I'm Steve Solga, private  
22 practice, gastroenterology, in Bethlehem,

1 Pennsylvania.

2 DR. IZEM: Good morning. I'm Rima Izem, the  
3 statistical reviewer of this application from the  
4 FDA.

5 DR. IARIKOV: Dmitri Iarikov, medical  
6 officer at the Division of Anti-Infective and  
7 Ophthalmology Products, and medical reviewer for  
8 this application.

9 DR. ALEXANDER: My name is John Alexander.  
10 I'm the medical team leader from the Division of  
11 Anti-Infectives.

12 DR. COX: Ed Cox, director of the Office of  
13 Antimicrobial Products, FDA.

14 DR. GOETZ: Thank you.

15 For topics such as those being discussed at  
16 today's meeting, there are often a variety of  
17 opinions, some of which are quite strongly held.  
18 Our goal is that today's meeting will be a fair and  
19 open forum for discussion of these issues and that  
20 individuals can express their views without  
21 interruption. Thus, as a gentle reminder,  
22 individuals will be allowed to speak into the

1 record only if recognized by the chair. We look  
2 forward to a productive meeting.

3 In the spirit of the Federal Advisory  
4 Committee Act and the Government in the Sunshine  
5 Act, we ask that the advisory committee members  
6 take care that their conversations about the topic  
7 at hand take place in the open forum of the  
8 meeting.

9 We are aware that members of the media are  
10 anxious to speak with the FDA about these  
11 proceedings. However, FDA will refrain from  
12 discussing the details of this meeting with the  
13 media until its conclusion. For the convenience of  
14 the media representatives, I would like to identify  
15 the FDA press contact, Erica Jefferson.

16 If present, could you please stand? There  
17 we are.

18 Also, the committee is reminded to please  
19 refrain from discussing the meeting topic during  
20 breaks or lunch. Thank you.

21 Now I'll pass it to Minh, who will read the  
22 conflict of interest statement.

### **Conflict of Interest Statement**

1  
2 DR. DOAN: The Food and Drug Administration  
3 is convening today's meeting of the Anti-Infective  
4 Drugs Advisory Committee under the authority of the  
5 Federal Advisory Committee Act of 1972. All members  
6 and temporary voting members of the committee are  
7 special government employees or regular federal  
8 employees from other agencies, and are subject to  
9 federal conflict of interest laws and regulations.

10 The following information on the status of  
11 the committee's compliance with the federal ethics  
12 and conflict of interest laws, covered by but not  
13 limited to, those found at 18 USC Section 208 and  
14 Section 712 of the Federal Food, Drug and Cosmetic  
15 Act, is being provided to participants in today's  
16 meeting and to the public.

17 FDA has determined that members and  
18 temporary voting members of the committee are in  
19 compliance with the federal ethics and conflict of  
20 interest laws. Under 18 USC Section 208, Congress  
21 has authorized FDA to grant waivers to special  
22 government employees and regular federal employees

1 who have potential financial conflicts when it is  
2 determined that the agency's need for a particular  
3 individual's services outweighs his or her  
4 potential financial conflict of interest.

5 Under Section 712 of the Federal Food, Drug  
6 and Cosmetic Act, Congress has authorized FDA to  
7 grant waivers to special government employees and  
8 regular federal employees with potential financial  
9 conflicts when necessary to afford the committee  
10 essential expertise.

11 Related to the discussions of today's  
12 meeting, members and temporary voting members of  
13 the committee have been screened for potential  
14 financial conflicts of interest of their own, as  
15 well as those imputed to them, including those of  
16 their spouses or minor children, and, for purposes  
17 of 18 USC Section 208, their employers.

18 These interests may include investments,  
19 consulting, expert witness testimony, contracts,  
20 grants, CRADAs, teaching, speaking, writing,  
21 patents and royalties, and primary employment.

22 Today's agenda involves discussion of new

1 drug application 20-1699 for fidaxomicin, sponsored  
2 by Optimer Pharmaceuticals, for the requested  
3 indication of treatment of adults with Clostridium  
4 difficile infection, also known as Clostridium  
5 difficile-associated diarrhea and prevention of  
6 recurrences.

7 This is a particular matters meeting, during  
8 which specific matters related to Optimer's  
9 fidaxomicin will be discussed. Based on the agenda  
10 and all financial interests reported by the  
11 committee members and temporary voting members, no  
12 conflict of interest waivers were issued in  
13 connection with the meeting.

14 To ensure transparency, we encourage all  
15 standing committee members and temporary voting  
16 members to disclose any public statements that they  
17 have made concerning the product at issue.

18 With respect to FDA'S invited industry  
19 representative, we would like to disclose that John  
20 Rex is participating in today's meeting as a  
21 nonvoting industry representative, acting on behalf  
22 of regulated industry. Dr. Rex's role at this

1 meeting is to represent industry in general and not  
2 any particular company. Dr. Rex is employed by  
3 AstraZeneca.

4 We would like to remind members and  
5 temporary voting members that if the discussions  
6 involve any other products, firms, or issues not  
7 already on the agenda for which an FDA participant  
8 has a personal or imputed financial interest, the  
9 participants need to exclude themselves from such  
10 involvement, and their exclusion will be noted for  
11 the record. FDA encourages all other participants  
12 to advise the committee of any financial  
13 relationships they may have with the firm at issue.  
14 Thank you.

15 DR. GOETZ: Both the Food and Drug  
16 Administration, FDA, and the public believe in a  
17 transparent process for information-gathering and  
18 decision-making. To ensure such transparency at  
19 the advisory committee meeting, FDA believes that  
20 it is important to understand the context of an  
21 individual's presentation.

22 For this reason, FDA encourages all

1 participants, including the sponsor's non-employee  
2 presenters, to advise the committee of any  
3 financial relationships that they may have with the  
4 firm at issue, such as consulting fees, travel  
5 expenses, honoraria, and interest in the sponsor,  
6 including equity interests and those based upon the  
7 outcome of the meeting.

8           Likewise, FDA encourages you at the  
9 beginning of your presentation to advise the  
10 committee if you do not have such financial  
11 relationships. If you choose not to address this  
12 issue of financial relationships at the beginning  
13 of your presentation, it will not preclude you from  
14 speaking.

15           So we'll move on now to the sponsor's  
16 presentation. Thank you.

17           **Applicant's Presentation - Sherwood Gorbach**

18           DR. GORBACH: Good morning, Mr. Chairman,  
19 members of the committee, and members of the FDA.  
20 My name is Sherry Gorbach. I'm chief scientific  
21 officer for Optimer Pharmaceuticals, and I've been  
22 involved in the development of fidaxomicin since

1 2002 and the treatment of antibiotic-associated  
2 diarrhea for 40 years.

3 We're here today to ask for your  
4 consideration in approving fidaxomicin for  
5 treatment of Clostridium difficile infection, also  
6 known as CDI or CDAD, and for reducing the risk of  
7 recurrence when used for treatment of initial CDI.

8 Fidaxomicin addresses an urgent medical  
9 need, in particular, the high level of C. difficile  
10 recurrences observed with current treatment  
11 options. As we'll demonstrate today, fidaxomicin  
12 is a safe and effective treatment against C.  
13 difficile infection. It is a novel antibiotic  
14 agent and the first representative of a new class  
15 of antibacterials referred to as macrocycles.

16 Macrocycles are characterized by an 18-  
17 membered macrocyclic ester structure with a unique  
18 mechanism of action, an inhibitory activity against  
19 bacterial RNA polymerase, which appears to interact  
20 at a site different from that of other approved  
21 antibiotics such as the macrolides.

22 Importantly, fidaxomicin has a narrow

1 spectrum antibacterial profile and potent  
2 bactericidal activity against Clostridium  
3 difficile. In addition, it is minimally absorbed  
4 and exerts its activity in the gastrointestinal  
5 tract. Therefore, fidaxomicin has an optimal  
6 profile to treat CDI.

7 CDI, Clostridium difficile, is a spore-  
8 forming, anaerobic, gram-positive bacillus.  
9 C. difficile infection is caused by an overgrowth  
10 of C. difficile in the colon. Once overgrown, C.  
11 difficile produces harmful toxins that cause a  
12 variety of complications, including diarrhea,  
13 abdominal pain, pseudomembranous colitis, toxic  
14 megacolon, perforations of the colon, sepsis, and  
15 in some cases, death.

16 Most cases of C. difficile infection are  
17 associated with antibiotic use, which eradicates  
18 the beneficial bacteria found in the gut, allowing  
19 C. difficile to proliferate. C. difficile is  
20 normally resistant to many antibiotics.

21 The rising incidence of CDI has been  
22 attributed to the frequent use of broad-spectrum

1 antibiotics among hospitalized patients.  
2 Recurrences are the most important unmet medical  
3 need with current CDI treatments. Twenty to 30  
4 percent of patients will recur. These recurrences  
5 can result in serious illness, which cause and can  
6 lead to hospitalization or death. Adequate  
7 treatment of recurrences has proven difficult.

8           The data we will present today is primarily  
9 from our two phase 3 multicenter, randomized,  
10 double-blind, vancomycin-controlled clinical  
11 studies in more than 1100 subjects. The phase 3  
12 studies clearly demonstrate that the clinical cure  
13 rate was noninferior to vancomycin for the  
14 treatment of C. difficile infection, and,  
15 importantly, fidaxomicin had significantly superior  
16 reduction of recurrences. The global cure rate for  
17 fidaxomicin was significantly superior to  
18 vancomycin. Fidaxomicin was well-tolerated, with a  
19 safety profile comparable to that of oral  
20 vancomycin.

21           With this overview in mind, I'd like to  
22 review our agenda and our speakers for today's

1 presentation. Dr. Mark Miller will present the  
2 burden of disease and the need for additional  
3 treatment options. Dr. Pamela Sears will review  
4 the microbiologic and pharmacologic aspects of  
5 fidaxomicin. I will return to review the trial  
6 design and efficacy data from our two phase 3  
7 clinical trials. And Dr. Michael Corrado will  
8 review the safety data from these trials, and then  
9 I will return to discuss Optimer's post-approval  
10 program and for closing remarks.

11 The outside experts who will represent  
12 information and assist in answering questions from  
13 the committee have been compensated for their time.

14 At this time I'd like to invite Dr. Mark  
15 Miller to the lectern.

16 **Applicant's Presentation - Mark Miller**

17 DR. MILLER: Thank you. Good morning. My  
18 name is Mark Miller. I am the head of infectious  
19 diseases and the head of infection prevention and  
20 control at the Jewish General Hospital, a McGill  
21 University teaching hospital in Montreal, Quebec,  
22 Canada.

1 I was involved in the analysis and control  
2 of the province-wide epidemic of CDI in Quebec in  
3 2002, which actually killed over 2,000 patients at  
4 that time. And our group described the  
5 hypervirulent strain which caused this epidemic in  
6 our New England Journal of Medicine article in  
7 2005. I have personally treated several hundred  
8 patients with CDI in the last 20 years.

9 I have been involved in CDI trial design or  
10 as a site investigator for CDI trials for 10 years,  
11 including the phase 3 fidaxomicin trials. And I am  
12 pleased to speak to you today about the burden of  
13 CDI and the need for additional treatment options  
14 for this very serious disease.

15 C. difficile is the most common cause of  
16 healthcare-associated infectious diarrhea in North  
17 America. It has been estimated that there are  
18 700,000 new cases per year in the United States  
19 alone, and this number has been increasing every  
20 year for the past decade. The spectrum of CDI  
21 varies from being a mild infection to a severe and  
22 sometimes fatal disease.

1           As you have heard, the symptoms range from  
2 mild diarrhea to pseudomembranous colitis to  
3 overwhelming pancolitis, intestinal perforation,  
4 and sepsis. CDI poses a significant morbidity and  
5 mortality burden. Dehydration and gastrointestinal  
6 bleeding occur frequently, and some patients may  
7 even require transfusions for this.

8           The mortality rate attributable to CDI has  
9 been documented to be up to 6.9 percent in  
10 outbreaks, and a staggering 15 percent among the  
11 frail elderly. Roughly 2 to 3 percent of  
12 individuals will require admission to an ICU for  
13 care of their CDI. As well, 1 percent will require  
14 emergency bowel surgery with colectomy for control  
15 of this infection.

16           A recent analysis has shown that CDI has  
17 actually surpassed MRSA in incidents and death as a  
18 complication of healthcare in the United States.  
19 In addition, community-acquired *C. difficile* is  
20 being reported as affecting otherwise healthy  
21 adults, peripartum women, and children with no  
22 recent history of hospital admission, and in some

1 cases even no history of antibiotic use.

2           Clearly, the prevalence of CDI is  
3 increasing, and it can be difficult to achieve a  
4 true treatment cure. In fact, the concept of cure  
5 after initial treatment of CDI is incomplete.  
6 Despite a cure at the end of the usual 10-day  
7 course of therapy, individuals are at risk of  
8 recurring, usually within 4 weeks after therapy.  
9 The high risk of recurrence of CDI after treatment  
10 and the problem of multiple recurrences are unique  
11 aspects of CDI.

12           Recurrence is a major problem associated  
13 with this disease. Recurrence is the reappearance  
14 of CDI symptoms and signs, and this occurs in 20 to  
15 30 percent of patients, and even more frequently in  
16 the elderly. Unfortunately, patients who suffer  
17 one recurrence often go on to multiple recurrences.

18           The clinical significance of CDI recurrences  
19 cannot be emphasized enough and can be gauged by  
20 the frustration, the fear, and the anxiety of every  
21 patient who knows that a recurrence of CDI or their  
22 next recurrence of CDI might be debilitating or

1 actually land them in the hospital. This is  
2 especially true for the frail or older CDI patient,  
3 who decompensates quickly at the onset of a  
4 recurrence. Hence, the concept of global cure for  
5 CDI has been introduced.

6 Looking at this circle representing all CDI-  
7 treated patients, those patients who achieve  
8 clinical cure are shown here in the blue section of  
9 the pie. These are patients who are cured at the  
10 end of a usual course of therapy. Those patients  
11 who have a clinical cure and do not experience a  
12 recurrence achieve what we call global cure,  
13 represented by the blue section of the circle on  
14 the right. Clinically, global cure is the true  
15 meaning of a cure for the patient with CDI.

16 Recurrences may vary in severity and  
17 actually may be worse than the first occurrence of  
18 this disease. And some individuals have repeated  
19 recurrences, and they occur sequentially over  
20 months or years, each recurrence starting promptly  
21 after finishing CDI therapy. Some recurrences,  
22 especially in the elderly, may require

1 hospitalization.

2           The treatment of CDI recurrences is variable  
3 and frustrating. No single approach has shown  
4 consistently successful results. Physicians often  
5 use oral vancomycin in repeated courses, long  
6 tapering doses, and even so-called pulse doses.  
7 Various probiotics are often taken by the patient  
8 in an attempt to reestablish intestinal flora.  
9 Off-label use of rifaximin has been tried, as has  
10 administration of intravenous immune globulin.  
11 Many desperate individuals seek out and undergo  
12 fecal transplants after multiple recurrences.

13           Unfortunately, current treatment options are  
14 limited. CDI can be treated with either oral  
15 vancomycin, the only approved treatment for CDI in  
16 the U.S. and Canada, or oral metronidazole, which  
17 is used off-label in both countries. The most  
18 significant drawback of oral vancomycin is the high  
19 CDI recurrence rate of 20 to 30 percent. While not  
20 absorbed, and associated with few adverse effects,  
21 it has a wide spectrum of activity at the levels  
22 achieved in the gut, and is able to disrupt the

1 normal intestinal flora.

2 With vancomycin, the treatment regimen is  
3 usually four doses per day, which may lead to some  
4 compliance issues. In addition, the administration  
5 of vancomycin increases the risk of vancomycin-  
6 resistant pathogens such as VRE and VISA.

7 Metronidazole, the other commonly-used  
8 treatment, also has several drawbacks. First of  
9 all, metronidazole has demonstrated a lower cure  
10 rate compared to vancomycin for treating severe  
11 CDI. It has a broad spectrum of activity, which  
12 disrupts the normal gut flora. Further issues with  
13 metronidazole include the fact that it is nearly  
14 fully absorbed, this absorption being associated  
15 with significant adverse effects, including nausea,  
16 metallic taste in the mouth, neuropathy,  
17 leukopenia, and seizures. Neuropathy is also a  
18 significant problem in prolonged administration of  
19 this antibiotic, so it is almost never used for  
20 multiple recurrences. New and better treatments  
21 for CDI are therefore urgently needed.

22 In addition to being safe and well-

1 tolerated, an ideal treatment would have the  
2 following characteristics. It would be  
3 administered orally as a convenient treatment  
4 regimen, with only one or two doses per day; it  
5 would be non-absorbable, working directly on *C.*  
6 *difficile* in the gut; it would have a narrow  
7 spectrum, with potent bactericidal activity against  
8 *C. difficile*; it would create minimal disruption  
9 of normal gut flora, which would not promote  
10 colonization with VRE or other multi-drug-resistant  
11 bacteria; and it would have a low potential of  
12 resistance development.

13           Clearly, we would want this drug to rapidly  
14 resolve the symptoms associated with CDI, such as  
15 diarrhea; have a high reliable efficacy in the  
16 presence of concomitant antibacterials, since many  
17 CDI patients must continue receiving their  
18 antibiotics for the primary infection that they  
19 have; it should have a high cure rate at the end of  
20 treatment, at least equivalent to the best  
21 currently available therapy; and it should retain  
22 that high cure rate for severe CDI. Most

1 importantly, it should also have a low recurrence  
2 rate post-treatment, which would mean a high global  
3 cure rate for the patient.

4 New therapies which possess all these  
5 attributes are needed, most notably, the ability to  
6 decrease the burden of recurrence.

7 Thank you very much for your kind attention.  
8 Dr. Pamela Sears will now present the data on the  
9 microbiology and pharmacology of fidaxomicin.

10 **Applicant's Presentation - Pamela Sears**

11 DR. SEARS: Thank you, Dr. Miller, and good  
12 morning. My name is Pamela Sears, and I'm the  
13 executive director of biology and preclinical  
14 science at Optimer.

15 Today I will be presenting an overview of  
16 the key features in the microbiology and  
17 pharmacology of fidaxomicin. For the microbiology  
18 section, I will discuss the mechanism of action of  
19 fidaxomicin, its microbiological spectrum, and  
20 resistance development. In the pharmacology  
21 section, I will discuss absorption and systemic  
22 exposure, fecal concentrations, and drug-drug

1 interactions.

2           Fidaxomicin has a unique mechanism of  
3 action. It works by inhibition of bacterial  
4 transcriptional initiation, which was confirmed  
5 using clostridial RNA polymerases. Fidaxomicin  
6 inhibited transcription by these enzymes, by IC50  
7 values near a micromolar.

8           In cross-resistance studies, it was shown  
9 that organisms resistant to other antibiotics, such  
10 as the rifamycins or the macrolides, were not  
11 resistant to fidaxomicin, and vice versa. The lack  
12 of cross-resistance with these antibacterials  
13 indicates that fidaxomicin has a unique mode of  
14 action, and this was also supported by mechanistic  
15 studies.

16           Fidaxomicin is a narrow-spectrum antibiotic  
17 and has high activity versus *Clostridium difficile*,  
18 with an MIC90 of 0.25 micrograms per mL. The  
19 activity of fidaxomicin against other bacteria has  
20 been assessed in several laboratories. These  
21 studies demonstrated that fidaxomicin has moderate  
22 activity versus gram-positive organisms such as

1 staphylococcus species, with an MIC90 of 2  
2 micrograms per mL, and enterococcus species, with an  
3 MIC90 of 8 micrograms per mL. And this includes  
4 activity versus vancomycin-resistant enterococcal  
5 species, leading to a low potential for VRE  
6 colonization. Finally, fidaxomicin has no activity  
7 versus gram-negative organisms or yeast.

8           Fidaxomicin, at concentrations greater than  
9 4 times the MIC, demonstrates bactericidal activity  
10 toward all strains of C. difficile tested, with at  
11 least a one-thousandfold drop in titer over 48  
12 hours. This killing was time- and not  
13 concentration-dependent.

14           The post-antibiotic effect, or PAE, measures  
15 the continued suppression of C. difficile growth  
16 following removal of the antibiotic. Fidaxomicin  
17 has a PAE of approximately 10 hours, and this means  
18 that fidaxomicin's bactericidal activity continues  
19 between dosing. This feature contributed to and  
20 supports our choice of twice-daily dosing. By  
21 contrast, the PAE for vancomycin is less than one  
22 hour.

1           Now I would briefly like to discuss  
2 antibiotic resistance development. In the  
3 laboratory, resistance in strains of *C. difficile*  
4 was infrequent, with a frequency of spontaneous  
5 resistance values for fidaxomicin being less than  
6  $4 \times 10$  to the minus 9th. In serial passaging  
7 experiments, the MIC reached a plateau of 2  
8 micrograms per mL at passage 14, and this was  
9 maintained for an additional 4 passages.

10           In our phase 3 studies, final isolates were  
11 collected in cases of failure or recurrence. All  
12 isolates had similar fidaxomicin MIC values at the  
13 start and at the end of therapy, which means that  
14 the MIC values were within 1 to 2 dilutions in  
15 either direction.

16           One subject had an isolate with a reduced  
17 susceptibility at recurrence, with an MIC value of  
18 16 micrograms per mL, which, as will be shown, is  
19 still well below the achievable concentrations of  
20 fidaxomicin in the gut.

21           Turning now to pharmacokinetics, fidaxomicin  
22 is predominately confined to the gut following oral

1 administration. Excretion of fidaxomicin or its  
2 metabolite in urine is less than 1 percent, and the  
3 drug is predominately excreted in the feces. In a  
4 radiolabel study in dogs dosed with approximately  
5 the human dose by weight, over 99 percent of the  
6 recovered radiolabel remained in the feces.

7 In healthy subjects, the pharmacokinetics of  
8 fidaxomicin and its main metabolite, OP-1118,  
9 following a single 200-milligram oral dose of  
10 fidaxomicin, show low systemic exposure. I should  
11 note that here and throughout the presentation, the  
12 plasma concentrations are presented in nanograms,  
13 not micrograms, per mL. The Cmax is 9.9 nanograms  
14 per mL and approximately that for the metabolite.

15 In subjects in our phase 3 studies, plasma  
16 concentrations of fidaxomicin were somewhat higher  
17 than in healthy individuals; however, they were  
18 still in the low nanogram-per-mL range. Here we  
19 see the plasma concentration of fidaxomicin on  
20 day 1 of dosing, with a mean of 22.8 nanograms per  
21 mL in phase 3 subjects.

22 The mean plasma concentrations in healthy

1 volunteers, after 200- and 400-milligram doses,  
2 were 5.2 and 3.6 nanograms per mL, respectively.  
3 There was no evidence of accumulation observed,  
4 based on the similarity between the day 1 and day  
5 10 levels of fidaxomicin in the phase 3 subjects.  
6 The healthy subject studies, I should note, were  
7 single-dose studies, so only day 1 data were  
8 collected and presented.

9 By contrast, with the low plasma  
10 concentrations of fidaxomicin, the mean fecal drug  
11 levels are upwards of 1000 micrograms per gram,  
12 which are several thousand times higher than the  
13 MIC90. These results indicate that fidaxomicin has  
14 a favorable PK profile for the treatment of CDI.

15 Fidaxomicin and its main metabolite have  
16 been investigated both in vitro and in vivo for  
17 their potential to interact pharmacokinetically  
18 with other drugs. Fidaxomicin and its main  
19 metabolite are not sufficiently mobilized by  
20 cytochrome P450 enzymes. Although they are weak  
21 inhibitors of certain CYP enzymes in vitro, they  
22 showed no interaction with CYP substrates

1 omeprazole, midazolam, or warfarin in a clinical  
2 drug-drug interaction study.

3           Fidaxomicin and its main metabolite are  
4 substrates for P-glycoprotein, or P-gp, which is an  
5 efflux transporter. And while administration with  
6 cyclosporine, a potent P-glycoprotein inhibitor,  
7 increased plasma concentrations of fidaxomicin and  
8 its main metabolite, they remained in the low  
9 nanogram-per-mL range, with no safety impact  
10 observed. And, therefore, this increase is not  
11 considered clinically relevant. Fidaxomicin is  
12 also a P-gp inhibitor, but no interaction was  
13 observed when it was administered with digoxin,  
14 which is a P-gp substrate.

15           In summary, fidaxomicin has excellent  
16 microbiological and pharmacological properties for  
17 treating C. difficile infection. It has cidal  
18 activity versus C. difficile across the many strain  
19 types that we've studied. It has no activity  
20 versus many of the other organisms found in the  
21 gut.

22           It has a prolonged post-antibiotic effect,

1 which may be helpful in diarrheal disease where the  
2 drug may be more rapidly cleared than in healthy  
3 individuals. Its mode of action is distinct from  
4 that of other marketed drugs and no cross-  
5 resistance has been observed. Thus, the current  
6 population of C. difficile is expected to be naive  
7 to this mechanism.

8 It is minimally absorbed, remaining  
9 primarily in the gut, which is the site of  
10 infection, where it achieves concentrations well  
11 above the MIC90 of the pathogen. Plasma  
12 concentrations, by contrast, are typically in the  
13 low nanogram-per-mL range, minimizing the chance of  
14 systemic side effects. And finally, no significant  
15 drug-drug interactions have been identified in  
16 clinical studies.

17 Thank you, and Dr. Gorbach will now return  
18 to review the efficacy that we saw in our phase 3  
19 studies.

20 **Applicant's Presentation - Sherwood Gorbach**

21 DR. GORBACH: Thank you, Dr. Sears.

22 In addition to the two phase 3 studies,

1       which we will present in detail, the safety and  
2       efficacy of fidaxomicin has been evaluated in  
3       multiple earlier studies, where we examined  
4       fidaxomicin and the effects on food,  
5       bioavailability, optimal dosing, and drug-drug  
6       interactions. The latter were discussed by Dr.  
7       Sears.

8               Looking at the phase 3 trials in more  
9       detail, both studies were identical in design.  
10       They were multi-centered, randomized, double-  
11       blinded studies using vancomycin as the comparator.  
12       Oral vancomycin was selected because it is  
13       generally accepted to be superior to metronidazole  
14       in the treatment of *C. difficile* infection. In  
15       addition, vancomycin is the only FDA-approved  
16       treatment for *C. difficile* infection in the U.S.

17               All subjects received study drug four times  
18       a day to maintain the double-blind, and the blind  
19       was maintained through database lock. Both trials  
20       followed the same dose and dosing regimen, 200  
21       milligrams every 12 hours for 10 days in the  
22       fidaxomicin arm, and 125 milligrams every six hours

1 for 10 days in the vancomycin arm. In addition,  
2 there was a 30-day follow-up period after the end  
3 of treatment.

4 In order to be randomized to either trial,  
5 subjects had to be 16 years of age or older. All  
6 subjects were required to have diarrhea, defined as  
7 more than 3 unformed bowel movements in the 24  
8 hours before randomization and a diagnosis of C.  
9 difficile infection confirmed by the presence of  
10 either toxin A or B in the stool. To alleviate the  
11 concern of physicians of the rapidly advancing  
12 nature of this disease, subjects could have  
13 received up to 24 hours of pretreatment with  
14 vancomycin or metronidazole.

15 Subjects were excluded from the trials if  
16 they had a life expectancy of less than 72 hours;  
17 for example, those with fulminant colitis, toxic  
18 megacolon, and ileus. Other notable exclusion  
19 criteria were conditions such as ulcerative  
20 colitis, Crohn's disease, drugs to treat diarrhea  
21 such as loperamide, or drugs effective in the  
22 treatment of CDI such as Bacitracin and fusidic

1 acid. No exclusions were allowed in either of the  
2 protocols for abnormal laboratory values, and  
3 specifically not excluded were subjects with  
4 cancer, leukemia, renal failure, or subjects  
5 admitted to the ICU.

6 In our phase 3 studies, two co-primary study  
7 populations were defined. First, we defined the  
8 modified intent to treat, or MITT. The MITT  
9 population was defined as the group of subjects  
10 that were randomized with a confirmed diagnosis of  
11 *C. difficile*  
12 infection, which was defined as having more than  
13 three unformed bowel movements in the 24 hours  
14 prior to randomization, and at least one positive  
15 toxin test, and at least one dose of study  
16 medication.

17 Secondly, we defined our other co-primary  
18 population, the per-protocol population. The per-  
19 protocol population had to meet all of the criteria  
20 of the MITT population. In addition, subjects  
21 needed to have at least three complete days of  
22 treatment for failure assessment, or eight complete

1 days of treatment for cure assessment. And all  
2 subjects had to have had an end-of-treatment  
3 clinical evaluation, and there could be no major  
4 protocol violation.

5 Study 003 enrolled 629 subjects with 306  
6 randomized to the fidaxomicin arm and 323 to  
7 vancomycin. The MITT population had 289 subjects  
8 for the fidaxomicin arm and 307 subjects for  
9 vancomycin. Most subjects were excluded from the  
10 MITT population because they either did not test  
11 positive for toxin A or B or because they did not  
12 meet the definition of diarrhea. For the per-  
13 protocol population, the numbers are 268 and 280,  
14 respectively. The main reason for not qualifying  
15 for the per-protocol population was insufficient  
16 duration of therapy.

17 Study 004 enrolled 535 subjects; 271 were  
18 randomized to the fidaxomicin arm and 264 to  
19 vancomycin. The MITT population had 253 and 256  
20 subjects respectively. The reason for excluding  
21 subjects from the MITT population were similar to  
22 those in study 003. And the per-protocol

1 population had 217 and 234 subjects, respectively,  
2 with insufficient duration of therapy as the main  
3 reason for not qualifying for per-protocol  
4 population, similar to study 003.

5 In each study, the primary endpoint was  
6 clinical cure. The definition of a clinical cure  
7 in both studies was a subject who had less than or  
8 equal to three unformed bowel movements for 2  
9 consecutive days, or a subject who at the end of  
10 therapy had a marked reduction in the number of  
11 unformed bowel movements but who had residual or  
12 mild discomfort, interpreted as recovering bowel by  
13 the investigator. Also, any subjects who required  
14 further C. difficile therapy within two days of  
15 completion of study medication was considered a  
16 failure.

17 The primary analysis for each of the two  
18 studies was conducted in two co-primary  
19 populations, the per-protocol and the MITT  
20 populations, using a noninferiority analysis with a  
21 margin of 10 percent. Success required  
22 demonstrating noninferiority in both populations.

1           A sensitivity analysis of the primary  
2 endpoint was done based only on the number of  
3 unformed bowel movements, and is defined as  
4 achieving less than or equal to three unformed  
5 bowel movements for two consecutive days. Subjects  
6 who did not meet this definition were considered  
7 failures in the sensitivity analysis.

8           Recurrence was specified as a secondary  
9 endpoint in both studies. The definition of  
10 recurrence was the reestablishment of diarrhea  
11 following clinical cure, with a frequency of  
12 unformed bowel movements that was greater than that  
13 noted on the last day of study medication, with the  
14 demonstration of toxin A or B, and that, in the  
15 investigator's opinion, would require retreatment  
16 with *C. difficile* anti-infective therapy. The  
17 recurrence endpoint was analyzed as a superiority  
18 analysis.

19           We also examined global cure. Global cure  
20 was achieved if a subject met the primary endpoint  
21 of clinical cure at the end of treatment and no  
22 recurrence during the 30 days of follow-up. Global

1 cure was defined as an exploratory endpoint in  
2 study 003 and as a secondary endpoint in study 004.  
3 The global cure endpoint was analyzed as a  
4 superiority analysis.

5 Now, looking at the actual study data, the  
6 demographic profile was similar in the two studies.  
7 The enrolled population reflects the general  
8 demographics of this disease, which is skewed  
9 towards the elderly. More subjects in the study  
10 004 were inpatients, but the two studies were  
11 otherwise similar. Within each study, the baseline  
12 characteristics were balanced in both treatment  
13 arms.

14 Here we have displayed the baseline severity  
15 statistics. As you can see, both studies and both  
16 arms of each study had representations of subjects  
17 with mild, moderate, and severe disease. As  
18 previously mentioned, subjects who were critically  
19 ill were excluded from these studies.

20 Turning now to the results of our primary  
21 endpoint of clinical cure, we see that in study  
22 003, the proportion of subjects cured at the end of

1 10 days' treatment was similar in both treatment  
2 groups. We'll highlight the per-protocol  
3 population for the noninferiority analysis.

4 The clinical cure rate was 92.2 percent in  
5 the fidaxomicin group and 89.6 percent for  
6 vancomycin. Similar results were seen in study  
7 004, 91.7 percent clinical cure rate for  
8 fidaxomicin and 90.6 percent for vancomycin. In  
9 both studies, the 95 percent confidence interval  
10 was well within the predefined noninferiority  
11 margin of 10 percent. The MITT results for both  
12 studies showed similar findings.

13 In study 003, the proportion of subjects  
14 cured using a sensitivity analysis of the clinical  
15 cure at the end of 10 days' treatment was similar  
16 in both treatment groups. The cure rate was 84.3  
17 percent in the fidaxomicin group and 86.1 percent  
18 for vancomycin. Similar results were seen in study  
19 004, 86.2 percent cure rate for fidaxomicin and  
20 84.2 percent for vancomycin. The MITT results for  
21 both studies were also similar.

22 Next we'll look at our secondary endpoints,

1 first recurrence. Only subjects who achieved  
2 clinical cure were assessed for recurrence  
3 assessment. A significantly lower number of  
4 subjects in the fidaxomicin arms experienced  
5 recurrence compared to those in the vancomycin  
6 arms. As this was a superiority analysis, we will  
7 highlight the MITT percentages.

8 The fidaxomicin recurrence rate in study 003  
9 was 15.7 percent versus 25.1 percent for  
10 vancomycin. In study 004, the fidaxomicin  
11 recurrence rate was 12.6 percent compared to 27  
12 percent for vancomycin. The differences are both  
13 statistically significant in favor of fidaxomicin,  
14 and clinically meaningful.

15 Next we'll review the global cure rates. As  
16 mentioned earlier, global cure was defined as  
17 achieving a cure rate without a recurrence. Global  
18 cure rates were significantly superior for subjects  
19 treated with fidaxomicin compared to vancomycin.  
20 Approximately, 75 percent of the fidaxomicin  
21 subjects achieved global cure compared to  
22 approximately 64 percent in the vancomycin group.

1 The differences are both statistically significant  
2 and clinically meaningful.

3 Another way of looking at global cure is  
4 reviewing the pooled data from our two phase 3  
5 studies. Considering the treatment failure rates  
6 were similar for fidaxomicin and vancomycin, it is  
7 clearly visible that the superior global cure rate  
8 for fidaxomicin is mainly driven by the  
9 significantly fewer recurrences for fidaxomicin,  
10 12.5 percent, versus 22.4 percent for vancomycin in  
11 this analysis.

12 Multiple pre-specified subgroup analyses on  
13 clinical cure and recurrence will now be presented.  
14 Here we see a forest plot of the clinical cure rate  
15 for the overall population for each study. We also  
16 analyze the data by basic demographic subgroups, by  
17 sex, age, and patient status at randomization.

18 As you can see, fidaxomicin was similar to  
19 vancomycin across these subgroups in both trials.  
20 Similarly, when we examine subgroups related to the  
21 disease state, we saw no notable differences. This  
22 was true for subjects with either single or no

1 prior episode; for severe CDI, using the ESCMID  
2 severity score; and when we reviewed outcome by the  
3 presence of the so-called hypervirulent BI strain,  
4 we see that fidaxomicin was similar to vancomycin.

5 Finally, we reviewed the clinical cure rate  
6 outcomes by antibiotic and P-gp inhibitor use. We  
7 looked at the use of CDI therapy within 24 hours of  
8 treatment, and concomitant use of systemic  
9 antibiotics, and the use of P-gp inhibitors.  
10 Again, here we see that fidaxomicin was similar to  
11 vancomycin.

12 We did the same type of analysis for  
13 recurrence rates. Fidaxomicin was superior in the  
14 overall population. In addition, all demographic  
15 subgroups had consistent and robust results  
16 favoring fidaxomicin, although, due to the small  
17 sample size, in some of the subgroups it did not  
18 reach superiority.

19 The disease state subgroups for recurrence  
20 rates are generally consistent with the overall  
21 population. All subgroups are favoring  
22 fidaxomicin, with the exception of the BI strain

1 subgroup in study 003. However, findings in the  
2 study 004 followed the usual trend of fidaxomicin  
3 for recurrence.

4 Finally, we reviewed the recurrence rates by  
5 antibiotic or P-gp inhibitor use, and similar  
6 results were seen in these subgroups. Even in  
7 subjects who were on concomitant P-gp inhibitors,  
8 fidaxomicin had a significantly lower recurrence  
9 rate than vancomycin in both studies.

10 In conclusion, these phase 3 studies  
11 establish that fidaxomicin was noninferior to  
12 vancomycin for the primary endpoint of clinical  
13 cure. In addition, the study demonstrated that  
14 fidaxomicin was significantly superior to  
15 vancomycin in reducing recurrence rates of  
16 C. difficile infection. Global cure rates were  
17 also significantly superior for subjects treated  
18 with fidaxomicin compared to vancomycin.

19 The advantage of fidaxomicin treatment over  
20 vancomycin treatment in higher global cure rates  
21 and lower recurrence rates were consistent between  
22 studies and within study population subgroups and

1 baseline characteristics, supporting the position  
2 that fidaxomicin is effective in the treatment of  
3 CDI.

4 Now I'm pleased to induce Dr. Michael  
5 Corrado, who will talk about the safety aspects of  
6 fidaxomicin.

7 **Applicant's Presentation - Michael Corrado**

8 DR. CORRADO: Thank you, Dr. Gorbach, and  
9 good morning. I'm Michael Corrado, chief  
10 scientific officer for INC Research. I've been  
11 involved in clinical drug development of  
12 anti-infectives for 30 years, and specifically  
13 involved in the fidaxomicin development since 2004.

14 Today, we will review the pooled adverse  
15 event data from two phase 3 studies, which  
16 represent 564 fidaxomicin-treated subjects. The  
17 safety data from phase 1 and phase 2 studies did  
18 not indicate any specific safety concerns.

19 Safety variables assessed in all studies  
20 consistent of the following: the occurrence of  
21 adverse events and serious adverse events; changes  
22 in laboratory values, vital signs; and ECGs. A

1 summary of the adverse events for subjects in these  
2 studies is presented here, and as can be seen, the  
3 overall incidence of adverse events was similar in  
4 the fidaxomicin and vancomycin treatment groups;  
5 68.3 percent and 65.5 percent of subjects  
6 respectively had adverse events.

7 Adverse events considered by the  
8 investigator as drug-related or leading to  
9 discontinuation was similar between regimens.  
10 Finally, we see that serious adverse events and  
11 all-cause mortality were similar between both  
12 groups.

13 For adverse events reported by more than  
14 5 percent of subjects in either treatment group,  
15 again the distribution is similar between the  
16 groups. Slightly more subjects receiving  
17 fidaxomicin had vomiting, hypokalemia, headache,  
18 and abdominal pain. Somewhat more subjects with  
19 diarrhea and pyrexia were seen in the vancomycin  
20 group.

21 All these events, with the possible  
22 exception of the headaches, could well be

1 associated with the underlying C. difficile  
2 infection. Thus, it is not surprising that they  
3 represent some of the most common adverse events  
4 seen in either group.

5 In the phase 3 studies, there was a low  
6 incidence of adverse events for which drug was  
7 stopped permanently or the subject discontinued  
8 from the study. The overall incidence of adverse  
9 events leading to study drug discontinuation was  
10 slightly lower in the fidaxomicin group than in the  
11 vancomycin group.

12 In the fidaxomicin group, all adverse events  
13 that led to discontinuation occurred in 1/2 percent  
14 of subjects or fewer. Vomiting was the most  
15 frequent fidaxomicin adverse event leading to drug  
16 discontinuation, and this occurred at an incidence  
17 of one-half percent in both groups. Many of these  
18 adverse events could be associated with the  
19 underlying CDI.

20 The serious adverse event profile between  
21 fidaxomicin and vancomycin were very similar, with  
22 25.7 percent of the subjects in the fidaxomicin

1 group and 23.2 percent of the subjects in the  
2 vancomycin group experiencing a serious adverse  
3 event. The most frequently reported serious  
4 adverse events were the types of events that one  
5 might expect in CDI or complications that  
6 frequently occur among the elderly, the  
7 hospitalized, and the very sick.

8 In the pooled phase 3 studies, a similar  
9 number of subjects died in the fidaxomicin arm --  
10 36 subjects -- compared to 38 deaths in subjects  
11 treated with vancomycin. The most common  
12 system/organ class among subjects who died was  
13 infections and infestations, with 11 in each group.  
14 All of these 74 deaths were assessed by the  
15 investigators as reflective of the underlying  
16 clinical condition of the subjects.

17 It is of interest to look at GI events since  
18 the majority of fidaxomicin stays in the intestinal  
19 lumen and exerts its effects there. The number of  
20 subjects with GI adverse events and serious adverse  
21 events was similar between the fidaxomicin and  
22 vancomycin group. The number of subjects with GI

1 adverse events leading to discontinuation was  
2 slightly higher, and the number of GI adverse  
3 events leading to death slightly lower in the  
4 fidaxomicin group.

5 GI bleeding is a specific GI adverse event  
6 that we investigated. There was a disproportionate  
7 number of GI bleeding adverse events reported in  
8 the fidaxomicin group, 20 versus 10. Even though  
9 these adverse events are the type of events that  
10 might be seen in CDI itself, we decided to review  
11 all safety data in detail to ensure that all  
12 episodes of GI bleeding had been captured.

13 We queried the database for terms related to  
14 bleeding. All records containing these terms were  
15 individually reviewed to ensure that the condition  
16 was, in fact, treatment-emergent. We also examined  
17 all serious adverse event narratives for bleeding  
18 events that may not have been stated as adverse  
19 events but merely contained within a serious  
20 adverse event. For example, a subject with  
21 ischemic colitis and which occurred with bloody  
22 stools had only ischemic colitis listed as a

1 serious adverse event, without bloody stools being  
2 noted as an adverse event.

3 This review resulted in 23 subjects in the  
4 fidaxomicin group and 18 in the vancomycin group  
5 who had adverse events related to bleeding in the  
6 GI tract. In nonclinical studies, GI bleeding was  
7 not observed even following dosing of 1 gram per  
8 kilogram per day for 3 months in the dog, which is  
9 approximately 150 times the human dose and nine  
10 times longer than 10-day treatment in humans. More  
11 specifically, there was no evidence of macroscopic  
12 GI bleeding and no microscopic findings indicative  
13 of GI toxicity.

14 In summary, the GI bleeding events were  
15 similar between the groups of fidaxomicin and  
16 vancomycin, 23 versus 18, and there was no signal  
17 for GI bleeding in nonclinical studies. There was  
18 a second apparent imbalance that we analyzed, that  
19 of leukopenia or neutropenia. In total, there were  
20 15 subjects in the fidaxomicin group and 5 in the  
21 vancomycin group who had leukopenia- or  
22 neutropenia-related adverse events. The most

1 common reported terms were leukopenia, neutropenia,  
2 or decreased neutrophil count.

3 It's important to note that two cases of  
4 serious adverse events -- one case of fever and  
5 neutropenia and one case of neutropenic  
6 sepsis -- had neutropenia already present at study  
7 entry. Finally, the majority of these events were  
8 resolved during the 40-day study period.

9 We reviewed each case in detail and found  
10 that more subjects in the fidaxomicin group began  
11 cytotoxic chemotherapy while on study, or had  
12 systemic lupus erythematosus, or had stem cell  
13 transplants. Furthermore, some subjects had more  
14 than one of these risks. These factors may be a  
15 partial explanation for the imbalance in white  
16 blood cell adverse events. The number of subjects  
17 with no clear explanation of neutropenia was  
18 similar between groups.

19 In nonclinical toxicologic studies,  
20 cellularity of bone marrow, spleen, and blood were  
21 examined in a number of species in repeat dose  
22 studies, including the dog, rat, rabbit, and

1 monkey. In these studies, white blood cell counts  
2 were not adversely affected by fidaxomicin  
3 treatment. Similarly, microscopic examinations  
4 showed no toxicity on tissue cellularity of bone  
5 marrow or spleen in any of the species, even at  
6 fidaxomicin exposure levels well in excess of  
7 plasma exposure in humans.

8           There was no toxicity of fidaxomicin on  
9 white blood cells noted in nonclinical studies,  
10 even at high exposure levels and dosing durations  
11 sufficient to manifest these toxicities, and, thus,  
12 no concerns for humans had been identified in any  
13 of these studies.

14           In summary, leukopenia-related adverse  
15 events were more frequent in the fidaxomicin group,  
16 but this could partially be explained by more  
17 subjects having treatment with chemotherapy, lupus  
18 erythematosus, or bone marrow transplant, or in  
19 some cases more than one risk factor.

20           We also examined a broad range of laboratory  
21 values and vital signs and cardiovascular measures.  
22 No clinically significant differences in clinical

1 chemistry parameters were noted between treatment  
2 groups. After analyzing ALT, AST, and bilirubin,  
3 it can be concluded that the hepatic chemistry  
4 profile is not significantly changed by either  
5 fidaxomicin or vancomycin, and most importantly, no  
6 subjects met Hy's law.

7 The fidaxomicin and vancomycin groups were  
8 similar with respect to vital signs and ECGs. In  
9 these phase 3 studies, as might be expected with  
10 two compounds that both have very low systemic  
11 bioavailability, fidaxomicin showed an incidence of  
12 adverse events, serious adverse events, and deaths  
13 that were similar to vancomycin. Reports of  
14 serious adverse events, including all of those with  
15 a fatal outcome, appear to be consistent with the  
16 underlying clinical condition of the individual  
17 subjects and do not suggest a role of fidaxomicin,  
18 as shown by similar rates for these events in  
19 subjects treated with vancomycin.

20 The GI or GI bleeding events were generally  
21 similar between the fidaxomicin and vancomycin  
22 groups, and there was no signal in high dose

1 preclinical toxicologic studies. There were more  
2 subjects with an underlying medical condition that  
3 could lead to leukopenia in the fidaxomicin group,  
4 and there was no signal in the long duration  
5 nonclinical studies. There were no clinically  
6 significant changes in vital signs and ECGs in  
7 either treatment group. And, overall, it can be  
8 concluded that fidaxomicin was a well-tolerated  
9 treatment.

10 I would now like to turn the podium back  
11 over to Dr. Gorbach for his closing comments.

12 Thank you.

13 **Applicant's Presentation - Sherwood Gorbach**

14 DR. GORBACH: Thank you, Dr. Corrado.

15 In closing, I would like to mention our  
16 plans for continued evaluation and studies of  
17 fidaxomicin.

18 In addition to standard pharmacovigilance  
19 practices, Optimer plans on a microbiological  
20 surveillance program to monitor the development of  
21 resistance and shifts in and among REA types of  
22 C. difficile strains. Since anaerobic cultures for

1 C. difficile is not routine in most clinical  
2 laboratories, we will ask six centers across the  
3 United States to set up anaerobic facilities to  
4 isolate C. difficile. Antibiotic sensitivity  
5 testing will be conducted using standard CLSI  
6 methods in a central laboratory on 450 isolates per  
7 year.

8 In addition, REA typing will be performed on  
9 200 isolates per year. We are also planning an  
10 intervention study to determine the effectiveness  
11 and safety of fidaxomicin in treatment of subjects  
12 with multiple recurrences. We are in the process  
13 of performing in vitro studies on the effects of  
14 fidaxomicin on sporulation, germination, and the  
15 inhibition of toxin production by C. difficile.

16 We have also requested and received orphan  
17 drug status for the pediatric population, and the  
18 pediatric plan is under discussion with the FDA.  
19 The proposed program will be conducted as two  
20 studies. Study 1 will be a safety and PK study,  
21 and study 2 will be a safety and efficacy study,  
22 with vancomycin as a comparator. Both studies will

1 enroll children 2 to 18 years of age, and an oral  
2 suspension formulation is currently under  
3 development for those children unable to swallow  
4 tablets. The precise design of the program will be  
5 finalized after feedback from the FDA.

6 I'd now like to summarize the data discussed  
7 by our presenters today. As Dr. Miller outlined,  
8 CDI is a serious disease with an increasing  
9 incidence with a high morbidity, sometimes fatal  
10 outcome. Recurrences are common and in the order  
11 of 20 to 30 percent following initial therapy.

12 The two current treatment options for  
13 C. difficile infection have serious limitations.  
14 No new treatments have been approved for almost  
15 three decades. There is a clear unmet medical need  
16 for treatments, especially those that will decrease  
17 recurrences and increase global cures.

18 In the microbiology section, we demonstrated  
19 that fidaxomicin has an excellent profile for  
20 treating C. difficile infections with its narrow  
21 spectrum bactericidal activity against C.  
22 difficile, which leads to almost no disturbance of

1 the normal gut microbiota. Fidaxomicin's low  
2 absorption and high fecal concentrations deliver  
3 the antibiotic effects where it is necessary. Due  
4 to its unique mechanism of action, fidaxomicin has  
5 a low potential for resistance development, and no  
6 cross-resistance has been shown.

7 The clinical development program shows that  
8 fidaxomicin meets all key criteria for an effective  
9 treatment against CDI. Two independent phase 3  
10 clinical studies have demonstrated that fidaxomicin  
11 has a clinical cure rate that is noninferior to  
12 vancomycin. Importantly, the reduction in  
13 recurrence rate is significantly superior in the  
14 fidaxomicin group, and global cure rate is  
15 significantly superior to vancomycin, thus  
16 providing a clear benefit to patients with this  
17 disease.

18 Also, fidaxomicin is well-tolerated. It  
19 acts locally within the GI tract with minimal  
20 systemic absorption, leading to a good safety  
21 profile similar to that of oral vancomycin. In our  
22 phase 3 studies, the incidence of adverse events,

1 discontinuation due to adverse events, serious  
2 adverse events, and deaths were similar for the  
3 fidaxomicin and vancomycin arms.

4 GI bleeding events were similar between  
5 groups after careful review of all safety  
6 information. There were more subjects with  
7 underlying medical conditions that could lead to  
8 leukopenia in the fidaxomicin group, and there was  
9 no signal for leukopenia in the nonclinical  
10 studies. And there were no clinically meaningful  
11 drug-drug interactions.

12 The data demonstrate that fidaxomicin has a  
13 high cure rate, similar to that of vancomycin. In  
14 addition, fidaxomicin has a significantly superior  
15 reduction of recurrences which meets a major unmet  
16 medical need. Also, fidaxomicin has a  
17 significantly superior global cure rate and less  
18 potential for colonization with vancomycin-  
19 resistant enterococcus, and with a safety profile  
20 similar to that of vancomycin. Therefore, it can be  
21 concluded that the benefit-risk profile is  
22 positive, and fidaxomicin should be approved as a

1 first-line treatment for CDI.

2 Thank you for your time and attention. We  
3 look forward to a meaningful dialogue and to  
4 answering all of your questions.

5 **Questions/Clarifications**

6 DR. GOETZ: Thank you.

7 The floor is now open for questions from the  
8 committee regarding clarifications of the sponsor's  
9 presentation. Dr. Follman?

10 DR. FOLLMAN: Yes. Thank you for the  
11 presentation. I was wondering if you could go to  
12 slide 33. This is a slide that talks  
13 about -- well, there it is.

14 So I wanted to understand this better. This  
15 is the concentration of fidaxomicin in the blood  
16 some time after administration. Is that right?

17 DR. CORRADO: That's correct.

18 DR. FOLLMAN: So I was struck by -- if you  
19 look at the first column there of numbers, you look  
20 at the range from .4 to 197. So it seemed like  
21 there was at least one individual who had a lot of  
22 exposure.

1           Do you have anything to say about that? Was  
2           that an isolated individual, or do you find a few  
3           people, maybe 5 or 10 or something, that tend to  
4           have a lot of exposure for some reason, do you  
5           understand why they have that?

6           DR. CORRADO: I'd like to ask Dr. Sears to  
7           come up to address that.

8           DR. SEARS: Yes. You certainly do notice  
9           that there is a range. Most individuals do have  
10          the low what you see as the mean, 20 to 30  
11          nanograms per mL. But you do see some individuals  
12          with higher. This is quite possibly due to just  
13          changes in the gut during the course of the  
14          disease.

15          It's been shown, for example, with  
16          vancomycin, there have been a number of  
17          publications that show that absorption of  
18          vancomycin in the context of C. difficile disease  
19          is higher than you might expect. So there have  
20          been some publications that have shown that people  
21          can get, for example, red man syndrome with oral  
22          vancomycin when they have C. difficile infection.

1 And this, we suspect, is probably the reason why  
2 you do see some individuals with higher  
3 concentrations.

4 DR. FOLLMAN: Just that their gut is weaker  
5 or more porous or whatever and lets the drug in.

6 Another thing you commented about toward the  
7 end of the study was the leukopenias and  
8 neutropenia, which seems strange, maybe, if it's  
9 mostly expelled through the GI tract. And I was  
10 wondering if you had examined those people who had  
11 leukopenia or neutropenia in terms of the exposure.

12 DR. SEARS: We have, and they aren't notably  
13 higher. I mean, if you look at the mean, it's a  
14 little bit higher because we have one  
15 individual -- well, here we have the median --  
16 slide on, please. If you look at the median here,  
17 it's 21.2, which is pretty similar to the overall  
18 population at 13.5.

19 So it's not a notable increase. We do have  
20 one in there that's 179. We've removed -- there's  
21 no mean here. It drives the mean up a small  
22 amount. But, in general, there's really no

1 increase in plasma exposure that would explain this  
2 kind of finding.

3 DR. FOLLMAN: Did you do a statistical test  
4 of this?

5 DR. SEARS: No. There was no statistical  
6 test of this. I should note, however, that these  
7 concentrations, certainly you see these kinds of  
8 concentrations in individuals that do not have  
9 leukopenia, and these concentrations are also far  
10 lower than the concentrations that we saw in  
11 nonclinical studies, with no evidence of  
12 leukopenia.

13 DR. FOLLMAN: Then I have another kind of  
14 question, which has to do with the global cure  
15 endpoint, which I think is a very strong argument  
16 for efficacy, really.

17 Was the study blinded over the 30 days? You  
18 had a 10-day primary evaluation. The global cure  
19 is more over the 30-day period. Was it blinded  
20 throughout that?

21 DR. CORRADO: The study was blinded -- it  
22 was blinded throughout the entire study. I'll have

1 Dr. Gorbach come up to describe the study blinding  
2 and a little bit more on global cure.

3 DR. GORBACH: The study was blinded to  
4 database lock, yes. So perhaps you want to  
5 continue with your question.

6 DR. FOLLMAN: Yes. No, I'm fine if you just  
7 say it's blinded.

8 Then I was just wondering just as a  
9 curiosity, do you have any ideas as to why you have  
10 higher global cure rates, lesser occurrence, when  
11 you stop drug in either arm at 10 days? And you  
12 say it's expelled very quickly and so on. So how  
13 could it have a lingering effect? Does it kill  
14 spores, or do you have any idea as to the  
15 explanation for why it has a better global cure  
16 rate?

17 DR. GORBACH: Well, the major argument  
18 that's used by many experts in this field is that  
19 change in flora is what allows for recurrences.  
20 That is, the anaerobic flora normally has an  
21 inhibition over organisms coming in, and it's  
22 inhibitory. They call it colonization resistance.

1 It's a well-known phenomenon.

2 So we presume that vancomycin, even though  
3 it's not known as a gram-negative drug, it's been  
4 shown by Sydney Feingold that in the concentrations  
5 achieved in the gut, very high concentration, it in  
6 fact suppresses gram-negative organisms in the gut.

7 There is another explanation, as you alluded  
8 to, and that's sporulation. And we do have some  
9 preliminary data from our laboratory -- not only  
10 our laboratory, but also Dr. Linc Sonenshein at  
11 Tufts University -- that this drug reduces spore  
12 count.

13 Slide on, please. So in clinical  
14 studies -- this is a study by Louie; it was  
15 presented at the ICAAC meeting -- the spore counts  
16 were two logs less in the fidaxomicin group. And  
17 there are also in vitro laboratory studies that  
18 show that fidaxomicin uniquely has, at one-quarter  
19 the MIC -- you obviously have to use a low dose so  
20 you don't kill the bug.

21 Slide on, please. If you look at the bottom  
22 line, you'll see the fidaxomicin at one-quarter the

1 MIC, which suppresses spore counts, whereas the  
2 upper lines are controls and also vancomycin as a  
3 comparator.

4 So it could either be this reduction in  
5 spores, which of course are the little nut, the  
6 acorn, kind of, from which the organism blooms, or  
7 it could be the preservation of colonization  
8 resistance. Thank you.

9 DR. GOETZ: Dr. Sepkowitz?

10 DR. SEPKOWITZ: Thanks for that  
11 presentation. I have a question also about  
12 recurrence.

13 You stopped at 30 days from diagnosis. The  
14 typical CDC range is eight weeks that we look at.  
15 I'm wondering if you could provide us with a  
16 frequency distribution of when recurrences occurred  
17 because it's noteworthy that in the hypervirulent  
18 strain, there doesn't seem to be a difference in  
19 prevention of recurrence. And I'm wondering if the  
20 study drug might just move the time of recurrence  
21 out past the 30-day mark but not get rid of it  
22 altogether.

1 DR. CORRADO: Dr. Gorbach?

2 DR. GORBACH: Yes. Thank you for that  
3 question because it allows me to elaborate a little  
4 more on recurrence that I couldn't in the core  
5 study.

6 So could we have slide on, please? So this  
7 is a Kaplan-Meier plot of time to recurrence. And  
8 I blocked off 5 to 15 days because you can see that  
9 the slope of the vancomycin-treated subjects is  
10 more acute during the first two weeks than in the  
11 later two weeks.

12 Now, this harkens back to studies in the  
13 late '80s by Stuart Johnson, and more recently by  
14 Frédéric Barbut, that point out recurrences which  
15 are, in their view, reinfection with the same  
16 strain, occur within the first two weeks following  
17 cessation of treatment.

18 Slide on, please. And this is what we  
19 observed, Dr. Sepkowitz. We found that -- here's a  
20 histogram, same data, really, of what I just showed  
21 you, but converted -- that most of the recurrences  
22 occurred within the first two weeks. And you can

1 see they dribbled off near the end. And this is  
2 what was reported by Johnson and Barbut. And then  
3 there were some cases very late, but there was an  
4 overall decline.

5 Now, the next slide shows you the difference  
6 in the treatments -- slide on please -- of the  
7 treatments. And you'll see that the early  
8 recurrences are associated with vancomycin-treated.  
9 And we would suggest that these are breakthrough  
10 reinfections with the same strain, whereas late  
11 recurrences, I think, are more likely due to  
12 environmental organisms.

13 So there is some explanation, and I don't  
14 think we're pushing out the recurrences because  
15 you'll note that the numbers decline rather rapidly  
16 in the latter 3 and 4 weeks. Thank you.

17 DR. SEPKOWITZ: Was there any attempt to  
18 look farther out? It does look like it's petering  
19 out at day 30, but, again, the CDC definition goes  
20 essentially two months. You went one month.

21 DR. GORBACH: Yes. No, I agree with you.  
22 And we didn't. It's very hard, as you know, to

1 collect -- 30 days was a real test, and we didn't.  
2 And I can just say that they are much less likely  
3 to occur, but we have not gathered that  
4 information.

5 DR. GOETZ: Dr. Solga?

6 DR. SOLGA: Two very simple questions.

7 Your definition of recurrence on slide 49 is  
8 consistent with the May 2010 IDSA guidelines that  
9 say recurrence is, in essence, defined the same way  
10 as the initial diagnosis.

11 Question one is what trouble do you see with  
12 calling recurrence by the same definition as the  
13 initial. And the second is, you had a lot of sites  
14 around the United States, Canada, and Europe. What  
15 instructions were given to investigators or  
16 meetings regarding education, and can we recognize  
17 recurrence accurately? And was there any signal  
18 between different centers having more recurrence  
19 versus less recurrence, and why don't you speculate  
20 on whether that may have been more investigator-  
21 driven than actual biology?

22 DR. CORRADO: Dr. Gorbach, please.

1 DR. GORBACH: That's a very nice, very  
2 perceptive question. And I'm going to make a few  
3 comments, and then I'm going to call on Dr. Miller.  
4 I've had, as a clinician, a lot of experience with  
5 recurrences, and in my experience the recurrence is  
6 remarkably similar to the first event, the number  
7 of bowel movements, whether it's severe diarrhea,  
8 whether it's a lot of fever; I mean, whatever.  
9 They are like a recapitulation of the first story.

10 We had a close relationship with our  
11 investigators and with our subjects. They were  
12 very loyal, I should say. We had over 90 percent  
13 adherence to our study. And we telephoned them  
14 every week. They had a workbook that they kept to  
15 keep track of recurrence. We reminded them to keep  
16 track and kept a close contact. And if anything  
17 changed in their bowel habits, they were instructed  
18 to contact us.

19 Now I'll ask Dr. Miller to comment, because  
20 he's had -- because he lives in Montreal, the lucky  
21 city for *C. difficile* -- a remarkable experience  
22 with recurrences.

1 DR. MILLER: Right. And your question is  
2 very pertinent. The investigators met on several  
3 occasions, and it was emphasized, again, the  
4 importance during that 30-day follow-up to get  
5 stool should symptoms reoccur and to test it for  
6 toxin. And as Dr. Gorbach mentioned, there was a  
7 very strict follow-up. There was a daily follow-up  
8 done during the time of the treatment. As well,  
9 there was a weekly follow-up done with mandatory  
10 telephone calls if the patients were at home, or if  
11 they were in the hospital, they were visited weekly  
12 and the testing was done.

13 Yes, the testing was at the discretion of  
14 the investigator, and, yes, the test was done at a  
15 local level. But there was a lot of emphasis put  
16 on the recurrences, as you can imagine.

17 DR. CORRADO: I'll also add to that that at  
18 each weekly telephone call, the subjects were  
19 reminded that should they have an episode of  
20 diarrhea, recurrent diarrhea, in between calls, not  
21 to wait but to contact the site.

22 DR. SOLGA: Thank you. Just a follow-up.

1       Because you had so many centers and we've alluded  
2       to a different biology of C. diff in different  
3       parts of the planet, was there a subanalysis of the  
4       different centers and how many recurrences were  
5       occurring in different places? Might that reflect  
6       a different biology of different strains of C.  
7       difficile or different biases of different  
8       investigators about how they called that?

9               DR. GORBACH: Yes. We did analyze carefully  
10       by center, and there were no differences. Now, I  
11       will have to caution, with multiple centers, you  
12       had somewhat small numbers. But those with large  
13       numbers, like lucky Montreal, we could see no  
14       differences with, for example, Calgary, the other  
15       side of Canada, where there are also large numbers,  
16       nor anywhere in the U.S., nor, for that matter, in  
17       Europe. 004 was a study with 40 percent subjects  
18       from Europe, and we could not see any differences  
19       in either the clinical characteristics of the cure  
20       or recurrence.

21               DR. GOETZ: Dr. Auwaerter?

22               DR. AUWAERTER: Yes. This is regarding

1 recurrence and regarding the use of systemic  
2 antimicrobial therapy in addition.

3           Was there any difference between in- and  
4 outpatient populations between the two arms? And  
5 then, as I think many people know, certain  
6 antibiotics are associated with much higher rates  
7 of recurrence, specifically clindamycin,  
8 fluoroquinolones, and cephalosporins. So was there  
9 a subgroup analysis between the two arms to make  
10 sure that there is no skewing?

11           DR. CORRADO: Dr. Gorbach?

12           DR. GORBACH: Yes. We became very  
13 interested in the issue of what we call concurrent  
14 antibiotics. Those were antibiotics given for  
15 other infections such as urinary tract and so on.  
16 It turned out to occur in 20 percent of subjects  
17 that received concurrent antibiotics.

18           Kate Mullane presented at ICAAC last year a  
19 paper, and it was currently favorably reviewed by a  
20 journal. And so it will be published shortly,  
21 where she showed that those on concurrent  
22 antibiotics could be divided into high-risk

1 antibiotics and low-risk antibiotics. And there  
2 was a difference, and you've already mentioned some  
3 of the high-risk antibiotics.

4 They had lower cure rates if they were on  
5 these concurrent antibiotics, and they had higher  
6 relapses. And it makes sense. I mean, these are  
7 the -- but on the other hand, doctors were forced  
8 to treat if a pneumonia occurred; they had to give  
9 a concurrent antibiotic.

10 But there's no doubt that patients and  
11 doctors pay a price for concurrent antibiotics.  
12 And we did do subgroup analyses. It would take a  
13 long time, but the paper will be out.

14 DR. AUWAERTER: But to follow up, so I guess  
15 the paper's not out. But I wasn't quite certain.  
16 Did you examine between the two treatment arms --

17 DR. GORBACH: Oh, yes. I'm sorry.

18 DR. AUWAERTER: -- whether there was a  
19 difference, especially in terms of the global cure  
20 or the recurrence rate?

21 DR. GORBACH: Yes.

22 DR. AUWAERTER: And then was there a

1 difference in outpatient or inpatient?

2 DR. GORBACH: Well, to the first of your  
3 questions, yes, there was. First of all,  
4 fidaxomicin preserved its advantage in recurrences  
5 even if you received concurrent antibiotics. And  
6 it was about the same percentage.

7 Now, inpatient/outpatient, it was higher in  
8 study 003. It was about 40 percent and 25 percent.  
9 That's because in Europe, they tend to hospitalize  
10 patients somewhat less. And there were differences  
11 that were perceived. The inpatients were certainly  
12 a sicker group. They were older. They had higher  
13 failure rates and more recurrences.

14 So it's clear that doctors, at least in  
15 North America, hospitalize patients who are sicker,  
16 and it makes sense, particularly the older ones.  
17 So there were differences. But the same  
18 changes -- with fidaxomicin, the improvement in  
19 recurrences still pertain whether they were  
20 inpatients or outpatients. So that delta, at about  
21 the same rate, was maintained in both inpatient  
22 antibody outpatient groups.

1 DR. GOETZ: Dr. Hilton, did you have a  
2 question?

3 DR. HILTON: I have a question about the  
4 adverse events. On the fidaxomicin arm, you had  
5 about a 3 and a half percent incidence of GI  
6 bleeding and a similar incidence of neutropenia or  
7 leukopenia. I wondered if those events occurred in  
8 the same patients or in different patients.

9 DR. CORRADO: They generally -- some of them  
10 were in the same patients, but frequently were not.

11 DR. GOETZ: I actually had a question, I  
12 think, for Dr. Gorbach.

13 If I follow properly, slides 65 and 66 that  
14 you presented were on the recurrent rates by  
15 subpopulations. Do you have similar slides  
16 regarding the global cure in these subpopulations?

17 DR. GORBACH: Yes, we do. Give us a moment.  
18 But, essentially, they were the same. I'll pull  
19 them up if you'd like. No, but the global cure  
20 matched, but --

21 DR. GOETZ: Yes. But to see that.

22 DR. GORBACH: Yes. I mean, don't forget,

1 global cure, you only subtract out the failures,  
2 and so you're left with essentially recurrences  
3 driving global cure.

4 DR. GOETZ: And then while those slides are  
5 coming up, I just had a question regarding --

6 DR. GORBACH: Excuse me. Slide on, please,  
7 and I'll be able to answer.

8 DR. GOETZ: Certainly. Yes.

9 DR. GORBACH: So here you have the forest  
10 plots, and they're pretty much the same. This is  
11 another -- this is the disease state. The previous  
12 one was other conditions. So they're pretty much  
13 the same as the original.

14 DR. GOETZ: Right. Do you have that also  
15 broken down by presence of BI strain and severity,  
16 or did that go past my eyes? I missed it.

17 DR. GORBACH: This is the one on the BI  
18 strain.

19 Pardon me? Oh, slide on, please. I'm  
20 looking at it.

21 [Laughter.]

22 DR. GOETZ: It's helpful for us all to see

1 that.

2 DR. GORBACH: Yes. Here's the BI strain.

3 It did go by fast.

4 DR. GOETZ: Right.

5 So a question, then, that emerges -- and  
6 you've touched on it before a number of different  
7 ways -- the differences between study 004 and 003  
8 regarding what happens with the BI strain here.

9 DR. GORBACH: Yes.

10 DR. GOETZ: And you also alluded recently as  
11 to differences in the rates of hospitalization in  
12 the two groups.

13 DR. GORBACH: Yes.

14 DR. GOETZ: What sort of exploratory  
15 analyses did you do? Because I'm certain they must  
16 have been -- well, I feel confident they must have  
17 been conducted to understand why there was such a  
18 difference, a relative difference, with the BI  
19 outcomes in terms of global cure in those two  
20 studies.

21 DR. GORBACH: We have done numerous studies,  
22 and the bottom line is we can't explain it. To be

1 perfectly honest, 003 is just different from 004.  
2 004 worked out to our expectations; 003 didn't.

3 I will tell you one thing about BI in  
4 Europe. As you know, in the U.S. about 35  
5 percent -- 36 percent of our isolates in the 003  
6 were BI and 32 percent in the other study were BI.  
7 And those were mostly from North America. And  
8 what's happened in Europe is that five years ago,  
9 BI was the number one strain in Europe. Well, now  
10 just recently in a Lancet article, it's pointed out  
11 that BI fell to fourth position and represents only  
12 5 percent of current isolates. And indeed, in our  
13 European centers, we only isolated 7 total BI  
14 strains.

15 So there are shifts in these types, and we  
16 do believe that shifts will come to North America.  
17 The BI burst on the scene initially in 2000, noted  
18 by CDC, but then really with Mark Miller's  
19 observation in Montreal. We hope it will go away.  
20 But because of the changes in multiple European  
21 countries, this could, we hope, happen here. And  
22 this is indeed a virulent strain.

1 DR. GOETZ: Then just once more, then,  
2 follow-up regarding strain-related issues. Study  
3 criteria allowed patients with either toxin A or  
4 toxin B to be entered. There's been a lot of  
5 debate over the years as to the relative importance  
6 of these toxins, with toxin B seemingly being the  
7 more important.

8 Now, do you have any analysis as to what  
9 proportion of patients had either toxin A alone  
10 or -- toxin A alone in particular is what I'm  
11 interested in.

12 DR. GORBACH: Well, this study was begun in  
13 2005, and the available tests at that time were the  
14 ELISA everywhere. And they were almost all toxin A  
15 or toxin B, so both were studied.

16 Now, Dr. Miller has -- and since he had a  
17 fair number of tests, he uses the tissue culture.  
18 He may want to -- which is mostly toxin B. He may  
19 want to remark on that.

20 DR. MILLER: Right. And the majority of  
21 centers did use an ELISA or an EIA. Again, because  
22 some centers at that time -- you have to

1 understand, you're going a number of years back.  
2 Some centers were still using toxin A testing,  
3 which has now been discouraged, and almost  
4 everybody has gone to A and B or B alone.

5 So at that time, it was allowed into the  
6 study. But it's safe to assume that the majority,  
7 the vast majority, of centers both in Europe and in  
8 North America were using either a combo test or B  
9 preferentially, and there was very little. It was  
10 allowed in the study because the study was started  
11 several years ago. Now, of course, people have  
12 moved on to PCR, but that was not at the time of  
13 the study.

14 DR. GOETZ: Thank you.

15 DR. MILLER: And there were numbers of  
16 centers like my own which used cytotoxicity.

17 DR. GOETZ: We'll go to Dr. Shyr next.

18 DR. SHYR: So if you will go back to slide  
19 65, still for the BI strains. So I did see a big  
20 difference 003 and 004 even though is explained  
21 that you looked at the different things. Have you  
22 ever done the multivariable data analysis to see

1 adjusted confidence interval? If you did, what  
2 were the variables you adjusted?

3 DR. CORRADO: Dr. Gorbach or Dr. Davis.

4 DR. DAVIS: Good morning. My name is Chuck  
5 Davis. I'm a statistical consultant to Optimer  
6 Pharmaceuticals.

7 Such a multivariant analysis has not been  
8 done. We've looked at some subgroup analyses, just  
9 looking at maybe the effect of one or two other  
10 variables, and as Dr. Gorbach mentioned, nothing  
11 came up about that.

12 The other thing I would like to caution,  
13 we're talking about small numbers here, and I  
14 typically do not like to over-analyze subgroups,  
15 especially when they have small numbers. And also,  
16 given the fact that the results from the two  
17 studies are different, and as Dr. Gorbach  
18 mentioned, we just don't have an explanation.

19 DR. GOETZ: Dr. Hasler?

20 DR. HASLER: Thank you. I have questions  
21 relating to the GI bleeding adverse events. I  
22 think I read in the briefing documents that these

1 occurred primarily in the post-treatment period.

2 My specific questions are, do you have any  
3 data on transfusion requirements in either group,  
4 and were there differences between fidaxomicin  
5 versus vancomycin? Did these bleeding episodes  
6 lead to either prolonged hospitalization,  
7 rehospitalization, or increased ICU stays? And my  
8 final question is, do you have any data on  
9 endoscopic evaluation of these patients? What sort  
10 of findings did they see that were potential causes  
11 of bleeding?

12 DR. CORRADO: Well, thank you for that  
13 question. Unfortunately, we don't have answers to  
14 all of those. The question about did they result  
15 in hospitalization or prolonged hospitalization is  
16 a very tricky one to answer because in the  
17 vancomycin arm, where we found most of these, the  
18 bleeding was incorporated in an SAE. The SAE, for  
19 example, was colonic perforation or necrotizing  
20 colitis, and then bleeding was noted in there.  
21 They did reach the point of being an SAE, but it  
22 wasn't noted that it was because of the bleeding.

1 So it's very difficult to analyze that kind of  
2 information.

3           There is, though, the fact that a lot of  
4 these occurred later in the illness. And when we  
5 started analyzing this, we actually had an epiphany  
6 of sorts, and it's ironic that the higher efficacy  
7 for fidaxomicin actually led to a longer period for  
8 observation of adverse events. And, in fact, the  
9 way that the protocol was written, adverse events  
10 were captured for a time frame, for 7 days after  
11 the last dose or the last study visit, which may  
12 have been recurrence, at the 4-week time frame.

13           What happened, since there were  
14 significantly more fidaxomicin subjects who did not  
15 have recurrence, the period of time over which  
16 adverse events -- both in the neutropenia, where  
17 they occurred late, and in bleeding -- may have  
18 tilted the number of cases.

19           Could I have the slide up, please?

20           In fact, we had a total of 18,000, almost  
21 19,000 days of observation of adverse events on the  
22 fidaxomicin subjects versus 17,400 days. So this

1 may be a partial explanation for any of the  
2 discrepancies.

3 DR. GOETZ: Dr. Kaplan?

4 DR. KAPLAN: I wonder if you could clarify,  
5 under the definitions of clinical cure, marked  
6 reduction in the number of unformed bowel movements  
7 at the end of therapy.

8 DR. CORRADO: Dr. Gorbach, please?

9 DR. GORBACH: Yes. You note that we have  
10 three definitions. That was the one used less  
11 frequently because mostly it was three or less.  
12 And that's the reason we did the sensitivity  
13 analysis, which took all of these subjective issues  
14 out. So sensitivity analysis was pure stool, for  
15 those that favor that, and it removed that. And if  
16 you recall, with the sensitivity analysis, they  
17 were virtually the same.

18 Diarrhea, and particularly an inflammatory  
19 diarrhea, as you know, can go on for days and days.  
20 It's not like traveler's diarrhea, where you  
21 generally get better. This is a highly  
22 debilitating illness, and so endpoint of diarrhea

1 is difficult to determine. But using the  
2 sensitivity analysis, we did find no difference.

3 DR. KAPLAN: So this would have been what  
4 the investigator determined was a marked reduction?  
5 There wasn't a specific 50 percent decrease or --

6 DR. GORBACH: Right. And, fortunately, that  
7 wasn't used very often. Perhaps Dr. Miller, who  
8 was an investigator, can comment on that.

9 DR. MILLER: Right. So that was left in for  
10 the type of patient who would be, for instance,  
11 from my center, over the age of 80, serious  
12 comorbidities, lots of diarrhea, abdominal pain.  
13 Goes on treatment, is much better at the end of  
14 treatment. However, they still may have one or two  
15 loose or unformed bowel movements, a little bit of  
16 abdominal pain. But for all intents and purposes,  
17 you think that they are markedly better, and you  
18 are not going to continue therapy.

19 So for that patient, it was left in because  
20 in the investigator's judgment, they were cured of  
21 their CDI. They had some residual abdominal pain.  
22 You can imagine a patient with pseudomembranous

1 colitis or pancolitis who goes on this study. They  
2 would be left with a little bit of discomfort at  
3 the end of day 10.

4 So that was left in. And as was mentioned,  
5 it wasn't used very often, but it was giving the  
6 investigator leeway. But again, the sensitivity  
7 analysis showed, whether you used it or not, the  
8 patients were cured significantly.

9 DR. GOETZ: Ms. Young?

10 MS. YOUNG: Yes. I have two questions.

11 First, I wondered if the sponsor looked at  
12 infection control protocols among the different  
13 settings, the hospital settings. And two, to what  
14 extent do you see this as a possible substitution  
15 for the broad spectrum vancomycin in practice?

16 DR. CORRADO: Dr. Gorbach?

17 DR. GORBACH: Well, thank you for that  
18 question. We did not intervene in the infection  
19 control policies. However, as an ethical company,  
20 we encouraged them. And when we met with  
21 investigators, there was a lot of discussion about  
22 wouldn't it be great if we didn't have to worry

1 about this disease and we had better infection  
2 control.

3 Dr. Miller has a very aggressive infection  
4 control program, and he might want to comment  
5 on -- and then I'll come back to your second  
6 question -- comment on the complexities of such a  
7 program.

8 DR. MILLER: Right. There's no question  
9 that infection prevention and control is the key to  
10 preventing this illness and preventing transmission  
11 in healthcare facilities; not so much the  
12 community, we don't really know, but in healthcare  
13 facilities. And all these institutions had IPC  
14 practices in place. There's no question that if  
15 they were perfect, we wouldn't be dealing with the  
16 C. difficile that we have.

17 However, in reality, many of our  
18 institutions, both in Canada and the United States,  
19 have multi-bedded rooms, sharing of toilets,  
20 imperfect handwashing, and everything else that  
21 goes along. And it looks like C. diff right now,  
22 unless these IPC practices are perfected, is going

1 to be with us for quite a while.

2 So certainly there was no -- but there was  
3 no monitoring of this, and the institutions that  
4 were used were quite large and good in IPC regular  
5 practices, the bundle, so to speak.

6 DR. GORBACH: To your second question, it's  
7 our view that the best advantage of our drug would  
8 be to use it in the first instance in order to  
9 prevent the subsequent recurrence because once a  
10 recurrence has occurred, 40 percent of patients go  
11 on to a second recurrence, and then another 40  
12 percent go on. So there is a diminishing number,  
13 but it's remarkable how many continue on with  
14 recurrence.

15 Now, whether or not it's allowed, of course,  
16 is up to you; it's your vote. But it's our view  
17 that initial treatment would be best in terms of  
18 reducing recurrence. And we also believe that the  
19 lack of impact on the microflora is important not  
20 so much -- partially for *C. difficile*, but it also  
21 brings in other bad bugs like *pseudomonas* and  
22 *Klebsiella* and so on. So we do believe that narrow

1 spectrum -- this narrow spectrum drug is an  
2 advantage.

3 Dr. Miller, a comment?

4 DR. MILLER: If I can just make one more  
5 point about the IPC. In infection prevention and  
6 control in healthcare facilities, the major cause  
7 of C. diff are other patients with C. diff. So if  
8 we can reduce the recurrences of these patients and  
9 decrease the overall number, we should be  
10 decreasing the overall incidence in hospitals,  
11 period.

12 DR. GOETZ: Dr. Surawicz?

13 DR. SURAWICZ: Thank you. I have a couple  
14 questions.

15 Every patient that was in this trial, was  
16 that their first episode of C. dif, or were there  
17 any patients enrolled who had already had an  
18 episode of C. diff?

19 DR. CORRADO: Thank you for the question.  
20 Dr. Gorbach, please.

21 DR. GORBACH: Yes. Thank you for that. We  
22 did allow one prior episode within the previous

1 three months. And it turned out that we had about  
2 15 percent of patients who entered, and they were  
3 stratified and randomized independently. And when  
4 we analyzed that stratum -- so it was like a nested  
5 intervention trial. We actually built in an  
6 intervention trial to see the results of treatment  
7 of that single prior occurrence.

8 Next slide, please. This slide shows this  
9 small -- and I don't want to over-blow this thing  
10 because, as you can see, the numbers were 66 and 62  
11 in both arms. But nevertheless, we did see the  
12 expected reduction with fidaxomicin in what is now  
13 the next recurrence.

14 By the way, vancomycin had a predictable  
15 35 percent risk of -- as I mentioned, 40 percent is  
16 the figure in the literature. We ended up with 35  
17 percent who went on to a subsequent occurrence.  
18 And by the way, if you look within the first 14  
19 days, where many of these recurrences occur, the  
20 results are even more dramatic.

21 So this will be a bigger trial, looking at  
22 recurrence. But it was built in. It was specified

1 in the statistical analysis plan and available for  
2 analysis. Thank you.

3 DR. SURAWICZ: The second question I have is  
4 about stool testing. We know that there's a lot of  
5 variability in the accuracy of stool testing. Your  
6 study was done over a number of times.

7 So I understand from the earlier question  
8 there was no standardization of diagnostic testing  
9 on stool among the different sites. Is that  
10 correct?

11 DR. GORBACH: That's correct. And the issue  
12 is, in 2005, this was kind of the state of the art.  
13 There was -- the ELISA, the EIA test, was the  
14 standard. Now we know better. But these new tests  
15 have only become available recently.

16 That test, the ELISA test, as you well know,  
17 is very good for diagnosing positives and has very  
18 few false negatives. So we don't think that there  
19 were people who were entered to the trial who did  
20 not have the disease. It's quite good at  
21 recognizing that. What it does miss is some people  
22 who do indeed have the disease and who are missed

1 on the ELISA test.

2 DR. SURAWICZ: Well, the reason I was  
3 interested in that is because anyone who's taken  
4 care of patients with recurrences know that the  
5 stool test is not always positive with the  
6 recurrence. So I was curious about the people who  
7 had recurrent diarrhea in that first 30 days but  
8 who had a negative stool test.

9 DR. GORBACH: Yes. I'm going to let -- we  
10 looked at this question -- and thank you  
11 for -- because this was a concern to us as well.  
12 So I'm going to let Dr. Sears deal with the  
13 sensitivity tests that we conducted --

14 DR. SURAWICZ: Right.

15 DR. GORBACH: -- in that regard.

16 DR. SEARS: Okay. I think we have a  
17 sensitivity analysis that directly answers your  
18 question because we did have some concerns about  
19 this, too. The toxin test is obviously not 100  
20 percent sensitive.

21 So what we looked at -- and I'll ask for the  
22 slide on, please. We did a variety of tests to

1 look at the impact of this. The top is, we call it  
2 ISE recurrence. That's what we defined in the  
3 protocol as what's in our integrated summary of  
4 efficacy.

5 Below that is -- we did these weekly follow-  
6 ups where we asked the subject, do you have  
7 recurrence? And if they said yes, they're listed  
8 in that second line. The third line is anybody who  
9 received an effective -- CDI-effective medication  
10 for diarrhea. That's the third line. And then the  
11 fourth is yes to any of the above. And what you  
12 can see is we still maintain a difference between  
13 treatment arms.

14 DR. GORBACH: SO these were people  
15 without --

16 DR. SEARS: Even if you look at all-cause  
17 diarrhea.

18 DR. GORBACH: These were people without the  
19 tests. These were based on the history, all-cause  
20 diarrhea. To do the sensitivity analysis, we  
21 ignored the tests. And they came out pretty much  
22 the same.

1 DR. GOETZ: Dr. Solga?

2 DR. SOLGA: Could I have slide 76, please,  
3 just to set out this question? I don't want to get  
4 into subgroup analysis in small numbers. We've  
5 already brought that up a couple times. But I  
6 couldn't help but notice, when looking at the  
7 slide, at the bottom part of the slide, the  
8 vancomycin was all about upper GI complications.  
9 The fidaxomicin was all about lower GI  
10 complications.

11 That made me wonder about PPI use, proton  
12 pump inhibitor use, amongst hospitalized patients.  
13 As you know, there's a wacky overuse of PPIs in  
14 American hospitals. Even without a stomach, people  
15 will end up on PPIs for no particular reason. And  
16 as they go home, they'll stay on the PPIs.

17 I was wondering, it's germane to C. diff in  
18 a couple of ways. I mean, one is the influence of  
19 acid suppression on gut flora. And the other is  
20 that PPIs will invariably cause some degree of  
21 diarrhea.

22 Did you look at PPI use amongst the

1 different centers? And could it have been the case  
2 that the folks with vancomycin actually did have  
3 more upper GI complications and actually went home  
4 on more PPI or higher doses of PPI, and therefore  
5 had more diarrhea later on?

6 DR. CORRADO: Your question is pertinent  
7 both for safety and efficacy. I'll have Dr.  
8 Gorbach discuss the efficacious aspect.

9 DR. GORBACH: Yes. PPI was widely used, in  
10 about 60 percent of subjects, as you predicted.  
11 Using a univariate analysis, it did have an effect  
12 on recurrences. There were higher  
13 recurrences -- this has been reported in your  
14 literature -- higher recurrences with PPI use. But  
15 when we used multivariate analysis on that data,  
16 the difference disappeared, and there was no  
17 difference.

18 The people who were given PPIs tended to be  
19 sicker based on lower serum albumen, higher serum  
20 creatinine, higher severity scores by multivariate  
21 analysis. But there was no effect on a cure or on  
22 recurrence, even in that large group that received

1 it.

2 So, I mean, our conclusion was in terms of  
3 CDI, it's okay to use PPIS, other issues, of  
4 course, notwithstanding. I'm not going to comment  
5 on their overuse.

6 DR. GOETZ: I think we have time for two  
7 final questions.

8 Dr. Chatterjee?

9 DR. CHATTERJEE: A quick question about the  
10 emergence of any multiply-drug-resistant organisms,  
11 particularly VRE, in either of the studies.

12 DR. CORRADO: Dr. Sears, please. Could you  
13 address the issue of VRE?

14 DR. GORBACH: Well, yes. Thank you for that  
15 question because Curt Donskey at Cleveland did a  
16 study of -- he used our stool specimens in patients  
17 who -- so we gave him about 250 matched pairs, gave  
18 them blinded, people before and after therapy.

19 He had about 230 or so that -- slide on,  
20 please -- which he could analyze the emergence of  
21 VRE during the course of therapy. Again, these  
22 were blinded, and not until he came to us did we

1 break the code. And you could see that the group  
2 receiving vancomycin had about a 31 percent  
3 colonization rate with VRE, whereas fidaxomicin was  
4 about 7 percent. That paper has been submitted for  
5 publication. It was presented at ICAAC two years  
6 ago.

7 DR. GOETZ: And Dr. Auwaerter, did you have  
8 a final question?

9 DR. AUWAERTER: Hopefully a quick one.

10 As studies go, the outpatient percentage is  
11 rather high compared to many prior studies, so this  
12 is perhaps a different population. Have you  
13 characterized the outpatient populations are  
14 skilled nursing facility patients, mostly? Are  
15 they patients at home? And then was there a  
16 difference in the two arms, again, in both studies  
17 3 and 4?

18 DR. CORRADO: Yes. Dr. Gorbach, please.

19 DR. GORBACH: Yes. Many of those  
20 outpatients came from our Canadian sites, and we'll  
21 have to ask our Canadian colleague here why so many  
22 patients are treated outpatient. But it was not so

1 true in U.S., and it was certainly not true in the  
2 European sites, about 25 percent. They were not  
3 nursing homes. They were generally treated, at  
4 least in the U.S. sites, at home.

5 There were no differences except that the  
6 disease was more severe. So there were lower  
7 numbers of cures in the outpatient groups and  
8 higher -- and lower recurrences.

9 Have I got that backwards? Yes, I'm sorry.  
10 There were more failures amongst outpatients and  
11 fewer recurrences.

12 So it seemed that doctors made the decision  
13 based on the severity of illness, which was  
14 reflected in outcomes. But in terms of drug, the  
15 outcomes with the drugs, they were the same whether  
16 they were inpatient or outpatient; that delta with  
17 fidaxomicin was maintained amongst recurrences, but  
18 the cures were the same.

19 Now, you can comment on your Canadian --

20 DR. MILLER: Right. I guess the  
21 clarification is that many of these patients are  
22 community onset. And community onset, as we know

1 from previous descriptions, many of these, probably  
2 about two-thirds, are actually healthcare-  
3 associated, but they occur in the community.

4 Certainly in Canada, in the Canadian sites,  
5 we didn't do a subanalysis of these. But in  
6 separate analyses, two-thirds of our community  
7 onset are actually healthcare-associated and have  
8 been in a healthcare facility in the past two  
9 months. But they did occur in the community, and  
10 that's how they were attributed in this study, as  
11 being community patients.

12 DR. AUWAERTER: And of the healthcare-  
13 associated, actively in an institution or not? And  
14 this just gets back to the antibiotic use and  
15 recurrence.

16 DR. MILLER: I'm not sure of the question.  
17 What do you mean, in?

18 DR. AUWAERTER: Well, healthcare-associated  
19 doesn't mean -- I mean, whether they're actually  
20 present at the time of diagnosis, for example, in a  
21 nursing home, versus --

22 DR. MILLER: Right. So in our analyses in

1 Canada, what we considered healthcare-associated,  
2 was an admission or regular visit such as a  
3 dialysis unit. It did not include, say, visits to  
4 an outpatient facility. And studies like that have  
5 been done by Erik Dubberke and others, and showing  
6 about two-thirds of these patients of community  
7 onset actually have been healthcare-associated  
8 through an admission or a regular appearance in a  
9 hospital.

10 DR. GOETZ: I want to thank everyone for  
11 their questions. We've run a few minutes over, but  
12 I think it's been a worthy discussion. We'll now  
13 take a short, 15-minute break.

14 Committee members, please remember that  
15 there should be no discussion of the meeting topic  
16 during the break amongst yourselves or with any  
17 member of the audience. We will resume at 10:40.  
18 Thank you.

19 (Whereupon, a recess was taken.)

20 DR. GOETZ: All right. I think we'll resume  
21 our presentations now with the FDA, with  
22 Dr. Iarikov. Thank you.

1                   **FDA Presentation - Dmitri Iarikov**

2                   DR. IARIKOV: Good morning. My name is  
3                   Dmitri Iarikov, and I'm a medical officer at the  
4                   Division of Anti-Infective and Ophthalmology  
5                   Products, and I'm the medical reviewer for  
6                   fidaxomicin NDA.

7                   Today I'm going to be discussing the safety  
8                   results of the fidaxomicin clinical program. My  
9                   presentation will be mostly based on the results of  
10                  fidaxomicin phase 3 trials. I'll begin with a  
11                  brief overview of fidaxomicin clinical development,  
12                  then present its overall safety findings, and  
13                  finally focus on a few selected aspects of  
14                  fidaxomicin's safety assessment.

15                  Fidaxomicin NDA for the treatment of  
16                  Clostridium difficile-associated diarrhea was  
17                  submitted by Optimer Pharmaceuticals on November  
18                  29th of 2010. Fidaxomicin is a macrolide, supplied  
19                  as 200-milligram tablets. The proposed dose  
20                  regimen is 200 milligrams twice daily for 10 days.

21                  Fidaxomicin clinical development program  
22                  included two multinational, multicenter, double-

1 blind and randomized clinical trials. The  
2 enrollment in the trials was initiated in May of  
3 2006 and completed in December of 2009. Both  
4 trials compared fidaxomicin with vancomycin. The  
5 dosing duration for both treatments was 10 days.  
6 The primary endpoint was clinical cure at the end  
7 of treatment. Secondary endpoints included  
8 recurrence and global cure rates within at least 25  
9 days after the last dose of study medication.

10 Subjects 16 years of age or older, having at  
11 least four unformed stools positive for *Clostridium*  
12 *difficile* toxin A or B, were enrolled in the  
13 trials. No more than 24 hours of prior treatment  
14 with metronidazole or vancomycin were allowed, and  
15 subjects with life-threatening disease were  
16 excluded.

17 Safety population in all trials included  
18 676 subjects who received at least one dose of  
19 fidaxomicin and had at least one safety evaluation.  
20 A total of 564 subjects received fidaxomicin in  
21 phase 3 trials. The comparator safety population  
22 of phase 3 trials included 583 subjects.

1           The majority of the safety population in the  
2 fidaxomicin development program was exposed to a  
3 daily dose of 400 milligrams, and the mean duration  
4 of exposure in phase 3 trials was 10 days.

5           The overall incidence of treatment-emergent  
6 adverse events, including death and serious adverse  
7 events, was comparable in the fidaxomicin and  
8 vancomycin arms in phase 3 trials. No significant  
9 differences in the rates or causes of death were  
10 found in a comparison of treatment groups in phase  
11 3 trials. There was one death in the phase 2 trial  
12 deemed not related to study drug.

13           There were no differences in adverse events  
14 resulting in death between the fidaxomicin and  
15 vancomycin group, and the adverse events resulting  
16 in death that occurred at the highest incidence in  
17 fidaxomicin-treated patients included sepsis,  
18 respiratory failure, and pneumonia.

19           No death deemed to be directly related to  
20 study drug. In 5 fidaxomicin and 4 vancomycin-  
21 treated subjects, death deemed to be possibly  
22 related to study drug by a lack of sufficient

1 response to study medication.

2           While the overall number of deaths and  
3 serious adverse events were similar between two  
4 groups, there were several categories of adverse  
5 events that were reported at high rates in  
6 fidaxomicin-treated patients. These events  
7 included gastrointestinal hemorrhage, megacolon,  
8 and decreases in white blood cell counts; plus,  
9 there was a case of duodenal perforation following  
10 fidaxomicin overdose, and a case of pregnancy  
11 complicated by intrauterine death and a congenital  
12 defect. In addition to these events, I will also  
13 discuss dropouts and discontinuations in phase 3  
14 trials, and interactions with P-glycoprotein  
15 inhibitors.

16           Moving on to gastrointestinal hemorrhage,  
17 there was a numerical imbalance in the rates of  
18 gastrointestinal hemorrhage between the treatment  
19 groups. The table presents preferred terms used to  
20 report these events. Upper GI hemorrhage was  
21 reported with the preferred terms of hematemesis,  
22 esophageal varices hemorrhage, and upper GI

1 hemorrhage.

2           According to our analysis, the incidence of  
3 adverse events related to GI hemorrhage in phase 3  
4 trials was 3.5 percent in the fidaxomicin and  
5 2.1 percent in the vancomycin group. In addition,  
6 1 vancomycin-treated subject experienced a GI  
7 hemorrhage in phase 2 trials. During the review,  
8 we added 2 subjects to the vancomycin group. We  
9 deemed that these subjects with ischemic colitis  
10 and large intestine perforation presented with  
11 signs consistent with gastrointestinal hemorrhage.

12           In the fidaxomicin groups, 7 episodes of  
13 GI hemorrhage were judged to be serious, including  
14 6 episodes in phase 3 and 1 episode in phase 2  
15 trial; plus, gastrointestinal hemorrhage was  
16 reported as a cause of death in 1, and as a reason  
17 for stopping study drug in 2 fidaxomicin-treated  
18 subjects. In the vancomycin group, 5 episodes of  
19 GI hemorrhage were reported as serious. There were  
20 no reports of death of study withdrawals related to  
21 GI hemorrhage in the vancomycin group.

22           Further analysis did not demonstrate obvious

1 association between GI hemorrhage and the severity  
2 of Clostridium difficile infection at baseline.  
3 Approximately 5 percent of fidaxomicin subjects  
4 with severe and 3 percent of fidaxomicin subjects  
5 with non-severe Clostridium difficile infection  
6 developed GI hemorrhage in phase 3 trials. In the  
7 vancomycin group, subjects with severe and non-  
8 severe infection at baseline developed  
9 GI hemorrhage in 1.3 and 2.3 percent, respectively.

10 In both groups, two-thirds of subjects  
11 developed GI hemorrhage after study drug was  
12 stopped, and almost all serious episodes occurred  
13 after study drug was discontinued. When a source  
14 of bleeding was suggested by clinical  
15 presentation or endoscopic findings, the majority  
16 of GI hemorrhages in the vancomycin group deemed to  
17 originate from the lower GI tract.

18 There was a case of study drug overdose  
19 followed by duodenal perforation in the  
20 fidaxomicin-treated subjects. This was a case of a  
21 64-year-old male with no history of peptic ulcer  
22 disease who received all four doses of study drug

1 at once on study day 3. There were no immediate  
2 reactions, and the patient was withdrawn from the  
3 study. His past medical history was notable for  
4 renal cell cancer with spinal metastases, and his  
5 concomitant medications included enteric-coated  
6 aspirin.

7 The patient condition deteriorated the next  
8 day after the overdose when he developed  
9 hypertension and required intubation. His  
10 condition remained critical, and on study day 5,  
11 the patient was taken for surgical exploration and  
12 was found to have a perforated duodenal ulcer. The  
13 patient subsequently recovered.

14 There were 3 cases of megacolon reported in  
15 the fidaxomicin group. All cases were caused by BI  
16 Clostridium difficile strain, and all subjects had  
17 severe Clostridium difficile infection at baseline.  
18 Two subjects failed 3 and 6 days of study drug  
19 therapy prior to being diagnosed with megacolon,  
20 and one of these subjects died. The third subject  
21 received only two doses of study drug prior to  
22 colectomy.

1           There was a case of pregnancy in the  
2           fidaxomicin group. This was the case of a 19-year-  
3           old female who was found to be pregnant on study  
4           day 25. The patient had negative pregnancy test at  
5           enrollment and completed 11 days of fidaxomicin  
6           with a resolution of her Clostridium difficile-  
7           associated diarrhea.

8           Her past medical history was notable for  
9           B cell acute lymphocytic lymphoma. The patient  
10          received Vincristine and methotrexate 3 weeks prior  
11          to enrollment. Ultrasound at 9 weeks of pregnancy  
12          showed 5 live fetuses. At 18 weeks of pregnancy,  
13          the patient delivered 2 deceased and 3 live  
14          fetuses, and one fetus had a cleft palate.

15          Now adverse events related to decreases in  
16          white blood cell counts. We found 23 fidaxomicin-  
17          treated subjects compared to 10 vancomycin subjects  
18          with adverse events related to decreases in white  
19          blood cell counts. When these adverse events,  
20          reported with several preferred terms, were  
21          categorized as neutropenia and lymphopenia,  
22          fidaxomicin-treated subjects were found to

1 experience twice as many adverse events in each  
2 category. Of note, if a subject had neutropenia  
3 and lymphopenia, both events were included in this  
4 table. A baseline decrease in WBC counts was  
5 observed in approximately half of the patients in  
6 each treatment group.

7 Further analysis demonstrated that 20 out of  
8 23 subjects with decreased WBC counts in the  
9 fidaxomicin group had underlying comorbidities that  
10 may have contributed to leukopenia. These  
11 conditions included lymphoma, leukemia, multiple  
12 myeloma, lupus, and severe sepsis. Plus, several  
13 patients were receiving chemotherapy or  
14 glucocorticoids.

15 In the vancomycin group, 7 out of 10  
16 subjects had underlying immunosuppressive states  
17 that may have contributed to the decrease in white  
18 blood cell count. Of note, no WBC abnormalities  
19 were seen in phase 1 and phase 2 trials, and no  
20 blood marrow toxicity were observed in nonclinical  
21 studies.

22 Dropouts and discontinuations. Overall,

1 discontinuation rates in the fidaxomicin arm were  
2 comparable to vancomycin arm. Our analysis showed  
3 that there were more discontinuations due to  
4 clinical failure in the fidaxomicin compared to  
5 vancomycin group, 2.3 percent versus .9 percent  
6 respectively.

7 On the other hand, during the treatment  
8 phase, the incidence of adverse events resulting in  
9 discontinuations was higher in vancomycin-treated  
10 subjects, 6.2 versus 3.9 percent respectively.

11 Vomiting was the primary adverse event leading to  
12 study drug discontinuation. It occurred at the  
13 incidence of .5 percent in each treatment group.  
14 During the follow-up phase, death was the single  
15 adverse event resulting in discontinuations for all  
16 fidaxomicin and all but one vancomycin subjects.

17 An impact of P-glycoproteins on efficacy and  
18 safety of fidaxomicin was examined because  
19 cyclosporin, a known P-gp inhibitor, was shown to  
20 increase plasma level of fidaxomicin in the healthy  
21 volunteer study. A potential concern was whether  
22 P-glycoprotein inhibitors affect efficacy and

1 safety of fidaxomicin by increasing its absorption  
2 and possibly decreasing intestinal exposure to the  
3 drug.

4           The list of medications identified as P-gp  
5 inhibitors in phase 3 trials included, among  
6 others, selected protein pump inhibitors, azoles,  
7 calcium channel blockers, and antibiotics. Low  
8 cure rates and even more significant decreases in  
9 global cure rates were observed in patients who  
10 received P-glycoprotein inhibitors in phase 3  
11 trials. However, decreases in cure rates were  
12 observed in both treatment groups, and the overall  
13 clinical response still favored the fidaxomicin  
14 group. Adverse event rates were high in subjects  
15 who received P-gp inhibitors, but similar rates  
16 were observed in both treatment groups.

17           I believe this concludes my presentation. I  
18 would like to thank my colleagues and the  
19 fidaxomicin review team for their advice and  
20 support during the review process.

21                           **FDA Presentation - Rima Izem**

22           DR. IZEM: Good morning. My name is Rima

1 Izem. I'm the statistical reviewer for this NDA.

2 My presentation will discuss the efficacy  
3 assessment and the efficacy endpoint as they relate  
4 to the two indications sought by the applicant.

5 The applicant is seeking two indications.

6 The first indication is for the treatment of  
7 CDI, which is the same indication as for oral  
8 vancomycin, the active control comparator in the  
9 current trial. The second indication, reducing the  
10 risk of recurrence when used for the treatment of  
11 initial CDI, is completely new. Because this  
12 indication is new, the path to go from efficacy  
13 assessment and efficacy endpoint to the indication  
14 is also new and would make a precedent if this  
15 indication is approved.

16 Notice here that although we have two  
17 assessments and two indications, there are three  
18 endpoints: clinical cure rate, recurrence among  
19 those cured, and global cure rate. In my  
20 presentation, I'll present the result for the  
21 clinical cure rate and the global cure rate. I'll  
22 also share with you my reservations in using the

1 difference in recurrence among cured for measuring  
2 treatment benefits. I'll also share my questions  
3 on the meaning of the second indication of reducing  
4 the risk of recurrence and how it relates to the  
5 three efficacy endpoints.

6           There were two efficacy assessments during  
7 the trial. The first was clinical cure and the  
8 second was recurrence. The primary population of  
9 interest is the modified intent-to-treat population  
10 or MITT. At the end of treatment, the first  
11 assessment was clinical cure. Those who are cured  
12 were followed up for up to 30 days after the end of  
13 treatment for recurrence.

14           So for every subject in the MITT population,  
15 there are three possible outcomes. The first  
16 outcome is clinical cure at the end of treatment  
17 and recurrence during the follow-up period. The  
18 second possible outcome is cure at the end of  
19 treatment sustained until the end of the follow-up  
20 period. That is what we call global cure. The  
21 third possible outcome is failure at the end of  
22 treatment.

1           This diagram will illustrate how these three  
2 possible outcomes relate to the endpoint in the  
3 trial. There was one primary endpoint and two  
4 secondary endpoints. So since we have three  
5 outcomes for each subject, in each treatment arm we  
6 have three possible groups. One is the subgroup of  
7 subjects who are cured at the end of treatment,  
8 with cure sustained until the end of follow-up.  
9 The second group is those who are cured at the end  
10 of treatment and recurred at follow-up. And the  
11 third group are those who failed at the end of  
12 treatment.

13           The primary endpoint is clinical cure at the  
14 end of treatment, which is defined as the  
15 proportion of subjects who are cured at the end of  
16 treatment among all MITT subjects. The first  
17 secondary endpoint is recurrence among those who  
18 are cured; that is the proportion of subjects who  
19 are cured at the end of treatment and recurred at  
20 follow-up among those who are cured at the end of  
21 treatment.

22           The second secondary endpoint, which was

1 exploratory in study 003, is global cure or the  
2 proportion of subjects who are cured at the end of  
3 follow-up, with cure sustained -- sorry -- cured at  
4 the end of treatment, with cure sustained until the  
5 end of follow-up, among all MITT subjects.

6 In summary, the primary endpoint of clinical  
7 cure is among all MITT subjects. The secondary  
8 endpoint of recurrence among cured is only among  
9 those who are cured, and the secondary endpoint of  
10 global cure is for all MITT subjects.

11 To control for multiple testing, a  
12 gatekeeping strategy was devised where one first  
13 tests for the noninferiority of fidaxomicin to  
14 vancomycin for the primary endpoint of clinical  
15 cure. And if that is successful, one would test  
16 for superiority of recurrence among those cured of  
17 fidaxomicin to vancomycin. And if that is  
18 successful, one would test for superiority of the  
19 endpoint of -- fidaxomicin to vancomycin for the  
20 endpoint of global cure.

21 Notice here that both the secondary endpoint  
22 of recurrence among cured and the secondary

1 endpoint of global cure take into account  
2 information on recurrence.

3           These are the three main points in my  
4 slides. First, I believe that efficacy at the end  
5 of treatment and after follow-up is best assessed  
6 by the two endpoints of clinical cure rate and  
7 global cure rate in the MITT population. In the  
8 next few slides, I will share with you my  
9 reservations with using the difference in  
10 recurrence among cured to measure treatment  
11 benefit.

12           My review supports the noninferiority of  
13 fidaxomicin to vancomycin for the endpoint of cure,  
14 and it supports the superiority of fidaxomicin to  
15 vancomycin for the endpoint of global cure.  
16 Although these results hold for most subgroups, one  
17 possible exception is the virulent strain of C.  
18 difficile subgroup.

19           Okay. So with this slide, I'll share my  
20 reservation on using the difference in recurrence  
21 among those cured as a measurement of treatment  
22 benefit.

1           Interpreting recurrence among those cured is  
2 fairly easy in any given treatment arm. For a  
3 given treatment arm, let's say the vancomycin arm,  
4 the recurrence among those cured measures the risk  
5 of recurrence at follow-up when the subject was  
6 cured in that treatment arm, vancomycin, at the end  
7 of treatment.

8           I believe it is hard to interpret the  
9 difference in recurrence among cured between two  
10 treatments because this would be comparing the risk  
11 of recurrence in one subgroup of subjects to the  
12 risk of recurrence to a potentially completely  
13 different subgroup of subjects.

14           For example, in study 003, under review,  
15 those cured in the fidaxomicin group were  
16 significantly younger than those cured in the  
17 vancomycin group. Thus, the difference in  
18 recurrence among those cured is comparing the risk  
19 of recurrence of younger subjects to the risk of  
20 recurrence of older subjects.

21           Another example is the trial that was  
22 published in a poster in 2007 of tolevamer versus

1 vancomycin. The recurrence rate in the tolevamer  
2 arm was 3 percent, and the recurrence in the  
3 vancomycin arm was 23 percent. However, the  
4 baseline severity of those cured with vancomycin  
5 was, on average, higher than the baseline severity  
6 of those cured with tolevamer.

7           So what is the alternative? One alternative  
8 would be to use the difference in recurrence over  
9 all MITT subjects instead of the recurrence over  
10 all cured subjects. I'll be showing the results  
11 for this endpoint at the end of my talk, and I'll  
12 be also commenting on its relationship to the other  
13 two endpoints, the difference in clinical cure and  
14 the difference in global cure rate.

15           Now I'll take a step back and I'll go back  
16 to the second indication, which is reducing the  
17 risk of recurrence. And I'll ask the question,  
18 what does this reducing the risk of recurrence  
19 mean, and how can we quantify it? More  
20 specifically, which set of endpoints support this  
21 indication? Is it the difference in recurrence  
22 over all MITT subjects alone; or is it the

1 difference in recurrence over all MITTs together  
2 with the difference in clinical cure; or is it all  
3 three endpoints together that would support this  
4 indication?

5 My second question is, what is the role of  
6 the gatekeeping testing strategy in this  
7 indication? Should we always test for  
8 noninferiority of the clinical cure first before  
9 even asking about recurrence? Does it matter,  
10 after we win in noninferiority, whether we test for  
11 superiority in global cure or whether we test for  
12 superiority of recurrence?

13 To further elaborate on these questions,  
14 I'll contrast the results of the current NDA to two  
15 hypothetical scenarios. So the question is still,  
16 what does reducing the risk of recurrence really  
17 mean?

18 In the current NDA, fidaxomicin is  
19 noninferior to vancomycin for the endpoint of  
20 clinical cure. Fidaxomicin is superior to  
21 vancomycin for the endpoint of recurrence over all  
22 MITT subjects, as I will show later in my talk.

1 And fidaxomicin is superior to vancomycin for the  
2 endpoint of global cure.

3 Is it these three findings together which  
4 support reducing the risk of recurrence?

5 Let me contrast that with two other  
6 hypothetical scenarios. The first scenario would  
7 show noninferiority of the test drug to the control  
8 drug and superiority of the test drug to the  
9 control drug, but would fail to show superiority of  
10 the test drug to the control drug for recurrence  
11 over all MITT subjects.

12 Would this hypothetical scenario support  
13 reducing the risk of recurrence since, overall, at  
14 the end of at the follow-up period, those who took  
15 the test drug were better off using -- those who  
16 were randomized in the trial would be better off at  
17 the end of follow-up period than those who were  
18 randomized to the control drug?

19 To illustrate this example -- to illustrate  
20 this situation, let me show you a hypothetical  
21 example. In this hypothetical example, the  
22 clinical cure rate and the recurrence over all MITT

1 subjects and the global cure rate for the control  
2 drug are shown in black, and those for the test  
3 drug are shown in blue.

4           So in this hypothetical example, the test  
5 drug is not only noninferior to the control drug,  
6 it is actually superior to the control drug for the  
7 endpoint of clinical cure. There is no difference  
8 in recurrence over all MITT subjects. However, the  
9 advantage that is observed in the clinical cure  
10 endpoint carries over to the global cure endpoint,  
11 and there is a significant advantage to the test  
12 drug over the control drug for the endpoint of  
13 global cure.

14           Would that hypothetical support a reducing  
15 the risk of recurrence indication?

16           Now my third scenario -- my second scenario,  
17 hypothetical scenario. In that hypothetical  
18 scenario, the test drug would should noninferiority  
19 to the control drug for the endpoint of clinical  
20 cure, and superiority -- the test drug would show  
21 superiority to the control drug for the endpoint of  
22 recurrence over all MITT subjects.

1           Would this scenario support reducing the  
2 risk of recurrence?

3           Again, I have a hypothetical example to  
4 illustrate this scenario. In my hypothetical  
5 example, the test drug is slightly worse than the  
6 control drug -- or, rather, the control drug is  
7 slightly better than the test drug for the endpoint  
8 of clinical cure. However, the test drug has a  
9 much better recurrence over MITT than the control  
10 drug, 18 percent versus 25 percent.

11           However, when we tally up to look at global  
12 cure, although there is a slight advantage to the  
13 test drug of 63 percent versus 60 to the control  
14 drug, this difference is not statistically  
15 significant.

16           Would this scenario support reducing the  
17 risk of recurrence? I do not know what the answers  
18 to these questions are, and I look forward to the  
19 deliberation of the committee.

20           This is the outline of the remainder of my  
21 talk. I'll show the results for the clinical cure  
22 endpoint and the sensitivity analysis that we

1 conducted at the FDA. Then I'll show the results  
2 for the global cure endpoint, recurrence, and our  
3 sensitivity analysis; and then finally show the  
4 results for the virulent strain subgroup.

5 The applicant proposed a noninferiority  
6 margin for clinical cure, the primary endpoint, of  
7 10 percent, and this margin was found to be  
8 acceptable. The noninferiority margin was derived  
9 from two recent large trials showing superiority of  
10 vancomycin to tolevamer where tolevamer was used as  
11 a putative placebo.

12 The results of these trials, as well as  
13 assessment of constancy assumption, was evaluated  
14 using publications of the trial in posters as well  
15 as a review paper and the definition of the  
16 clinical cure that was published along with the  
17 phase 2 result.

18 Clinical cure was assessed by the clinician;  
19 that is, the clinician reported outcome. It was  
20 assessed -- the test of cure occurred up to 2 days  
21 after the end of treatment, although most of the  
22 time it happens at day 10 or day 11.

1           The definition of cure is quite long, and  
2 I'm not going to read it. Instead I will look at  
3 the complement of clinical cure, which is failure.  
4 The definition of failure is requiring additional  
5 CDAD therapy, and whether or not a subject needed  
6 additional CDAD therapy was based on lack of  
7 resolution of signs and symptoms of CDAD.

8           This slide shows the clinical cure results  
9 for the applicant and for the FDA's sensitivity  
10 analysis. The motivation for conducting a  
11 sensitivity analysis was the review of the case  
12 report form. The review of a sample of case report  
13 form showed some possible inconsistency with the  
14 assessment of clinical cure at the end of  
15 treatment. Those possible inconsistencies with the  
16 assessment of clinical cure were either death  
17 before study day 10 or taking CDAD concomitant  
18 medication during the treatment period.

19           Across both studies, there were only 13  
20 possible inconsistencies. When we treat, in the  
21 FDA sensitivity analysis, these inconsistencies as  
22 failure, we get a difference between fidaxomicin

1 and the vancomycin arm of 4.2 percent in study 003  
2 and 0.2 percent in study 004. Notice that the  
3 lower bound of the 95 percent confidence interval  
4 in both studies is above negative 10 percent, the  
5 noninferiority margin. Thus, the FDA sensitivity  
6 result support the noninferiority of fidaxomicin to  
7 vancomycin for the endpoint of clinical cure.

8 Now I'll move on to the results for the  
9 global cure endpoint, the recurrence over all MITT  
10 subjects and sensitivity analysis that we conducted  
11 on the global cure endpoint.

12 The recurrence assessment window, it was  
13 study days 36 to 40, or 25 days after the end of  
14 treatment. Recurrence is also a clinician-reported  
15 outcome. It is assessed by clinician. And the  
16 definition of recurrence is reestablishment of  
17 diarrhea together with a positive toxin of *C.*  
18 *difficile* and requiring CDAD therapy.

19 Between the end-of-treatment visit and the  
20 recurrence assessment visit, there were three  
21 scheduled visits in the follow-up period after  
22 cure, at day 17, day 24, and day 31. An assessment

1 of global cure was clinical cure at the end of  
2 treatment, together with a no-recurrence assessment  
3 during the recurrence assessment visit window.

4 We noticed during our review that the  
5 recurrence assessment visit didn't always happen  
6 between day 36 and day 40. So for our sensitivity  
7 analysis, we had to decide where to draw the line  
8 between how early was too early to assess no  
9 recurrence.

10 When we looked back at the protocol, the  
11 protocol had allowed to impute a value -- an  
12 assessment of global cure if the recurrence  
13 assessment was missing in the following situation:  
14 when there was clinical cure at the end of  
15 treatment, when the three visits were available  
16 during the follow-up period, and when no diarrhea  
17 was reported at any of these visits. Thus, day 31  
18 is the earliest protocol-allowed day to assess  
19 global cure.

20 So why did we conduct sensitivity analysis  
21 on the endpoint of global cure? When the medical  
22 review team reviewed the case report forms, we

1 noticed some inconsistency with the assessment of  
2 global cure. There were three possible  
3 inconsistencies with the assessment of global cure.  
4 Those were either death before study day 31, taking  
5 CDAD concomitant medication during treatment or  
6 during the follow-up period, or having the  
7 recurrence assessment visit occur earlier than day  
8 31, the earliest protocol-allowed day for assessing  
9 a no-recurrence.

10           These three categories overlap, and when we  
11 tallied up the number of inconsistencies with the  
12 assessment of global cure across all these  
13 inconsistencies, we found a total of 44  
14 observations in study 003 and a total of 41  
15 observations in study 004. There were more  
16 inconsistencies noticed in the vancomycin arm than  
17 in the fidaxomicin arm in both studies.

18           So what did we do with that information? We  
19 decided to conduct some sensitivity analyses. We  
20 conducted three sensitivity analyses. In the first  
21 sensitivity analysis, all inconsistencies with the  
22 applicant's assessment of global cure were treated

1 as failures.

2 In the second sensitivity analysis, death or  
3 suspected CDAD were treated as failures; when there  
4 was concomitant medication during the follow-up  
5 period but no evidence of diarrhea, these were  
6 treated as missing; and when the recurrent  
7 assessment visit happened too early, that was also  
8 assessed as missing. To be consistent, we also set  
9 to missing those who were cured at the end of  
10 treatment and had a missing recurrence assessment  
11 visit.

12 For the third sensitivity analysis, it's  
13 almost the same as the second sensitivity analysis,  
14 except that deaths prior to day 31 are now treated  
15 as missing.

16 So in sensitivity analyses 2 and 3, we have  
17 missing values. What did we do with them? We  
18 actually imputed these missing values using a  
19 multiple imputation method. That is a logistic  
20 regression that takes into account the treatment,  
21 baseline characteristics such as demographic  
22 variables and also CDAD history variables, follow-

1 up information for diarrhea, and timing variables  
2 such as the length of treatment. With this  
3 logistic regression, we could impute those missing  
4 values, and we did it 25 times, using the chained  
5 equation algorithm.

6 The advantage of these multiple imputation  
7 methods is that the confidence interval for the  
8 difference between fidaxomicin and vancomycin will  
9 not only account for the sampling variability, but  
10 will also account for the uncertainty due to  
11 missing values.

12 These are the results of the applicant as  
13 well as the result of the three sensitivity  
14 analyses for study 003 and study 004 in each  
15 treatment arm. Notice here that no matter which  
16 sensitivity analysis we look at, the global cure  
17 rate for both the fidaxomicin arm and the  
18 vancomycin arm are lower than those reported by the  
19 applicant; however, when we look at the difference  
20 between fidaxomicin and vancomycin for the endpoint  
21 of global cure, the results of the sensitivity  
22 analysis are consistent with those of the

1 applicant.

2 o the figure on top shows the results for  
3 study 003, and the bottom figure shows the results  
4 for study 004. This is a forest plot showing the  
5 applicant results compared to the results for the  
6 three sensitivity analyses. The difference here is  
7 between fidaxomicin and vancomycin, so a positive  
8 percentage is in favor of fidaxomicin, and the  
9 negative is not even in the plot, but would favor  
10 vancomycin.

11 So in study 003, because there were more  
12 inconsistencies in the vancomycin arm than in the  
13 fidaxomicin arm, in the three sensitivity analyses,  
14 the point estimate was higher than the one found by  
15 the applicant. In study 004, the three sensitivity  
16 analyses give us similar results than that of the  
17 applicant. Notice here that sensitivity analyses 2  
18 and 3 have a wider confidence interval than that  
19 found by the applicant because the confidence  
20 interval is taking into account the uncertainty due  
21 to the missing values.

22 Okay. So I showed the clinical cure results

1 and the global cure results. This slide will show  
2 the results for the recurrence over all MITT  
3 subjects. It will also show the relationship  
4 between the difference in clinical cure, the  
5 difference in recurrence, and the difference in  
6 global cure.

7 The top figure is for study 003 and the  
8 bottom figure for study 004. Percentages from 0 to  
9 25 are differences that favor fidaxomicin, and  
10 percentages from 0 to negative 5 favor vancomycin.

11 The clinical cure results for study 003 and  
12 study 004 are shown in blue. Those are the results  
13 from the applicant. In purple is the global cure  
14 result. Those also are the results from the  
15 applicant. And in red is the result for recurrence  
16 over all MITT subjects. We see that for this  
17 endpoint, there is a significant difference in  
18 favor of vancomycin for recurrence over MITT  
19 subjects in both study 003 and study 004.

20 The reason I chose these colors is blue plus  
21 red is purple.

22 [Laughter.]

1 DR. IZEM: So the difference in -- you can  
2 think of global cure, basically, as -- the  
3 difference in global cure as measuring the total  
4 benefit to the patient population. And this total  
5 benefit could be decomposed into benefit at the end  
6 of treatment that is measured by the difference in  
7 clinical cure, and benefit during the follow-up  
8 period that is measured by the difference in  
9 recurrence over all MITT subjects.

10 Finally, I will go over the results for the  
11 virulent strain of *C. difficile*.

12 When we looked at the treatment effect for  
13 the endpoint of global cure and for the endpoint of  
14 clinical cure, we found that the effect was  
15 consistent in most subgroups; that is age and CDAD  
16 history. One possible exception is the virulent  
17 strain of *C. difficile*.

18 The applicant tested the strains of  
19 *C. difficile* by restriction endonuclease analysis  
20 as to whether they were part of the group BI or  
21 not. This is one testing method to find the  
22 epidemic strain of *C. difficile* that has been

1 increasing in the U.S. and Canada and is associated  
2 with more severe infection.

3 This figure shows the count in each of the  
4 subgroups -- no virulent, virulent, and  
5 missing -- the counts in each category and in each  
6 treatment group. So we have here study 004 and  
7 study 003. In blue is the fidaxomicin counts and  
8 in pink is the vancomycin count.

9 The nonvirulent group made up about half of  
10 the strains tested in the MITT population. The  
11 virulent group made up about a quarter of all the  
12 strains tested in the MITT population. And the  
13 missing group made up the last quarter of all  
14 samples in the MITT population.

15 Notice that randomization worked. There is  
16 balance between the fidaxomicin arm and the  
17 vancomycin arm for the nonvirulent group and the  
18 virulent group. There is a slight imbalance for  
19 the missing subgroup, but this imbalance was not  
20 found to be significant.

21 These are the results for the virulent,  
22 nonvirulent, and those missing the virulence

1 information for the endpoint, the primary endpoint,  
2 of clinical cure. The difference here is the  
3 difference between clinical cure of fidaxomicin and  
4 vancomycin. Rates from 0 to 15 percent favor  
5 fidaxomicin, and rates from 0 to negative 15  
6 percent favor vancomycin.

7 We see that there is no notable difference  
8 between the virulent group and the nonvirulent  
9 group for the endpoint of clinical cure, although  
10 we start noticing differences for the missing group  
11 between study 003 and study 004.

12 This slide shows the results for the  
13 endpoint of global cure for the difference between  
14 fidaxomicin and vancomycin. The rates from 0 to 30  
15 percent favor fidaxomicin, and the rates from 0 to  
16 negative 20 percent favor vancomycin.

17 We see here that in the nonvirulent  
18 subgroup, there is still a significant difference  
19 between fidaxomicin and vancomycin in favor of  
20 fidaxomicin. However, the results are inconclusive  
21 for the virulence subgroup in study 003 and in  
22 study 004.

1           For those missing in study 003, there is a  
2 significant benefit of fidaxomicin versus  
3 vancomycin. However, the results are inconclusive  
4 in study 004.

5           This concludes my talk. This is the summary  
6 of what I presented today. I believe that the  
7 efficacy at the end of treatment and after follow-  
8 up is best assessed by the endpoints of clinical  
9 cure rate and global cure rate in the MITT  
10 population.

11           My review supports the noninferiority of  
12 fidaxomicin to vancomycin for the endpoint of cure,  
13 and the superiority of fidaxomicin to vancomycin  
14 for the endpoint of global cure. In the virulent  
15 strain of *C. difficile*, there is no significant  
16 global cure difference between fidaxomicin and  
17 vancomycin.

18           I thank you for your attention.

19                           **Questions/Clarifications**

20           DR. GOETZ: Thank you. I believe we will  
21 now proceed to the committee's questions to the  
22 FDA.

1 [No response.]

2 DR. GOETZ: Well, then, I have a question.  
3 I'll start off here.

4 For Dr. Iarikov, I have a question about the  
5 relationship between levels of the drug in serum  
6 and patient age and such. But before I get to  
7 that, in the patient you presented in your slide  
8 15, the overdose, were there any serum  
9 concentrations in this person who took the four  
10 capsules of the fidaxomicin and then suffered the  
11 perforation, the perforated duodenal ulcer?

12 Do we have any levels in that regard?

13 DR. IARIKOV: I'll have to look at that it.  
14 I don't know about the levels for this patient.

15 DR. GOETZ: All right.

16 Dr. Sepkowitz?

17 DR. SEPKOWITZ: I also have questions about  
18 the safety, one set of questions about the GI  
19 issues and the other about the leukopenia.

20 On the GI issues, we talked about serum  
21 levels. But were stool levels of study drug or at  
22 the main metabolite, the OP-1118, were those

1 examined in the group that had hemorrhagic colitis  
2 or hematochezia or whatever? I know that the  
3 company has given some stool level information.  
4 I'm wondering if that was looked at.

5 DR. GOETZ: I believe the company has some  
6 comments they wish to make in this regard.

7 DR. CORRADO: Thank you for the questions.  
8 First, a point of clarification. They did not take  
9 four doses of fidaxomicin. There were two placebos  
10 so that we could keep the blinding.

11 With respect to fecal levels, we do have  
12 that for the subjects who had GI bleeding. Slide  
13 up, please. And what this demonstrates, and I want  
14 to point something out clearly here, these are the  
15 concentrations in the 23 people who had GI  
16 bleeding, the fecal levels, and then the fecal  
17 levels in the study as a whole, which recapitulates  
18 those same 23, although they would not have, as you  
19 could tell, any significant impact.

20 There was no increased concentration in  
21 people who had GI bleeding in the fecal levels. If  
22 we were to look at the plasma levels, you would see

1 no difference in those, either.

2 DR. SEPKOWITZ: That includes the main  
3 metabolite as well, which seems to --

4 DR. CORRADO: Yes. You see the -- could I  
5 have the next slide, please?

6 This is the main metabolite. The main  
7 metabolite was slightly higher, but still within  
8 the range of what we see in subjects, as you can  
9 see. There was one subject that was a far outlier  
10 with the main metabolite.

11 DR. SEPKOWITZ: The issue with the  
12 leukopenia, working at a cancer hospital, I'm very  
13 keen on understanding this better. And the  
14 mishmash of explanations, like chemotherapy, kind  
15 of struck me the wrong way.

16 So chemotherapy is not a monolithic fact,  
17 and not all chemotherapy is the same in terms of  
18 induction of neutropenia. And, indeed,  
19 corticosteroids, which were invoked as a cause of  
20 neutropenia, typically are causes of an increase in  
21 white cells.

22 So is there a better breakdown of that?

1       Because I'm actually very worried about this. Lots  
2       of antibiotics cause drops in white counts, and we  
3       live with it. But I think that as this drug goes  
4       forward and gets used longer and longer, I think  
5       this might become an issue. So I'm wondering if  
6       you drilled down farther beyond just chemotherapy.

7               DR. IARIKOV: Most subjects who received  
8       glucocorticoids were reported to have lymphopenia,  
9       which was expected. And several subjects with  
10      severe sepsis and high neutrophil count were also  
11      reported to have lymphopenia, which is also  
12      expected.

13             I did not break it down, but in terms of  
14      chemotherapy, it was patients started, for example,  
15      on chemotherapy for hematopoietic cells  
16      transplantation induction regimen. It was  
17      chemotherapy when you can expect drops.

18             There were 3 patients when it was -- for my  
19      review, when it was unexplained for fidaxomicin,  
20      and 3 patients when it was unexplained for  
21      vancomycin.

22             DR. GOETZ: Dr. Shyr, you have a question?

1 DR. SHYR: I do have a question for the  
2 statistical reviewer.

3 First question: I do agree with your  
4 concerns a baseline balance, possibility of  
5 baseline balance, when we assess the recurrence  
6 model. My question to you is, have you ever  
7 adjusted for those baseline covariates when you  
8 looked at recurrence as the endpoint? And if you  
9 did, what was the result?

10 DR. IZEM: No. I did not -- what you have  
11 in mind is like a logistic regression that would  
12 correct for --

13 DR. SHYR: Yes.

14 DR. IZEM: No, I did not look at that.

15 DR. SHYR: So you never pay attention -- for  
16 this particular study, any concern with baseline  
17 balance based on those --

18 DR. IZEM: Oh, let me restate that. At  
19 baseline, the two treatment groups were the same.

20 DR. SHYR: Yes. But for the recurrence  
21 endpoint?

22 DR. IZEM: I did not compare, no.

1 DR. SHYR: Okay. And the second question  
2 is, we did find one patient, they drop out because,  
3 actually, they don't have four drugs in the same  
4 day. Have you checked the compliance, the patient  
5 compliance, other than this one particular subject?  
6 Did you realize -- did you find out any other  
7 possible noncompliance patient?

8 DR. IZEM: I did look at the -- I did  
9 include the number of days in the treatment group  
10 as a predictor when I did my sensitivity analysis,  
11 but I didn't look at that further.

12 DR. SHYR: I'm curious because for the  
13 treatment arm, there are two real drugs, two  
14 placebo, because that's a Q12 edge, so you have to  
15 take that in order. So I don't know if you looked  
16 at it.

17 DR. IZEM: That's a very good question. No,  
18 I haven't looked at compliance.

19 DR. SHYR: Okay. And another question,  
20 which is I have, when you did missing data  
21 analysis, when you did logistic regression, you  
22 include all the variables on right-hand side. Did

1       you do any model selection first or just include  
2       every covariates on the right-hand side to conduct  
3       your missing data?

4               DR. IZEM: I included all of them. And the  
5       model converged pretty well, so I didn't do any  
6       model selection after that.

7               DR. GOETZ: Dr. Follman?

8               DR. FOLLMAN: I guess I just have a comment,  
9       really. I'd like to thank the FDA for the  
10       sensitivity analysis they did looking at different  
11       definitions of cure. And it was striking, I guess  
12       when one of the sponsor's analyses counted death as  
13       a cure. But the bottom line was that the results  
14       were consistent, especially in terms of global cure  
15       that the FDA had, that FDA agreed with the sponsor.

16               The other comment I wanted to make had to do  
17       with the recurrences in endpoint. And I agree with  
18       the FDA completely on this. I think when you're  
19       comparing the recurrence rate, it's no longer a  
20       randomized comparison because to be in the  
21       comparison group, you have to get cured to get  
22       started with.

1           So you can imagine all sorts of crazy  
2 scenarios that would be misleading. I think the  
3 FDA tried to give some examples of those. You  
4 could also think, maybe if I had a placebo and  
5 compared that against the drug, the very few people  
6 on placebo who got cured might be very hardy people  
7 and would never recur. So what would it mean to  
8 say placebo is a better recurrence rate?

9           So anyway, I don't know if that's practical  
10 or not, but I'm very uneasy about looking at  
11 recurrence rate. In my mind, it's sort of a  
12 nonstarter because it's not a comparison of  
13 randomized groups. And, furthermore, you have the  
14 wonderful global cure, which gets sort of all of  
15 those issues and tells you something about the  
16 long-term benefit, which is really what you're  
17 interested in as well. Whether you call it  
18 recurrence or global cure, it doesn't matter so  
19 much to me. I think the fact that you have global  
20 cure here is an important way to describe the  
21 benefit of the drug without the problems of  
22 recurrence.

1 DR. GOETZ: I think there's a question from  
2 Mr. Makowka, our patient representative.

3 MR. MAKOWKA: Yes. Having undergone a stem  
4 cell transplant and running a support group, that  
5 particular model of the class, everyone seems to be  
6 very close to or having CDI. Is there any real  
7 reason why there's such a minor number included  
8 here; seems that they're at risk more than the  
9 general population?

10 DR. GOETZ: I don't know if the sponsor  
11 wishes to comment on that at all.

12 DR. CORRADO: I'll have Dr. Gorbach describe  
13 the distribution of the kinds of patients that  
14 you're talking about, including those people with  
15 malignancies.

16 DR. GORBACH: Yes. Thank you. We know that  
17 30 percent of stem cell transplants will have CDI.  
18 However, the total number per year is about 50,000,  
19 and therefore, for whatever reason, the centers  
20 that we were working with did not enroll. We  
21 certainly didn't discourage them. We would have  
22 liked them.

1           In fact, this is one of our target groups  
2           for looking in the future because if 30 percent of  
3           you, I should say, have a chance of CDI, it's  
4           obviously really important to know the benefits in  
5           that group. But we're kind of at the mercy of our  
6           investigators. We did not put any barriers to  
7           enrolling in stem cell transplants.

8           DR. GOETZ: Dr. Sepkowitz?

9           DR. SEPKOWITZ: It's me again? Okay. This  
10          is a question, I guess, of Dr. Miller. But for all  
11          randomized trials, there's often an informal  
12          unblinding that usually the study nurses are able  
13          to make in terms of what the pill looks like, feels  
14          like, tastes like, what the patient's complaining  
15          of.

16          This study is unusual and somewhat  
17          concerning to me because it's really a subjective  
18          clinician's -- I love subjective clinicians, but  
19          it's really a clinician's assessment of cure. It's  
20          not a two-log drop of this or that. So it's your  
21          sense or the investigator's sense.

22          From your perspective, and you've done other

1 studies, could the nurses crack the code, I guess  
2 is what I'm asking, and was that information, as is  
3 typical, generally spread, or was it a really tight  
4 blind? And I know this is a very weird question or  
5 subjective question.

6 DR. MILLER: It's very kind of you to say  
7 the nurses break the code, but some physicians try  
8 to break the code as well in other studies. So  
9 people try to break the code to see what patients  
10 are on.

11 This study was extremely difficult to break  
12 any kind of code. The medication was blister  
13 packed identically. The capsules looked identical.  
14 You could not undo them to check what was inside.

15 In addition, the physicians in the study  
16 were very concerned about the first tablet being a  
17 placebo and the patient having a delayed treatment  
18 for potentially 6 hours, and so it was created that  
19 the first tablet was always active, whether it was  
20 vanco or fidaxo, so that when you started them on  
21 the treatment, they always got an active drug as  
22 their first dose.

1           We could not tell. I can tell you, having  
2 done many of these trials in CDI, this one was very  
3 well blinded. We could not tell. And the blinding  
4 was continued until data lockdown. We were not  
5 told even after recurrence.

6           DR. GOETZ: Yes, Dr. Kaplan?

7           DR. KAPLAN: I think this went by me a  
8 little quickly. Could you just go over again slide  
9 21, global cure, clinical cure, especially the  
10 recurrence over MITT, for me, please? Either I  
11 heard it wrong or I'm confused.

12           DR. IZEM: So there are two figures here.  
13 The top one shows the results for study 003, and  
14 the bottom shows the results for study 004. The  
15 result in blue is the difference between  
16 fidaxomicin and vancomycin for the endpoint of  
17 clinical cure. In red is the difference between  
18 vancomycin and fidaxomicin for the endpoint of  
19 recurrence over all MITT subjects. And in purple  
20 is the difference between fidaxomicin and  
21 vancomycin in the endpoint of global cure. So  
22 anything positive favors fidaxomicin, and anything

1 negative would favor vancomycin.

2           So what I was saying earlier is you can  
3 think of the global cure, or the difference between  
4 the two treatment groups and global cure, as the  
5 sum of the difference in clinical cure and the  
6 difference in recurrence. So if you look at the  
7 point estimate, at least for the global cure, it's  
8 exactly the sum of the difference of clinical cure  
9 and the difference in recurrence.

10           So in other words, you can think of global  
11 cure as the overall benefit of the drug in the  
12 treatment period and follow-up period. You can  
13 think of the difference in clinical cure as  
14 capturing the benefit of the drug during the  
15 treatment period. And you can think of the  
16 difference in recurrence as capturing the benefit  
17 of the drug between the end of treatment and the  
18 end of follow-up. So it's just one possible  
19 decomposition of the treatment benefit across the  
20 whole time period.

21           DR. KAPLAN: But in no case was vancomycin  
22 favored?

1 DR. IZEM: In this particular case, no. In  
2 this particular -- in two studies, no. Clinical  
3 cure is slightly in favor, although not  
4 significantly better, slightly in favor of  
5 fidaxomicin. And there wasn't much of a difference  
6 between vancomycin and fidaxomicin for the endpoint  
7 of clinical cure in study 004, yes.

8 But what this diagram illustrates is just  
9 that the benefit that you see in global cure mostly  
10 is different by recurrence over all MITT subjects.  
11 What I was trying to illustrate with my two  
12 hypothetical scenarios is that there could be  
13 different ways to get that result.

14 DR. GOETZ: I wonder whether the FDA has  
15 explored this issue about clinical cure or  
16 recurrence and global cure in other disease states.  
17 I'm not familiar with anything in infectious  
18 diseases looking at it in that regard.

19 Are there examples that lead to the issue  
20 that -- you've shown some hypotheticals where drugs  
21 might misalign on your slide 8. I accept fully the  
22 hypothetical considerations, but of course they'd

1 be given even stronger validity were there to be a  
2 proof positive or a case positive.

3 I don't know whether the FDA wants to  
4 comment on that at all.

5 DR. ALEXANDER: So I can start out. I have  
6 been thinking about this question with regards to  
7 how we treat various infectious diseases, and this  
8 really is a different model because of what's  
9 recognized as sort of a higher recurrence rate for  
10 C. difficile infections.

11 In most other infectious diseases that we're  
12 considering, with regards to treatment of  
13 pneumonia, treatment of skin structure infections,  
14 things like that, that we typically deal with, a  
15 lot of the assessments that we have been doing up  
16 until now have been assessments that take a look at  
17 a clinical cure at a follow-up period after people  
18 have been off antibiotics so that the definitions  
19 that we had been using with regards to clinical  
20 cure have taken the relapse rate that occurs after  
21 treatment has stopped into account in assessing a  
22 global clinical cure.

1 DR. GOETZ: So in that regard, if you look  
2 at skin soft tissue infections, there's been a lot  
3 of debate as to when the endpoint should be.  
4 Endpoint, is it at the end of therapy or is it at  
5 some follow-up time? And in this regard, we're  
6 looking at those -- the initial proposals look at  
7 those endpoints a little bit differently than we do  
8 some other infectious diseases.

9 Would that be a reasonable way of summing up  
10 what you said, do you think?

11 DR. ALEXANDER: Yes, I think so. And that  
12 does have implications for what we're doing with  
13 regards to the clinical trials that we're planning  
14 because we are moving the endpoint a little  
15 earlier, looking at time points when we think that  
16 there really is a large treatment difference  
17 between antibiotic and what a placebo would do.  
18 But that does mean that we are also still cognizant  
19 and still concerned about following up, as  
20 secondary endpoints, what happens to those patients  
21 beyond that time point to make sure that we don't  
22 see later differences in relapse or recurrences

1 that raise concerns.

2 DR. GOETZ: Ms. Young?

3 MS. YOUNG: Yes. I just wanted to clarify.  
4 So you're not recommending this new antibiotic for  
5 pregnant women and for children at this time?

6 DR. IARIKOV: It's a labeling question. We  
7 had one case. And we have no experience, of  
8 course, with administration of this drug in  
9 pregnancy. I have to mention that all general  
10 toxicity data and reproductive data were negative  
11 for fidaxomicin, but it doesn't answer your  
12 question.

13 Yes, we do not have any data to judge in  
14 pregnancy.

15 DR. ALEXANDER: We would expect, with  
16 regards to children, that the current labeling  
17 would be just that the safety and effectiveness  
18 hasn't been established for that pediatric age  
19 group, and would hope that we would try and quickly  
20 gather data in order to be able to address the  
21 safety and effectiveness of the drug in the  
22 pediatric population.

1           For the pregnancy, as Dr. Iarikov pointed  
2 out, most of the labeling is based on what's done  
3 with regards to reprotoxicity studies. We can't  
4 really make much out of the single case that  
5 occurred in the pregnant woman in this example. So  
6 we would expect that the labeling would still be  
7 based mainly on what we saw with regards to the  
8 animal studies.

9           DR. GOETZ: Dr. Rex?

10           DR. REX: Thank you. Two comments. The  
11 first one is to pick up just a little bit on the  
12 theme that John Alexander highlighted so nicely.

13           Patients come to us saying two things. They  
14 say, "Doc, make me feel better," which is what  
15 happens early in the course of therapy. They also  
16 come in saying, "Doc, don't let something bad  
17 happen to me later," and, thus, the importance of  
18 the downstream endpoint as the one that the  
19 patients and physicians care about the most.

20           My second comment has to do with the  
21 discussion -- we've had a couple times when we've  
22 talked about clinician-based assessment as being

1 part of the global cure endpoint here. The phrase  
2 "clinician-based" is used, not just today but in  
3 other conversations, to suggest that it is an  
4 unreliable measure.

5 The counter-observation that I'd remind you  
6 of is -- we've discussed this many times  
7 before -- is that clinicians do not create their  
8 assessment from a distance. You don't make it up  
9 from standing outside of the room. In fact, what  
10 the clinician checks on the box is the summary of a  
11 discussion with the patient in one way or another.

12 So that assessment would be more correctly  
13 called the joint patient and physician-agreed  
14 assessment of the patient's state, and, as such, I  
15 think actually has rather a lot of merit. It's up  
16 to the sponsor to document the logic that supported  
17 it. There always are individual elements that tell  
18 you why -- the clinician can tell you why he and  
19 the patient, or why she and the patient, agreed  
20 that the patient was better on that day. It's  
21 documentable fact. But the fact that a clinician  
22 is involved in interpreting it doesn't a priori

1 make it an irrelevant measure. Thank you.

2 DR. GOETZ: Thank you.

3 Dr. Hilton?

4 DR. HILTON: On Dr. Iarikov's presentation,  
5 slide 6, I see a variety of daily doses. And I  
6 wonder if any subgroup analyses were done for AEs  
7 according to dose or treatment duration.

8 DR. IARIKOV: Most of these doses were  
9 administered during phase 1 trials. There were  
10 dose-ranging studies, and during these studies,  
11 patients were exposed to 100, 200, and 400  
12 milligrams, 16 patients in each group. But this  
13 exposure, once again, it's full interaction studies  
14 or -- not necessarily in particular, but it's phase  
15 1 studies and phase 2. Right. Right.

16 DR. HILTON: I'm just wondering about the  
17 choice of dose in relation to the adverse events.

18 DR. IARIKOV: I mean, the current dose was  
19 established during phase 2 dose-ranging studies as  
20 the most effective dose, and it was not associated  
21 with an increase in adverse event rates. So this  
22 is what was tested.

1 DR. GOETZ: Following up on that, there was  
2 a statement in the FDA briefing document that there  
3 was a higher incidence of adverse events in  
4 subjects with high plasma levels, greater than 150  
5 nanograms per mL. There's also a statement that  
6 those higher levels are somewhat more common in  
7 older patients.

8 We have the range at which the  
9 concentrations of the drugs were, but neither are  
10 the adverse events described in detail as to how  
11 they relate to the briefing document, nor is the  
12 frequency of higher drug concentrations -- there's  
13 no histogram, if you will, of the drug  
14 concentrations in older patients.

15 I wonder whether either the FDA or the  
16 sponsor has broken down the data in that regard for  
17 us to explore further.

18 DR. CORRADO: What you say is exactly true,  
19 that in higher plasma levels, there are a higher  
20 incidence of adverse events. What makes it very  
21 difficult to interpret is, in that same population,  
22 they are more frequently inpatient. They're older.

1 Their serum albumin levels are lower. Their  
2 creatinine clearances are lower. And I can't make  
3 any -- there are so many confounding issues.

4 I can say one thing: They're also sicker  
5 people. They have more luminal damage, probably.  
6 They're ESCMID severity indices are higher, their  
7 scores. It's hard to know which of those, or all  
8 of those in concert, are what leads to a higher  
9 incidence of adverse events.

10 DR. GOETZ: And not being a statistician,  
11 I'm a little bit loath to tread on the field. But  
12 I wonder whether some sort of propensity analysis  
13 might have been done, looking at patients who had  
14 the higher levels of fidaxomicin versus the control  
15 population of vancomycin patients having similar  
16 characteristics, and look at the adverse events.

17 Again, I don't have the statistical  
18 wherewithal to comment on the validity of the  
19 approach, but I wonder whether you might comment on  
20 whether --

21 DR. CORRADO: If you'd like, I'll put the  
22 data up so that you can have that.

1           Could I have the slide up, please?

2           DR. GOETZ: Thank you.

3           Certainly a more severe disease.

4           Sort of a corollary question that I was  
5 trying to go to -- and, you know, age is an  
6 imperfect discriminant. I don't know what it means  
7 to be older any more as the years go on.

8           [Laughter.]

9           DR. GOETZ: But more seriously, is there, as  
10 I say, a frequency distribution amongst older  
11 patients as to what their levels are? I see that  
12 here, that the mean age of people with greater than  
13 150 nanograms was 74.6. But if you looked at all  
14 people over the age of 65, what proportion of them  
15 had levels in that range or close to?

16           DR. CORRADO: I don't believe we have that  
17 data available, but we could look at that. I will  
18 also say that I personally think that the use of 65  
19 as elderly is not appropriate.

20           DR. GOETZ: I am getting closer and closer  
21 to agreeing.

22           [Laughter.]

1 DR. GOETZ: Dr. Follman?

2 DR. FOLLMAN: Just to comment on what you  
3 raised earlier, there certainly are statistical  
4 ways to try and essentially level the playing  
5 field. So you could, a little technically, form a  
6 logistic regression with all these potential  
7 confounders and then say, for people who have the  
8 same sort of severity score, if you will, based on  
9 this logistic regression, is there a greater  
10 incidence among those who got the drug versus  
11 vancomycin?

12 So there are -- without getting into it,  
13 there are different ways that you or the FDA could  
14 look at this particular issue and try and tease it  
15 out better than just recognizing that there's a  
16 confounding issue.

17 DR. CORRADO: We could look at that.

18 DR. GOETZ: Dr. Solga?

19 DR. SOLGA: Yes. Picking up on that theme,  
20 I guess I have a question for the FDA. 003 and 004  
21 were basically the same study, and they were  
22 catch-all everybody. As long as you're not going

1 to be dying in the next 72 hours, by Friday, we'll  
2 take you, and if you don't have Crohn's or colitis,  
3 we'll take you. But we'll take everybody else,  
4 which is very real world and certainly helps with  
5 recruitment, to get 1200 studies.

6 But would it have been maybe better to have  
7 one study that did that, 003, and another study  
8 that took maybe relatively well patients or a more  
9 controlled outpatient setting, folks who weren't on  
10 chemotherapy, so then we could look at the  
11 neutropenia data, for example, and not have that  
12 confounder in there?

13 Could you have creative, you know, the  
14 hospitalized older sickies many different ways, and  
15 then maybe narrow the field a bit? Because the GI  
16 hemorrhage issue and the neutropenia issue, I don't  
17 know that I'm -- the need to be overly concerned  
18 about. It may have just well have been background  
19 noise; but it's background noise because they were  
20 all sick in so many different ways.

21 DR. ALEXANDER: Yes. So this would be one  
22 of those difficult issues that we have to deal with

1 frequently, the problem getting to be that if you  
2 were to try and design the study differently and  
3 include a milder patient population, then the  
4 question gets to be, you know, how applicable is  
5 that to the patients that you treat every day in  
6 the real world?

7           So we have typically tried and made more  
8 efforts to actually try and include more of the  
9 sicker patients, and recognize that we end up with  
10 questions like the ones that we're facing now with  
11 the committee with regards to some of these adverse  
12 effects, whether the hematologic or the GI, in  
13 trying to really understand and interpret, well,  
14 how much of that can we actually ascribe to an  
15 effect of the drug treatment?

16           I think that, overall, I would still be  
17 biased in favor of trying to include sicker  
18 patients, and then trying to do what we can to  
19 discriminate between what the effects are with  
20 regards to adverse events, than trying to then take  
21 a pure population where you're not concerned about  
22 what the effects of other things might be, but then

1 you don't necessarily know applicable that is to  
2 the patient population that people are going to be  
3 treating.

4 DR. GOETZ: Dr. Auwaerter?

5 DR. AUWAERTER: Just one question, probably  
6 more for the sponsor, regarding global cure and the  
7 virulent 003/004, with vancomycin versus  
8 fidaxomicin.

9 Were the years -- I forgot the years of the  
10 study. Were they done at the same time? Because,  
11 of course, there doesn't seem to be statistical  
12 significance, at least from the FDA perspective,  
13 but there certainly is a trend in one study  
14 favoring vancomycin versus --

15 DR. CORRADO: Dr. Gorbach, please.

16 DR. GORBACH: The study 003 started one year  
17 earlier because we were not organized. You know,  
18 we're a small company. We weren't organized in  
19 Europe. So that began in like 2006, and Europe  
20 began in 2007. So there was -- they each ran about  
21 two years. So there was one year independent of  
22 each on either end, but the middle year, it was

1 overlapped.

2 DR. GOETZ: Dr. Kaplan?

3 DR. KAPLAN: Do we have the characteristics  
4 comparing the patients cured in each of these  
5 groups sort of as a baseline for the recurrences?  
6 You mentioned that one group was older than the  
7 other. Do we have other characteristics where  
8 that's been --

9 DR. IZEM: I compared all the other baseline  
10 characteristics for those cured in vancomycin to  
11 those cured in vancomycin [sic]. Age was  
12 significant. The other ones, there were slight  
13 differences, but they weren't significant.

14 DR. KAPLAN: And what were the age  
15 differences between the two?

16 DR. IZEM: I have them in my notes, so if  
17 you could bear with me for a moment.

18 DR. GORBACH: Sir, could I -- I'm sorry, I  
19 don't mean to jump in. But I have some data --

20 DR. GOETZ: Well, we certainly -- I don't  
21 want to --

22 DR. GORBACH: Oh, I'm sorry. I didn't know

1 she wasn't finished. Excuse me.

2 DR. IZEM: So the median age for those cured  
3 in fidaxomicin was 60 years old, and the median age  
4 for those cured with vancomycin was 64. The mean  
5 was 59.22 for those cured in fidaxomicin, and it  
6 was 62.69, so almost 63, for those cured in  
7 vancomycin.

8 I checked whether this was driven by an  
9 outlier. No. It was really a distribution. The  
10 two distributions were different in study 003.

11 DR. GOETZ: Dr. Gorbach?

12 DR. GORBACH: Yes. Let me first say that  
13 Optimer would be very content with your agreement  
14 with us on global cure, so we're not disagreeing  
15 with that. But before I give up on recurrence, I  
16 would like to make two points.

17 One is that we believe that "recurrence" is  
18 a term that's much more recognized by medical  
19 professionals. "Global cure" is kind of a new  
20 concept, and I'm pleased that Dr. Alexander  
21 recognizes the importance, not just for this study  
22 but for others. So there is some benefit in

1 communicating to users, to the medical  
2 professionals, that recurrence is what we're  
3 talking about. As we pointed out, global cure is  
4 driven by recurrence.

5 Now, with regard to the statistical  
6 question -- and, pardon me, I'm not a statistician.  
7 But I do want to show some data because the  
8 difference between -- after all, what we're  
9 subtracting out are the failures. And it's about  
10 8 percent in the fidaxomicin arm and about 9 and a  
11 half percent in the vancomycin arm. So it's not  
12 that many.

13 Then if you -- slide on, please. What we  
14 did is looked at the recurrence people, that 90 to  
15 92 percent or so that were left over. One of the  
16 reasons for doing randomization -- and we do agree  
17 with you that this is not a protected randomized  
18 trial. But one of the reasons for doing it is to  
19 achieve comparable groups.

20 What we're showing here, by subtracting out  
21 that 8 and 10 percent, we end up indeed with  
22 comparable groups. And we have other subgroups we

1       could show you. But they essentially do end up as  
2       two comparable groups.

3                So I would just ask you to -- next slide,  
4       please. This is other subgroups as well. And they  
5       all pretty much show comparable subgroups. So I'm  
6       not so sure that the recurrence definition should  
7       be thrown out, sir, but you're the statistician.

8                DR. GOETZ: One last comment from  
9       Dr. Follman.

10               DR. FOLLMAN: Well, just in terms of  
11       randomization, it's not really to get balance in  
12       terms of what you can measure. It's also to get  
13       balance in terms of what you can't measure or can't  
14       imagine. And so this is not -- this is not sort  
15       of -- this is something, but it really is still a  
16       non-randomized study. And I think the bigger  
17       concern is what you can't measure. And I think  
18       also a bigger concern is maybe a precedent or if  
19       this would be applied in future for other  
20       licensings.

21               DR. GORBACH: But you might acknowledge that  
22       you can't do a trial of recurrence unless you

1 remove people who have failed. I mean, how else  
2 are we going to do this trial?

3 DR. FOLLMAN: You could -- I mean, you're  
4 doing a prospective study, aren't you, of those who  
5 failed on vancomycin or something. And so in some  
6 sense, that's your recurrent study. It's not what  
7 you want, really, I know. But I just think the  
8 term "recurrence" is problematic. You know, it's  
9 seductive. It's something that we kind of think we  
10 understand what it means, and maybe we do, but it's  
11 problematic. And so that's why I think "global  
12 cure" is the answer.

13 DR. GORBACH: Yes. We'll accept that. But,  
14 you know, as a doc, recurrence resonates in my  
15 head, and I hope for the clinicians that it  
16 resonates as well. It certainly means more  
17 than -- global cure is, I agree, a really important  
18 point, and that's why we put it in there.

19 DR. FOLLMAN: Yes. As I say, there's  
20 clinical language, statistical --

21 DR. GORBACH: But don't throw out this  
22 concept of recurrence, which is so meaningful to

1 clinicians and patients.

2 I'll keep quiet. I'm sorry.

3 DR. GOETZ: There's clinical language,  
4 statistical language, and policy language  
5 sometimes.

6 So, really, two more questions because we do  
7 want to have lunch.

8 Dr. Surawicz, you had a question?

9 DR. SURAWICZ: I don't have a question. I  
10 have a comment. You certainly can do trials of  
11 patients who only have recurrent Clostridium  
12 difficile infection. We did that when we studied a  
13 probiotic. So it definitely can be done, but was  
14 not done in this study.

15 DR. GOETZ: And Ms. Young, did you have a  
16 question you wanted -- or a comment?

17 MS. YOUNG: No. Just that if we're going to  
18 use the term "global cure," somehow there be a  
19 definition of that that might include the  
20 recurrence issue.

21 DR. GOETZ: Okay. I want to thank everyone  
22 for their comments. We will now break for lunch.

1 We will reconvene again in this room in one hour  
2 from now, which should be 1:00 p.m. Please take  
3 any personal belongings you may want with you at  
4 this time.

5 Committee members, please remember that  
6 there should be no discussion of the meeting during  
7 lunch among yourselves, with the press, or with any  
8 member of the audience. Thank you.

9 (Whereupon, at 12:00 p.m., a luncheon recess  
10 was taken.)

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## 1 A F T E R N O O N S E S S I O N

2 (1:01 p.m.)

3 **Open Public Hearing**

4 DR. GOETZ: If everyone can take their  
5 seats, we'll get started in just a moment with the  
6 open public hearing portion. If we can all settle  
7 in here as the lunch hour comes to a close.

8 All right. So I think we'll start the open  
9 public hearing now.

10 Both the Food and Drug Administration, FDA,  
11 and the public believe in a transparent process for  
12 information-gathering and decision-making. To  
13 ensure such transparency at the open public hearing  
14 session of the advisory committee meeting, FDA  
15 believes that it is important to understand the  
16 context of an individual's presentation.

17 For this reason, FDA encourages you, the  
18 open public hearing speaker, at the beginning of  
19 your written or oral statement to advise the  
20 committee of any financial relationship that you  
21 may have with the sponsor, its product, and if  
22 known, its direct competitors. For example, this

1 financial information may involve the sponsor's  
2 payment of your travel, lodging, or other expenses  
3 in connection with your attendance at the meeting.

4 Likewise, FDA encourages you at the  
5 beginning of your statement to advise the committee  
6 if you do not have any such financial  
7 relationships. If you choose not to address this  
8 issue of financial relationships at the beginning  
9 of your statement, it will not preclude you from  
10 speaking.

11 The FDA and this committee place great  
12 importance in the open public hearing process. The  
13 insights and comments provided can help the agency  
14 and this committee in their consideration of the  
15 issues before them.

16 That said, in many instances and for many  
17 topics there will be a variety of opinions. One of  
18 our goals today is for this open public hearing to  
19 be conducted in a fair and open way where every  
20 participant is listened to carefully and treated  
21 with dignity, courtesy, and respect. Therefore,  
22 please speak only when recognized by the chair.

1 Thank you for your cooperation.

2 We will now have our first speaker, Marya  
3 Zilberberg, thank you, yes, who's at the  
4 microphone.

5 DR. ZILBERBERG: Good afternoon. Thank you  
6 for this opportunity to present to you. I'm Marya  
7 Zilberberg. I have collaborated with both  
8 ViroPharma and Optimer, and Optimer Pharma has  
9 supported my attendance at this meeting via funding  
10 for travel and lodging. None of the data that I'm  
11 going to show you was supported by either public or  
12 private funding.

13 I wanted to share with you some of my  
14 thoughts, as a health services researcher, on some  
15 populations in the hospital that are particularly  
16 vulnerable to CDI. And as a background, we  
17 recently showed that between the years 2000 and  
18 2005, the rate of hospitalizations with CDI in the  
19 U.S. nearly doubled, as has the age-adjusted case  
20 fatality.

21 As you've already heard, the highest burden  
22 is felt among the older population. I won't call

1       them the elderly, but certainly the population over  
2       65, and the growth is even more pronounced in the  
3       85 and older population.

4               Now, with this as a background, not all  
5       hospitalized patients are the same or at the same  
6       risk for CDI, and there are a couple of populations  
7       that we have dug deeper into. One of these  
8       populations we have described in great detail, that  
9       is called prolonged acute mechanical ventilation.  
10       It is identified by the continued need for  
11       respiratory support beyond the first 96 hours in  
12       the ICU. It is easy to identify, and fairly  
13       accurately identify, in large administrative data  
14       sets, making it attractive to study in the health  
15       services research setting.

16               It is a very large population. It is  
17       growing exuberantly. Its growth is outpacing the  
18       underlying population shift. It's an extremely  
19       resource-intensive population; although it  
20       represents one-third of all mechanically ventilated  
21       patients in the hospital, it uses up two-thirds of  
22       the total resources.

1           Now, we ask the question, does CDI do  
2 anything among these patients? Are they at risk  
3 for CDI? What are the outcomes of CDI in these  
4 patients? And we did a database study in the HCUP  
5 NIS database, which is a very large and  
6 representative database maintained by the AHRQ, and  
7 what we found was fairly startling.

8           We found that the prevalence of CDI in this  
9 population is more than tenfold higher than in the  
10 general hospitalized population. The prevalence,  
11 as you would imagine, increases with age. Although  
12 the mortality in this very old population does not  
13 seem to be impacted by CDI, it is very high at 35  
14 percent. CDI is associated with increased length  
15 of stay and increased resource utilization.

16           So that's PAMV. Another population that we  
17 have been digging into a little bit is the elderly  
18 critically ill population, again, over 65, the  
19 older critically ill population. And in this  
20 particular study -- this was a relatively small  
21 single-center cohort study which previously defined  
22 6 percent attributed mortality among all ICU

1 patients with CDI -- we discovered that more than  
2 half of these patients in the ICU with CDI were 65  
3 and older.

4           What was interesting -- one interesting  
5 observation was that the time to the onset of CDI  
6 in the older population was a lot shorter than in  
7 the younger population. Thirty-day mortality was  
8 nearly twice that seen in the younger population.  
9 Another critical observation was that routine  
10 discharge to home was about one-third as likely in  
11 the older ICU patients with CDI than the younger  
12 ones. This implies continued morbidity, continued  
13 disability, and continued need to utilize  
14 resources.

15           So these are the two populations that we've  
16 been exploring, and clearly they seem to be at a  
17 higher risk for CDI. We still need to look at  
18 issues like recurrence, how health-related quality  
19 of life is impacted by CDI among this population.  
20 But what we can conclude is that we do know that  
21 CDI and its attendant mortality are on the rise  
22 overall among hospitalized patients in the U.S.

1           The elderly and the critically ill  
2 specifically of the elderly represent a large and  
3 growing risk pool. And we really do need to  
4 examine these new prevention and treatment  
5 paradigms among these high-risk populations vis-a-  
6 vis the outcomes that I just described, such as  
7 mortality recurrence, quality of life certainly is  
8 important, and discharge destination and other  
9 resource utilization parameters.

10           Thank you.

11           DR. GOETZ: Thank you for your comments.

12           We will now have our second speaker,  
13 Christina Shultz, if you could come up to the  
14 microphone. Thank you.

15           MS. SHULTZ: Although Optimer paid for my  
16 travel here today, I am here because of my passion  
17 for helping others who are fighting C. diff. By  
18 sharing my story with all of you today, I hope to  
19 do just that.

20           My name is Christina Shultz. I am an  
21 otherwise healthy 40-year-old wife and mother of  
22 two. I have been fighting C. diff since 2005. The

1 first time I got C. diff was in 2005 following  
2 prolonged antibiotic use. That time, my C. diff  
3 lasted for 18 months, with 13 recurrences. I  
4 failed multiple rounds of Flagyl and vancomycin. I  
5 also had a stool transfer via NG tube, which I also  
6 failed. I was finally symptom-free for 18 months  
7 following three rounds of IVIG.

8 In 2008, I wound up with C. diff again  
9 following 7 days of penicillin for strep throat.  
10 That time my C. diff came back somewhat mild, and  
11 no aggressive treatment was needed.

12 Then in August of 2010, I wound up with  
13 C. diff again. This time I had not taken an  
14 antibiotic since the strep in 2008. I lost 10  
15 pounds in 3 weeks and got yet another positive C.  
16 diff test result. Due to the severity of my  
17 symptoms, I had no choice but to seek treatment  
18 with vancomycin once again. I was treated for  
19 three months, and have recently tested positive  
20 with -- wait. I have recently tested positive four  
21 months later with mild symptoms. Once again, I am  
22 waiting to see if this will back down or go full-

1       blown.

2               Not only has C. diff changed my life, but it  
3       has changed my family's life as well. I am no  
4       longer always that reliable mother who can get my  
5       children to and from their many activities. Due to  
6       this, we recently sold our home and moved so that  
7       my daughter could get the bus to and from school  
8       every day.

9               Also, because of my complicated, often  
10       misunderstood C. diff history, I travel outside of  
11       the state in which I reside in order to receive the  
12       best possible care and treatment. This assures me  
13       that I will not wind up in the emergency room,  
14       admitted to the hospital, or go undiagnosed for  
15       long periods of time, which would only add to the  
16       dangers of what C. diff already is.

17              Currently there are only two drugs of choice  
18       available to treat C. diff, one of which has such  
19       debilitating side effects that it is not an  
20       available treatment option for me. With only one  
21       drug to lean on, I often fear, over time, with its  
22       repetitive use, what will happen. If at any point

1 the drug fails me, C. diff will have won its  
2 battle.

3 As you can see from my C. diff experiences,  
4 it is imperative that there are other drug options  
5 available. For me and others like me, it would be  
6 a great feeling of relief to know that I could  
7 possibly live without the fear of recurrence, and  
8 ultimately without the fear of someday losing my  
9 battle with C. diff. Thank you.

10 DR. GOETZ: Thank you.

11 We will move on to our third public speaker,  
12 Bobbie Smith. Thank you.

13 MS. SMITH: I'm Bobbie Smith. Optimer paid  
14 for my trip expenses, but my story is my own.

15 In June 1979, our 4-year-old son, Sam, was  
16 hospitalized in a coma and almost died. Doctors  
17 diagnosed pseudomembranous colitis, one of the most  
18 severe forms of C. difficile infection. Sam was  
19 the youngest and one of the first people ever put  
20 on oral Vancocin. When Sam recognized his hero,  
21 the Incredible Hulk, on TV, I knew he would be all  
22 right. He had two relapses and two more

1 hospitalizations before he was -- before he  
2 recovered. Sam had CDI again in 1985. He's  
3 36 years old now. He hasn't had it recently. He  
4 has had health problems.

5 In March 1993, I developed pseudomembranous  
6 colitis, and eventually I was hospitalized with  
7 pneumonia, sinusitis, a UTI, and C. diff. I was on  
8 antibiotics, including vancomycin, had sinus  
9 surgery, and recovered from the infections except  
10 for C. diff.

11 In September 1993, I went to a prestigious  
12 clinic while on Vanco, tested negative, and was  
13 diagnosed with IBS. When I returned home and  
14 stopped Vanco, per instructions, I became ill again  
15 and tested positive. I ground my teeth from  
16 stress, broke three teeth, and developed  
17 osteomyelitis in my jaw.

18 My infectious disease doctor put me first on  
19 penicillin and then on IV Vanco for 8 weeks, plus  
20 oral Vanco. The following year, I had my mouth  
21 rebuilt, an orthodontist and a dentist, with braces  
22 and bridges.

1           Later I enrolled in a blind study for a new  
2 treatment at another medical center and was  
3 on (indiscernible) for two years, unsuccessfully.  
4 A new probiotic also failed. I tried every method  
5 of (indiscernible) and was off Vanco for 6 weeks  
6 twice before relapsing. Several C. diff experts  
7 were wonderful to me, but nobody could help me.

8           I had CDI, or C. diff, for four years. In  
9 1997, a gastroenterologist in Kansas City performed  
10 an endoscopic infusion of good bacteria. He had  
11 done it once before and it was unsuccessful; this  
12 time it was successful. In 1999, however, after a  
13 fourth bout of pneumonia and antibiotics including  
14 Vanco, I had a recurrence of CDI and was  
15 hospitalized. Another infusion was successful.

16           Vanco helped control some of my symptoms,  
17 and I was able to work during most of my illness.  
18 Fortunately, my office was right across from the  
19 women's bathroom. Before C. diff, I was healthy.  
20 Now I have recurrence GI, immune, respiratory, and  
21 other health issues. C. diff hasn't ruined my  
22 life, but it's often ruled it.

1           As a volunteer coordinator of a support site  
2 for 12 years, I've read horrendous stories. The  
3 site has over 2300 registered users and many  
4 visitors. As both the parent of a C. diff patient  
5 and a patient myself, I know the physical, mental,  
6 and financial damage the infection causes.

7           Many cured patients are terrified of having  
8 it again, with good reason. It's a depressing,  
9 disgusting, lonely disease with symptoms that  
10 engender little sympathy. I was 52 years old when  
11 I first developed C. diff. I'm now 70. I know I'm  
12 at risk of getting it again because of my history  
13 and my age. I'd rather die than have it again.

14           In the 32 years since my son's first  
15 illness, C. diff is still little known, although  
16 cases have drastically increased. It's often  
17 misdiagnosed and has become more difficult to  
18 treat. It's as prevalent as MRSA in many areas, but  
19 MRSA is well-known. Many patients die in nursing  
20 homes, and some undiagnosed people die at home that  
21 are undiagnosed. So C. diff can kill.

22           In a study in 2008, William Jarvis

1 determined 301 patients in U.S. hospitals die from  
2 C. diff every day. This is over 13 times the  
3 number of U.S. soldiers who died each day in  
4 Vietnam.

5 Thank you for your time and your patience.

6 DR. GOETZ: Thank you.

7 We will now have our forth speaker at the  
8 open public hearing. Anthony Mazzuca, if you could  
9 come up to the microphone. Thank you.

10 MR. MAZZUCA: Good afternoon, Madam [sic]  
11 Chairman, distinguished committee members, ladies  
12 and gentlemen. My name is Anthony Mazzuca. I am a  
13 73-year-old resident in New Lenox, Illinois and  
14 recently retired special education teacher from the  
15 school district of Hammond, Indiana. Let me begin  
16 by stating that Optimer has coordinated my travel  
17 to speak to you today, but I am here at my own  
18 accord to discuss my experience with fidaxomicin.

19 Approximately 3 years ago, I began to  
20 experience symptoms of severe abdominal pain and  
21 diarrhea. These became so unbearable that I had to  
22 stop teaching. By the way, it's a career that I

1 really enjoyed. My students had a lot of trust in  
2 me, and being away from them was really taxing on  
3 me at that time.

4 I was eventually diagnosed with Clostridium  
5 difficile, or CDI, an infection, as I found out. I  
6 was hospitalized in a local community hospital, and  
7 within two days my fever had subsided and I was  
8 released.

9 Soon afterward, the same symptoms  
10 reoccurred, and my doctor admitted me to the  
11 University of Chicago Hospital. This was  
12 necessitated by the infection interfering with my  
13 concurrent struggle with type 2 diabetes,  
14 congestive heart failure, and two episodes of  
15 spinal meningitis.

16 At the University of Chicago, I met with an  
17 infectious disease specialist who asked if I would  
18 volunteer in a medication trial, and I agreed. I  
19 was not informed of the medication I received. I  
20 remained at the University of Chicago Hospital for  
21 four or five days and received the study  
22 medication. My symptoms subsided, and I returned

1 to teaching and living the life I once enjoyed.

2 I later learned that I was treated with  
3 fidaxomicin. I participated in the follow-up lab  
4 work for six months and continue to take part in  
5 labs and discussions with the University of Chicago  
6 Hospital personnel regarding my fidaxomicin  
7 treatment.

8 To this day I have not had a recurrence of  
9 these symptoms. This treatment cleared up the CDI,  
10 and I was able to return to teaching and living the  
11 life I had previously enjoyed. I am grateful to my  
12 doctors and Optimer for being able to regain my  
13 life and health because of the use of fidaxomicin,  
14 and I thank you for granting me the opportunity to  
15 speak to you in this manner.

16 DR. GOETZ: Thank you.

17 The open public hearing portion of the  
18 meeting has now concluded and we will no longer  
19 take comments from the audience. The committee  
20 will now turn its attention to address the task at  
21 hand, the careful consideration of the data before  
22 the committee as well as the public comments.

1           So we will move now to the questions, which  
2 will be posed by the FDA.

3                           **Charge to the Committee/Questions**

4           DR. LAESSIG: Good afternoon. I'm Katy  
5 Laessig, the deputy director of the Division of  
6 Anti-Infective and Ophthalmology Products.

7           So we've heard many excellent presentations  
8 this morning and this afternoon, and we thank the  
9 speakers both for the applicant, the agency, and  
10 from the open public hearing for those  
11 presentations. We've also heard your thoughtful  
12 questions and discussions from the committee  
13 members, and we thank you for those and for your  
14 advice that you've given.

15           Now we ask that you synthesize all of that  
16 information, both what you've heard and what you've  
17 read from the background material, and tackle our  
18 two questions. You'll note that both of these are  
19 votes, and we ask that during your discussion after  
20 the vote is taken, that you please include your  
21 rationale for your vote.

22           So we can see question 1 is up on the board,

1 and we can start with that. So the first question  
2 is:

3 Has the applicant demonstrated the safety  
4 and effectiveness of fidaxomicin for the requested  
5 indication, treatment of Clostridium difficile-  
6 associated diarrhea?

7 If your answer is yes, are there any  
8 specific issues that you think should be addressed  
9 in the product labeling? And if your answer is no,  
10 are there additional data that you suggest to be  
11 obtained?

12 Thanks.

13 DR. GOETZ: Are there any questions that the  
14 committee has regarding the wording of the question  
15 itself?

16 [No response.]

17 DR. GOETZ: I gather not, then. No one  
18 seems to be posing that question straightforward.

19 Any questions or issues that the committee  
20 members would like to discuss at this time, or are  
21 we ready for a vote at this time?

22 [No response.]

1 DR. GOETZ: The committee seems to be ready  
2 for a vote at this time.

3 We will be using the electronic voting  
4 system for this meeting. Each of you have three  
5 voting buttons on your microphone, "Yes," "No," and  
6 "Abstain." Once we begin the vote, please press  
7 the button that corresponds to your vote. The vote  
8 will then be displayed on the screen. I will read  
9 the vote from the screen into the record.

10 Next, we will go around the room, and each  
11 individual who voted will state their name and vote  
12 into the record, as well as the reason why they  
13 voted as they did. So we have the flashing buttons  
14 now, which means that we are ready to vote. Thank  
15 you.

16 [Vote taken.]

17 DR. GOETZ: The vote is in. The voting  
18 results are 13 yes, zero no, and zero abstain. So  
19 everyone's vote is yes, as expected.

20 So we will go around the room and ask people  
21 to state their name, their vote, and explain the  
22 rationale for their vote. We'll start to my far

1 right.

2 Dr. Surawicz, if you could begin. Thank  
3 you.

4 DR. SURAWICZ: I'm Christina Surawicz. I  
5 voted yes. I think the trials were both well-done.  
6 The methodology was excellent, the data analysis  
7 was clear, and the results were very positive. I  
8 have no reservations.

9 DR. SHYR: So I voted yes. Reason is there  
10 is no clear baseline. The baseline is very  
11 balanced, and all the trial is very rigorous. The  
12 data analysis, including missing data, including  
13 sensitivity analysis, all them show -- we can  
14 reject the null hypothesis, which is we think it's  
15 a vote. That's why I voted yes.

16 MR. MAKOWKA: Ken Makowka. I voted yes  
17 also. Very conclusive data, equal to or better  
18 than the comparative drug. The only point I would  
19 like to make is that the labeling should address  
20 special consideration for people with compromised  
21 immune systems.

22 DR. HASLER: William Hasler. I voted yes.

1 I think, from an efficacy standpoint, the data is  
2 quite strong. If we follow the FDA's lead and  
3 eliminate the use of the term "recurrence" and go  
4 with a complete cure, then in fact I think the data  
5 suggests this drug is superior to vancomycin from a  
6 safety standpoint.

7 Some minor concerns about risks of GI  
8 bleeding and leukopenia, but I believe these are  
9 relatively minor and can be followed postmarketing.

10 DR. HILTON: I voted yes. I'm also in favor  
11 of disregarding the recurrence outcome data and  
12 focusing on the short-term and the global clinical  
13 cure data.

14 I'm concerned about the adverse events. I  
15 recall a slide that said that SAEs and fatalities  
16 are consistent with the underlying clinical  
17 condition. But the sponsor also showed that  
18 they're consistent with a higher concentration of  
19 treatment. So I would urge them to continue to  
20 study the possibility of a lower dose in more  
21 severely ill patients.

22 MS. YOUNG: Kathy Young, and I voted yes

1 because I thought the clinical trials were very  
2 rigorous, and the FDA cross-checking validated many  
3 of the major concerns.

4 In terms of the global cure, I think it  
5 would be good to include something about this takes  
6 into account recurrence. And I would hope that the  
7 global cure, if it's going to be used as a  
8 precedent, would have a separate discussion by this  
9 committee because I think it's appropriate for this  
10 particular drug, but it may not if we consider all  
11 the innuendos for other antibiotics. Thank you.

12 DR. KAPLAN: Shelly Kaplan. I also voted  
13 yes. I think the multiple analyses of these two  
14 excellent phase 3 studies showed conclusively that  
15 this drug is effective in treating C. difficile-  
16 associated diarrhea.

17 Obviously, I think that additional  
18 information will be forthcoming about any bleeding  
19 tendencies, and I applaud the company for having a  
20 plan in place for looking at pediatric patients.  
21 Undoubtedly it will be used in that population.

22 DR. SEPKOWITZ: I'm Kent Sepkowitz. I voted

1       yes. Clearly, it's a noninferior drug to  
2       vancomycin on the efficacy side. The safety side  
3       is a little bit concerning, but not overly  
4       concerning. The specific issues that I think do  
5       need to be addressed include pregnancy, albeit one  
6       bad outcome in a pregnancy does not an association  
7       make. But it was a dramatically concerning  
8       outcome.

9               I think that the hemorrhagic colitis group  
10       of symptoms is something that will need further  
11       explanation, and I don't think we've had good  
12       explanations from it here. I think the fact that  
13       elderly seem to have higher levels of drug, and  
14       that -- unless I've misinterpreted it -- and that  
15       higher levels of drug are associated, not  
16       necessarily causally, with more adverse events and  
17       need some work.

18               Also, I was concerned that there was such a  
19       large amount of misclassification that the FDA  
20       found about 10 percent across everything that you  
21       reclassified in terms of endpoints. Although it  
22       was distributed evenly, it made me worry about the

1 rigor -- about the quality of the study.

2 Finally, I think that we didn't get good  
3 answers, and I don't think there are good answers,  
4 but I think that C. diff more than any other  
5 disease is a disease with a moving target in terms  
6 of diagnostic test. And the toxin was used in  
7 Canada; the EIAs were used everywhere else, but  
8 soon we will all be using or many will be using a  
9 PCR test.

10 So I do worry that this is being approved  
11 around a test that will probably be obsolete, or is  
12 becoming obsolete, and that the implications of the  
13 PCR test, to the efficacy, have not been explored.  
14 They couldn't have been explored. But PCR does  
15 identify many, many, many more cases, 30 percent  
16 more cases, and I would hope that the company has a  
17 plan to address in the PCR environment what the  
18 efficacy is.

19 DR. GOETZ: My name is Matthew Goetz. I'm  
20 the chair. I voted yes. Clearly, I thought that  
21 the study satisfied the noninferiority criteria for  
22 treatment of C. difficile-associated diarrhea.

1 I use the term "diarrhea" quite purposely  
2 because I echo Dr. Sepkowitz's concern that we are  
3 dealing with a moving target regarding the  
4 diagnosis of C. difficile disease and for the  
5 increased reliance on PCR, which may lead to a  
6 slightly different case mix as we move forward.  
7 That's not the fault of anybody. It's the way  
8 medical science is; times change, things move  
9 onwards.

10 I also have some concern, I'll say, not  
11 undue concern but concern, about the observed  
12 leukopenia, increased drug levels with some  
13 association with increased treatment-emergent  
14 adverse effects, which were observed in the study;  
15 not so undue that I didn't vote for approval, but I  
16 think that's something that will warrant further  
17 observation as we go forward.

18 We'll get to issues regarding recurrences  
19 versus global cure in the second question. My vote  
20 does not imply anything in that regard. We'll  
21 address that in a few moments.

22 DR. CHATTERJEE: Archana Chatterjee. I

1 voted yes as well for some of the reasons already  
2 stated. C. difficile-associated diarrhea is  
3 clearly a significant problem in primarily the  
4 adult population, especially the elderly. However,  
5 it is an increasing problem in children. These are  
6 the patients that I care for. And for the first  
7 time, I think, I have come to this committee  
8 meeting and am not pleading for a plan for a  
9 formulation for children. So I congratulate the  
10 company for having that plan already in place.

11 In terms of the efficacy, I thought the two  
12 studies that were presented supported the  
13 contention that this is a more effective drug in  
14 treating this condition. I share some of the other  
15 committee members' concerns about adverse effects,  
16 specifically the concern for bleeding and  
17 neutropenia, but also would like something in the  
18 labeling to reflect a concern for potential risks  
19 to pregnant women. Although there was only one  
20 case, it still is something that might be a signal  
21 and I believe should be taken into account.

22 DR. AUWAERTER: Paul Auwaerter. I voted

1       yes. And the inferiority was clearly met in terms  
2       of the standards of the study, and voted for  
3       approval.

4               I share with many of the prior comments. I  
5       think, with the release of this medication, if that  
6       comes to bear, it'll be used in areas outside of  
7       the current study standards, and especially in  
8       perhaps more severely ill patients who might be  
9       more prone to bleeding, also hematological  
10       abnormalities, toxic megacolon. So I think it will  
11       bear some observation as the drug reaches a wider  
12       audience in use.

13              DR. FOLLMAN: My name is Dean Follman. I  
14       voted yes. Pretty much I agree with everything  
15       that was said. I thought the studies were well-  
16       done. I thought the sponsors presented them  
17       nicely. I was grateful for the sensitivity  
18       analyses that the FDA did, so I thought it was a  
19       very easy decision in terms of efficacy.

20              I don't have much to add about safety,  
21       except I think it would be interesting to do some  
22       of the analyses we talked about before, where you

1 try and evaluate the effect of systemic exposure  
2 while controlling for the confounding effects of  
3 old age and poorer health and so on in terms of  
4 leukopenia, neutropenia, and bleeding.

5 DR. SOLGA: I agree with the other speakers.  
6 I think this is a relatively straightforward vote.  
7 Sure, postmarketing surveillance needs to be done.  
8 The question reads, though, "Should there be  
9 specific issues addressed in the labeling?" I  
10 think to me the answer to that is no.

11 These were sick patients in many, many ways.  
12 There was some signal of GI bleeding and  
13 leukopenia. But, gosh, there could have been many  
14 other signals that weren't there. And as a  
15 prescribing physician who runs around the hospital  
16 a lot, I don't find overly long, cumbersome drug  
17 labels to be useful to me. I find clear, blunt,  
18 black box warnings to be useful to me, and this  
19 isn't even close to getting to that point.

20 Of course, these are very nice, very well-  
21 done studies. Vancomycin, the original studies in  
22 the '70s, I'm sure weren't held to this standard,

1 and I wouldn't want this label to be all mucked up  
2 in different ways where vancomycin's isn't because  
3 these studies were better.

4 DR. GOETZ: Thank you.

5 We will now move to the charge for the  
6 second question.

7 DR. LAESSIG: Okay. Pretty much the same  
8 drill as for the first question, and thank you for  
9 your responses to the first question.

10 So question number 2 is: Is the finding of  
11 lower recurrence of CDAD at day 31 in the  
12 fidaxomicin-treated subjects of clinical  
13 significance? If yes, does it warrant discussion  
14 in the product labeling? And if no, what  
15 additional data are needed? Thank you.

16 DR. GOETZ: Are there any clarifications  
17 regarding wording that the committee would like to  
18 discuss, or is this clear again?

19 DR. SURAWICZ: I'd like to hear a little bit  
20 more about what this means, what are the  
21 implications of our vote in terms of product  
22 discussion and labeling.

1 DR. LAESSIG: Well, you've heard,  
2 particularly with respect to the efficacy, the  
3 clinical significance and relevance of recurrence  
4 rate as well as the statistical limitations of  
5 those analyses, and then also the use of global  
6 cure as an endpoint.

7 So we're looking for some additional advice.  
8 You have covered some of it in your discussions  
9 this morning, but sort of where you see that going.

10 DR. SURAWICZ: Is it more of a question as  
11 to whether this can be used for marketing, or is it  
12 something that's going to be buried in the product  
13 information? I guess that's what I'm not clear  
14 about.

15 DR. LAESSIG: Well, pretty much anything  
16 that gets put in the label can be used in  
17 advertising. So, yes.

18 DR. SURAWICZ: Maybe to clarify, what would  
19 be the two choices?

20 DR. LAESSIG: Well, the choices would be  
21 including recurrence in the label or not including  
22 it, including global cure in the label or not

1 including it, or any combination of the three  
2 endpoints that were covered. Clearly, the primary  
3 efficacy analysis would be in there.

4 DR. COX: Another thing that's very helpful  
5 to us, too, you've heard the discussions on the  
6 issue of global cure versus recurrence, and with  
7 your vote, there's the opportunity, too, to discuss  
8 your answer in this setting. I think the rationale  
9 and the discussion will be very important to our  
10 understanding how you're looking at the science  
11 here.

12 DR. GOETZ: Dr. Sepkowitz, I believe?

13 DR. SEPKOWITZ: Yes. Thanks. To re-re-  
14 reclarify that, so the words "global cure" do not  
15 appear in the question. So we're going just with a  
16 vote regarding "lower recurrence," and recurrence  
17 means whatever we think recurrence means. And it's  
18 not -- I mean, it was never rigorously defined, and  
19 that's been one of the collective hesitancies about  
20 it. Correct?

21 DR. LAESSIG: Correct.

22 DR. GOETZ: Yes, Dr. Hasler?

1 DR. HASLER: I guess my question relates to  
2 the question itself. What would the label say? A  
3 lower recurrence rate compared to what?

4 DR. LAESSIG: That's a good point, and that  
5 we would ask you to answer.

6 [Laughter.]

7 DR. GOETZ: Ms. Young?

8 MS. YOUNG: I was just wondering, has this  
9 global cure category been used before, and in what  
10 instances?

11 DR. LAESSIG: Not for C. difficile. I mean,  
12 as noted by the applicant, there has not been a  
13 drug approved for this indication in several  
14 decades.

15 DR. GOETZ: So where we are here, and where  
16 I sense in the committee, or maybe it's only in my  
17 own mind, is a little bit of discomfort with no  
18 discussion on recurrence because it has -- it had a  
19 clear meaning, I think, in the protocol as written  
20 and the data as presented by both the FDA and the  
21 sponsor. And then there was also extensive  
22 discussion about a non-primary outcome, secondary

1 outcome, global cure.

2           Would the FDA consider a separate vote on an  
3 issue of global cure or a sense of the committee on  
4 that, or would that not be helpful or appropriate  
5 at this time?

6           DR. COX: Yes. I think that's a reasonable  
7 way to go. I mean, I think the discussions that  
8 we've had here today have helped to further flesh  
9 this issue out since we wrote the question. So I  
10 think it's reasonable to think about the question  
11 of recurrence, thinking about how it was defined in  
12 the protocol, and then, based on the discussions,  
13 too, that we've had here today, the issue of global  
14 cure.

15           So how actually were you proposing to do  
16 that?

17           DR. GOETZ: Well, what I was thinking  
18 about -- and, again, appropriateness is something  
19 others may determine -- is that we would put forth  
20 a question 3 to follow this about global cure.

21           I guess if the committee votes as a whole  
22 one way, it may not be necessary to have a question

1 on global cure, I guess. But I'm thinking that it  
2 would be -- I would find it myself personally  
3 clarifying to have question 3 appear, saying, are  
4 the overall results of the study indicative of  
5 superiority in global cure rates with fidaxomicin?

6 I don't know whether that's something that's  
7 appropriate at this time, as I say.

8 DR. COX: I think we are trying to get at  
9 the same issue, which is, in essence, how do we  
10 communicate to folks what it is that we've seen  
11 with the results of these trials as far as what  
12 happens as you move beyond the end of therapy? And  
13 I think that's really the heart of what we're  
14 trying to get at here; how do you communicate this;  
15 what's the best way to do so?

16 The question does focus on recurrence. I'm  
17 just wondering, for fear of getting into a whole  
18 new question, can we try and do it by trying to  
19 work through the discussion, in essence, of  
20 question 2 to have people talk about what they  
21 think the important message is to communicate to  
22 healthcare providers and patients about what's

1 happening at these later time points?

2 Is that one way to try and approach this  
3 that sounds feasible?

4 DR. GOETZ: Yes. I think with this  
5 discussion that helps frame the vote and can be  
6 useful, at least speaking to myself personally.  
7 Other committee members may see it otherwise.

8 Just as a point of clarification again, in  
9 the presentation that Dr. Izem provided, there was  
10 a discussion. If we vote on recurrence, it is the  
11 first time we're voting on recurrence as an outcome  
12 for C. difficile, and this would be, in a sense,  
13 precedent-setting; just to again frame that.

14 DR. COX: Well, let me back away from the  
15 precedent-setting issue. But maybe the way to  
16 think about this is, I really think that the value  
17 in this question is going to be from the discussion  
18 that we hear from people and how people think we're  
19 going to communicate what's happening beyond the  
20 end of treatment.

21 If people are uncomfortable with voting on  
22 the question because the discussion has evolved

1 over the course of the meeting here, maybe the way  
2 to go here is to focus on the discussion part here  
3 so that we hear from people what they think  
4 scientifically the best way to communicate this  
5 particular point is.

6 DR. GOETZ: I'm going to turn to Dr. Kaplan  
7 and Dr. Surawicz.

8 DR. KAPLAN: Well, I guess I'm a little  
9 confused only because the specific indication, or  
10 one of the indications, is reducing the risk of  
11 recurrence. And then the question is, is this of  
12 clinical significance and does it warrant  
13 discussion?

14 Well, I would never oppose discussing it in  
15 the label. But that's different, I think, than  
16 saying that it's indicated for reducing the risk.  
17 Maybe I'm being too black and white.

18 DR. COX: So, in essence, you're  
19 saying -- and correct me if I'm wrong here because  
20 I'm not sure I understood you. You said you would  
21 not put the information in the label, is what  
22 you're saying.

1 DR. KAPLAN: No. What I'm saying is, as  
2 requested by the sponsor, they were asking for an  
3 indication that would include reducing the risk of  
4 recurrence. But the question that we're being  
5 asked is, do we think that a finding of lower  
6 recurrence is of clinical significance? And if  
7 yes, does that warrant discussion versus giving it  
8 actual approval as an indication? I think those  
9 are two different things.

10 DR. COX: Yes. No, that is really -- I  
11 agree with you; there are different shades of that  
12 question. And I think really what we are trying to  
13 get at here is, given the discussion about the  
14 issue of recurrence, and then another way to look  
15 at a later time point, which is the issue of global  
16 cure, it would be helpful to hear the committee's  
17 thoughts on that with regards to communicating that  
18 scientific information to healthcare providers and  
19 patients.

20 I understand the question is a little  
21 difficult to vote on. But maybe the way to go here  
22 is to hear the discussion and hear what people

1 think about this as far as information to  
2 communicate what it is that we're seeing later on  
3 as we move away from the end of treatment and how  
4 best to inform healthcare providers and patients  
5 about that.

6 Does that help at all, or are you still in  
7 the same quandary?

8 DR. KAPLAN: Oh, I'm happy. I think if you  
9 want further discussion, I don't think that'll be a  
10 problem. But I guess I'm still not sure if we're  
11 actually voting that this is a specific indication  
12 that is to reduce the risk of recurrences versus  
13 just having information in the package insert that  
14 discusses it.

15 DR. LAESSIG: If that's what you feel the  
16 data support, then you're free to say that. You  
17 think that they should get the indication. If you  
18 think it should just be in a clinical study section  
19 of somewhere in the label, that's all a valid issue  
20 to bring up.

21 So I know we're trying to cover a lot of  
22 ground with this one question, which may be part of

1 the problem here.

2 DR. COX: And if the question is such that  
3 people don't feel that they can vote on it because  
4 of a lack of clarity, again, I think the most  
5 important thing is going to be the discussion and  
6 understanding the rationale for the way to describe  
7 what we're seeing at this later time point in  
8 product labeling.

9 DR. GOETZ: Dr. Surawicz?

10 DR. SURAWICZ: I think it's important, in  
11 talking about recurrence of C. diff, to recognize  
12 there are two things. One is preventing the  
13 recurrence, and then the other is treating the  
14 recurrence.

15 My concern is if you put something in the  
16 label about preventing recurrence, that people are  
17 going to think that this drug also treats  
18 recurrence, and those studies weren't done. So  
19 that's a concern that I have about that.

20 I am, however, excited at the idea of a drug  
21 that will decrease recurrences because, as we've  
22 heard, it's a really difficult problem and there's

1 no single uniform therapy that's effective.

2 DR. GOETZ: Oh, there is further discussion.

3 Dr. Hasler?

4 DR. HASLER: Yes. I guess I'll just throw  
5 in my two cents. I guess I agree with what Dr.  
6 Surawicz said. I think that that is a real issue.  
7 But I think at the end of the day, what patients  
8 are going to want to know is not how they're doing  
9 10 days out, but they're going to want to know how  
10 they do 1 or 2 or 3 or 6 months out.

11 So recurrence is very interesting. But I  
12 think from a standpoint -- and I don't know how  
13 you'd work this into a label, but the standpoint of  
14 what is a more important parameter would be the  
15 global cure rate, I think.

16 DR. GOETZ: Well, if there is no further  
17 discussion on this question, we will now begin the  
18 voting process. Please press the button on your  
19 microphone that corresponds to your vote.

20 [Vote taken.]

21 DR. GOETZ: We're missing one vote. You may  
22 be uncertain as to who you -- I wasn't meaning to

1 single anybody out.

2 [Laughter.]

3 DR. SURAWICZ: I'm still struggling with  
4 this.

5 DR. GOETZ: All right. I think we  
6 saw -- well, if you had voted one way or the other,  
7 it would not have been a tie, is all I can say, I  
8 think. I don't want to put you on the spot there.

9 So the voting results are 6 yes, 6 no, and  
10 1 abstain. I trust we will have a vigorous  
11 discussion, then. And what we will do is go to my  
12 left this time, and I will begin with Dr. Solga.

13 DR. SOLGA: Sure. I voted yes, but like the  
14 rest of the committee, I'm split on this. I think  
15 global cure expresses what we mean a bit better,  
16 and it may be less confusing. And the fact that  
17 we've talked about this for as long as we have, and  
18 we're still not all on the same page about the  
19 question, suggests that labeling and recurrence may  
20 not be a good idea.

21 Nevertheless, I don't want to be dismissive  
22 of what I feel is important information the sponsor

1 provided in terms of what seemed to be patients  
2 doing better at day 30. They just seemed to be  
3 less likely to be bothered with this concern.

4 Sure, additional studies are needed. This  
5 is a problem definition to begin with about  
6 recurrence. And surely these studies weren't  
7 designed to answer exactly how many times these are  
8 coming back. But I think the data do merit some  
9 consideration, and whether it gets into the  
10 labeling, that may be reasonable. The actual  
11 indication may not be such a good idea, but I'll  
12 leave that to the wisdom of the FDA.

13 DR. GOETZ: Thank you. Dr. Follman?

14 DR. FOLLMAN: I'm Dean Follman. I voted no.  
15 As I mentioned earlier in the discussion before  
16 noon, I don't like the recurrence endpoint because  
17 it's not a comparison to the two randomized groups.  
18 And so, in my mind, that basically makes it a  
19 nonstarter.

20 I think the sustained cure -- I don't really  
21 like global cure, either, because it suggests  
22 something that's more nebulous, I think, than what

1 you have here, which is success at 30 days. So I  
2 like a sustained cure or a 30-day cure or something  
3 like that as a term for that.

4 So no matter what we call it -- let's say  
5 the sustained cure -- there's still -- I pretty  
6 much think that this should be part of the  
7 information in the label. I thought a little bit  
8 about whether there is some kind of cherry-picking  
9 going on; in some sense, this is a secondary  
10 endpoint, you could say formally, and maybe we  
11 shouldn't be elevating our interpretation of it.  
12 But I'm kind of dismissive of that concern here.

13 To me, the way to design this trial would  
14 have been have the 30-day endpoint from the get-go  
15 and use a superiority design. That wasn't done.  
16 I'm not sure why. But, to me, that was the  
17 clear -- that's kind of how I would have done the  
18 study. And so I like the idea of having something  
19 about a sustained cure in the label.

20 DR. AUWAERTER: Paul Auwaerter. I voted  
21 yes. Although this was a secondary endpoint, I  
22 think the study design impressed me enough that I

1 think this was clinically significant and  
2 meaningful to the patient populations under study.  
3 And I thought the communication to clinicians and  
4 patients using the global cure or a 30-day standard  
5 would be reasonable to include in the label.

6 My thought might be that you could -- it  
7 needs to be more descriptive, that patients who  
8 have had treatment for CDI at 30 days without  
9 recurrence may be one way. So we're not saying it  
10 prevents recurrence, but they did not have  
11 recurrence. So it's without recurrence, which I  
12 think maybe captures the spirit of what we're  
13 trying to convey here. So that's just one  
14 suggestion, perhaps.

15 DR. CHATTERJEE: Archana Chatterjee. I  
16 voted yes. And I'll just say a few things about  
17 some of the terms that I've heard used today. For  
18 the first time, I think I've heard this term  
19 "global cure," and I'm thinking from the standpoint  
20 of a patient specifically, we might be able to get  
21 this across to clinicians, maybe, but for a  
22 patient, a global cure, I think, means I'm cured

1 forever. And so this can be actually misleading to  
2 the people that we are trying to reach.

3 So I think I like the terminology that you  
4 suggested of somehow distinguishing the two drugs  
5 at 30 days, that there is definitely a benefit of  
6 treatment with one drug over the other. What you  
7 call it, I think, you have to craft the language  
8 for that very carefully in order to make sure that  
9 there is not misunderstanding of what exactly the  
10 difference was. And I'll just leave it at that.

11 DR. GOETZ: I'm Matt Goetz. I voted no, as  
12 indicated on the screen. I was swayed by the  
13 statistical arguments about the relative weaknesses  
14 in the recurrence analyses.

15 Dr. Izem's presentation where she, if you  
16 will, unwrapped the question as to what is  
17 contained in the global cure -- and global cure may  
18 not be the right term, but it's the phrase that  
19 we've been using today -- and showing how there can  
20 be a disconnect between the overall effectiveness  
21 of an agent and what its effect is on the  
22 recurrence rate led me to concerns that were the

1 committee to endorse this language of recurrence,  
2 there might be some sort of slippery slope that  
3 opened up, recognizing that we're not setting  
4 mandates here in our discussions. But nonetheless,  
5 it has some influence rather than no influence.

6 Nonetheless, I am also very encouraged by  
7 the results of -- I'll call it the 30-day  
8 resolution rate, which I think captures some of the  
9 nuance in the terms. Global cure can be  
10 misleading, just as recurrence can be misleading.  
11 But anyway, that 30-day resolution rate clearly  
12 favored, with superiority, the fidaxomicin.

13 I do have some concerns about the disconnect  
14 between study 003 and 004, which may be partially  
15 related to differences in strains, which may be  
16 partially related to the BI strain, or other  
17 evolution of strains as time goes on. Clearly,  
18 this is an area globally for fidaxomicin, as for  
19 all antimicrobial therapy, so we have to be  
20 concerned about the evolution of our strains. What  
21 was true 5 years ago with the emergence of BI was  
22 not true 15 years ago. What will be true 5 years

1 from now -- well, if I knew that, I'd be in a  
2 different place.

3 But quite seriously, we do need to monitor  
4 things. I think the 30-day resolution rate is a  
5 better language that we can communicate to  
6 patients, and recurrence is just one thing that  
7 contributes to that 30-day resolution. Patients, I  
8 think, overall are much more interested knowing,  
9 "How will I be doing 30 days from now, Doc?" rather  
10 than, "Am I going to have" -- "Am I going to get  
11 better, then get worse again?" I think it's really  
12 that 30-day resolution which is important. Thank  
13 you.

14 DR. SEPKOWITZ: Yes. I'm Kent Sepkowitz. I  
15 voted no, for all the reasons stated. Again, what  
16 was not demonstrated -- many good things were  
17 demonstrated here, but what was not demonstrated  
18 here was a reduction for the risk of recurrence, so  
19 for all the reasons stated. I also remain  
20 disturbed by the lack of effect vis-a-vis  
21 recurrence in the BINAP or the BI strain in one of  
22 the two studies.

1 DR. KAPLAN: Shelly Kaplan. I voted yes.  
2 I'm looking specifically at the question. I  
3 thought the data did demonstrate -- I know there  
4 are nuances, that there was a lower recurrence at  
5 30. And I think, for all the same reasons, that  
6 that type of information can certainly be included  
7 in the label.

8 I'm glad to hear no one else -- or other  
9 people hadn't heard about global health -- global  
10 health -- that's what I think about when I hear  
11 "global" -- global cure because I thought, well,  
12 maybe I missed something somewhere else.

13 But this information clearly will be -- the  
14 details of the study will be, I'm sure, in the  
15 package insert, the specifics, and hopefully the  
16 definitions and all the particulars. And people  
17 can -- and in the publications, they'll be able to  
18 determine for themselves what they think about what  
19 happens by 30 days.

20 MS. YOUNG: And I voted that, yes, we should  
21 find a benefit for the 30-day resolution. I like  
22 using the term "resolution" after 30 days. Global

1       cure, I think that using that terminology, it needs  
2       to be defined by this committee, drug by drug,  
3       probably, unless we have, really, a hearing on  
4       that.

5               I just want to take the opportunity to say  
6       from a resistance standpoint, you know, we're  
7       talking about a disease that really is created by  
8       healthcare. And so the fact that we have a drug  
9       coming in that is targeted, that has novel  
10       mechanisms of action, that has a post-approval  
11       surveillance system that's built into it, I think  
12       these are the criteria we should have for  
13       antibiotics as they come through if we're going to  
14       address the resistance issue. So I'm happy to say  
15       yes.

16               DR. HILTON: I'm Joan Hilton. I voted no  
17       because I focused on the outcome of recurrence  
18       rate. And because that was in a subset analysis,  
19       not from a randomized MITT population, I don't want  
20       to rely on those data.

21               I agree with my colleagues who are not  
22       comfortable with the phrase "global cure rate." I

1 think that that might have been a handy phrase to  
2 use during the trial, but I don't think that it  
3 should be used subsequently.

4 I think that a good way to put it would be  
5 to describe the two endpoints as the 10-day  
6 recurrence-free survival rate or the 30-day  
7 recurrence-free survival rate. And I also agree  
8 with my colleague, Dr. Surawicz, I think, who  
9 pointed out that having had a prior episode was not  
10 one of the eligibility criteria of this study.

11 So these studies did not treat recurrent  
12 C. difficile. Only a subset of the patients had a  
13 repeat episode, as far as I understood. And I  
14 think it's really important to make that clear  
15 because my heart goes out to the open forum  
16 speakers who described their experience, and I  
17 wouldn't want to mislead them when we haven't shown  
18 that it can definitely address -- it can definitely  
19 treat recurrences.

20 DR. HASLER: I'm William Hasler. I voted  
21 no, for many of the same reasons that were stated  
22 by the other committee members. And I do also have

1 problems with the term "global cure," and given the  
2 study did examine data specifically at 30 days, I  
3 strongly would support putting that number in a  
4 label. I think one of the other committee members  
5 said that there are consensus documents that follow  
6 these patients out to 8 weeks before they consider  
7 people cured. And so I think a 30-day response  
8 should be included in the label.

9 MR. MAKOWKA: Ken Makowka. I voted no. I  
10 did not think that the design of the trial was  
11 specifically geared to show information regarding  
12 recurrence. As the public forum stated, it's an  
13 ongoing, recurrent disease, if you want to call it  
14 that. But I don't think it was designed to go that  
15 far -- maybe it should be -- before you can say or  
16 make a claim that it's going to prevent recurrence.

17 DR. SHYR: My name is Yu Shyr. I vote yes.  
18 It's very hard for me; as a statistician, looked at  
19 the data. Let me tell you why I vote yes as  
20 slightly better than no.

21 I totally agree the data for the recurrence,  
22 not from pure, randomized trial data, that's true.

1 But when we look at the baseline between the two  
2 treatment arms, very balanced. That's for the  
3 known. I totally agree with Dr. Follman's comment,  
4 was unknown factors we don't know.

5 So for the other part of what my decision  
6 is, I used the global cure, which is pure  
7 randomized trial result, used that result as a  
8 surrogate for the unknown factors. I think I  
9 phased that information into my decision. So  
10 including that, I believe these two data -- these  
11 two arms very compatible, is no baseline imbalance,  
12 therefore, answering the question recurrence.

13 I really wish I can see the data on really  
14 adjusted confidence interval adjust for all the  
15 other baseline covariates shown in the slides from  
16 FDA, but I did not see that. But add all this  
17 together, I do think I still vote yes to answer  
18 this, recurrence.

19 However, in the labeling I think we should  
20 clearly say this data is based on 31 days, and that  
21 this is to prevent the recurrence, not the  
22 treatment for the patient who already recurred. So

1 this is quite important. We should clearly say  
2 this only prevents the happening of recurrence, but  
3 not for the patient who recurred. So that's all my  
4 comment.

5 DR. SURAWICZ: So I'm the abstain vote,  
6 which I think I will change to a no vote. So my  
7 point is that recurrent *Clostridium difficile* is  
8 different than the primary episode. The symptoms  
9 may be the same, but once you have one recurrence,  
10 you're more likely to have more recurrences.

11 All we know is that this prevented the first  
12 recurrence. A fair number of people with one  
13 recurrence actually get better with a second round  
14 of treatment. It's the people, once you have that  
15 second, third, and fourth recurrence, that they get  
16 into that vicious cycle.

17 So that's the group that we're really  
18 concerned about. So preventing the first  
19 recurrence, that's wonderful, but I don't think we  
20 can then say it prevents -- well, let me just end  
21 my comment there.

22 I think this could be looked at. First of

1 all, I think we need to look at longer follow-up,  
2 60 days. That was brought up earlier. Also, we  
3 need better diagnostic tests to diagnose recurrence  
4 because my concern is that some of the patients who  
5 had diarrhea after that 30 days, or even in the 60  
6 days where they weren't looked at, actually did  
7 have recurrences and were missed because the  
8 diagnostic tests were poor.

9 Then I would propose that the sponsors  
10 consider doing a study specifically on patients  
11 with recurrent C. difficile disease, patients who  
12 have had two or more recurrences. I think that  
13 would be fantastic.

14 DR. GOETZ: Thank you.

15 Dr. Cox?

16 DR. COX: Yes. I just want to thank  
17 everybody for your thoughtful comments on the  
18 question. I think we've heard a lot of very  
19 helpful thoughts as we've gone around the table.  
20 So thank you all, and recognize that the question  
21 was a challenging question. So thank you very  
22 much.

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**Adjournment**

DR. GOETZ: And with that, I believe we are at the end of the meeting. And I will ask the meeting participants to please leave their nametag at the table. Thank you, everyone.

DR. LAESSIG: Yes. Thank you all again for your very helpful conversations today.

(Whereupon, at 2:03 p.m., the committee was adjourned.)