

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201699Orig1s000**

**STATISTICAL REVIEW(S)**

**Addendum to Statistical Review  
May 18, 2011**

**NDA/BLA Serial Number:** 201699/000

**Drug Name:** Fidaxomicin 200mg tablet

**Indication(s):** Treatment of Clostridium Difficile Associated Diarrhea (CDAD)

**Applicant:** Optimer Pharmaceutical Inc.

**Date(s):** Submitted: 11/29/2010  
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**Biometrics Division:** Division of Biometrics IV

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**Keywords:** non-inferiority, gate-keeping multiple testing strategy, missing values

This addendum to the statistical review of NDA 201699 (submitted in DARRTS 04/15/2011) has additional efficacy results in Section 1 and a correction and a clarification in Section 2.

## **1 Sensitivity Analyses Results on Global Cure at Study Day 36**

The additional efficacy results in this addendum are sensitivity analyses results for global cure at study day 36. The following tables show results of the same sensitivity analyses as in Section 3.2.5.4 Results for Global Cure in the Statistical Review but with cut off point study day 36 instead of study day 31.

In the original statistical review (submitted in DARRTS in 04/15/2011), sensitivity analyses for global cure at study day 31 were conducted. Study day 31 was used as cut-off point because it was the earliest protocol defined time to impute success for a missing recurrence assessment visit outcome.

In the following tables, the same sensitivity analyses as in the statistical review are conducted for global cure at study day 36. (b) (4)



The main efficacy conclusions do not change with this later time point. At study day 36, there are slightly more potential inconsistencies than at study day 31 (due to 2 deaths and 30 recurrence assessment visits occurring between study day 31 and study day 35). Thus, there are more missing values to impute with this later time point in Sensitivity Analyses 1-3. The results of these sensitivity analyses support the superiority of fidaxomicin to vancomycin for global cure rate at study 36. The tables below are similar to Tables 10-15 in the original statistical review with the only difference being using study day 36 as cut-off point for global cure instead of study day 31. That is, the method of imputation are the same as described in the original review, but the outcome of global cure at study day 36 has more missing values to impute.

**Table 1: Potential Inconsistencies with Assessment of Global Cure at Study Day 36**

Study	003		004	
	fidaxomicin (N= 215)	vancomycin (N = 197)	fidaxomicin (N = 194)	vancomycin (N = 162)
Treatment (Applicant's global cure)				
Total Inconsistencies with Applicant's Assessment of Global Cure	27 (13%)	33 (17%)	22 (11%)	27 (17%)
Inconsistency due to death <b>before study day 36</b>	5	7	8	5
Inconsistency due to CDAD Concomitant Med during trt or follow up [ <b>up to study day 36</b> ]	12	18	12	13
Inconsistency due to recurrence visit <b>before study day 36</b>	19	21	12	16

**Table 2: Global Cure Rate- Sensitivity Analysis 1, Treating Inconsistencies as Failures**

Study	003			004		
	fidaxomicin (N= 289)	vancomycin (N = 307)	<b>Difference<sup>1</sup> (95% CI)<sup>2</sup></b>	fidaxomicin (N = 253)	vancomycin (N = 256)	<b>Difference<sup>1</sup> (95% CI)<sup>2</sup></b>
Global Cure (Applicant's results)	215/289 (74%)	197/307 (64%)	<b>10.2% (2.8, 17.5)</b>	194/253 (77%)	162/256 (63%)	<b>13.4% (5.4, 21.1)</b>
Inconsistencies Total	27/289 (9%)	33/307 (11%)		22/253 (9%)	27/256 (11%)	
<b>Global Cure at study day 36 (FDA- Sensitivity 1)</b>	188/289 (65%)	164/307 (53%)	<b>11.6% (3.7, 19.3)</b>	172/253 (68%)	135/256 (53%)	<b>15.2% (6.8, 23.4)</b>

1. Difference = Cure Rate fidaxomicin treatment arm – Cure Rate of vancomycin treatment arm.
2. 95% CI is derived using Wilson's score method.

**Table 3: Missing Values and Disagreements in Sensitivity Analysis 2 for Global Cure at Study Day 36**

Treatment	fidaxomicin (N= 289)	vancomycin (N = 307)	fidaxomicin (N = 253)	vancomycin (N = 256)
<b>Disagreement: Applicant's Global Cure Success and FDA Global Cure Failure at study day 36</b>				
Total Disagreements	<b>9</b>	<b>13</b>	<b>12</b>	<b>11</b>
Deaths before study day 36	5	6	8	5
Concomitant Med to treat CDAD and Diarrhea	4	6	4	6
<b>Missing Values: Applicant's Global Cure Success and FDA Global Cure Missing at study day 36</b>				
Total <sup>1</sup>	<b>18</b>	<b>20</b>	<b>10</b>	<b>16</b>
<b>Missing Values: Applicant's Global Cure Failures and FDA Global Cure Missing at study day 36 <sup>2</sup></b>				
Clinical cure at end of treatment and missing recurrence assessment visit	<b>3</b>	<b>1</b>	<b>3</b>	<b>7</b>

1: The total includes those subjects with inconsistencies who are alive at study day 36 and either did not receive concomitant medication to treat CDAD or received concomitant medication to treat CDAD but did not have documented diarrhea.

2: These observations were clinical cure at end of treatment but had missing information for recurrence and were assessed as global cure failure by applicant.

**Table 4: Global Cure Rate at Study Day 36 in Sensitivity Analysis 2**

Study	003		004	
<b>Global Cure Rate at Study Day 36 in Sensitivity 2</b>	fidaxomicin 70%	vancomycin 57%	fidaxomicin 72%	vancomycin 57%
<b>Difference<sup>1</sup> 95% CI<sup>2</sup></b>	12.7% (4.4%, 21.0%)		14.6% (5.8%, 23.3%)	
<b>Percent Total Variability Due to Missingness<sup>3</sup></b>	5.5%		3.8%	

1. Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm
2. 95% CI accounts for within imputed samples variability W and between imputed samples variability B
3. Percent of total variability due to missingness is the ratio  $(1+1/25)*B/V$ , where  $V = W + (1+1/25)*B$ , B is the between imputed samples variation and W is the within imputed samples variation.

**Table 5: Disagreement and Missing Values in Sensitivity Analysis 3**

Treatment	fidaxomicin (N= 289)	vancomycin (N = 307)	fidaxomicin (N = 253)	vancomycin (N = 256)
<b>Disagreement: Applicant's Global Cure Success and FDA Global Cure at Study Day 36 Failure</b>				
Concomitant Med to treat CDAD and Diarrhea	4	6	4	6
<b>Missing Values: Applicant's Global Cure Success and FDA Global Cure at Study day 36 Missing<sup>2</sup></b>				
Total <sup>1</sup>	23	27	18	11
<b>Missing Values: Applicant's Global Cure Failures and FDA Global Cure at Study day 36 Missing<sup>2</sup></b>				
Clinical Cure at end of Treatment and missing Recurrence Assessment visit	3	1	3	7

- 1: The total include those subjects with inconsistencies who did not receive concomitant medication or received concomitant medication but did not have documented diarrhea
- 2: These observations were clinical cure at end of treatment but had missing information for recurrence and were assessed as global cure failure by applicant.

**Table 6: Global Cure Rates in Sensitivity Analysis 3**

<b>Study</b>	<b>003</b>		<b>004</b>	
<b>Global Cure Rate at Study Day 36 in Sensitivity 3</b>	fidaxomicin 71%	vancomycin 57%	Fidaxomcin 73%	vancomycin 58%
<b>Difference<sup>1</sup> 95% CI<sup>2</sup></b>	13.2% (5.0%, 21.5%)		14.9% (6.2%, 23.7%)	
<b>Percent Total Variability Due to Missingness<sup>3</sup></b>	6.2%		4.3%	

1. Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm
2. 95% CI accounts for within imputed samples variability W and between imputed samples variability B
3. Percent of total variability due to missingness is the ratio  $(1+1/25)*B/ V$ , where  $V = W + (1+1/25)*B$ , B is the between imputed samples variation and W is the within imputed samples variation.

## 2 Correction and Clarification

This addendum has one correction for a rounding off error in Table 13, page 26 of the statistical review. The correct rounding off of global cure rate at study day 31 for vancomycin in trial 003 in sensitivity analysis 2 is 58%.

This addendum has a clarification to the method used to derive 95% confidence interval for difference in proportions. The “method recommended in Agresti and Caffo (2000) and Newcombe (1998)” in the original statistical review refers to Wilson’s score method.

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/s/  
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05/18/2011

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05/18/2011



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA Serial Number:** 201699/000

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## 1 EXECUTIVE SUMMARY

This is a summary of the most important findings from the statistical review for NDA 201699 for oral fidaxomicin 200 mg, twice daily for ten days. The two indications under review are first, treatment of *Clostridium difficile* infection (CDI), also known as *Clostridium difficile* associated diarrhea (CDAD) and second, reducing the risk of recurrence when used for treatment of initial CDI. Results of this NDA were presented at an advisory committee in April 5<sup>th</sup> 2011.

The main efficacy findings are: fidaxomicin is non-inferior to vancomycin for the endpoint of clinical cure at the end of treatment and fidaxomicin is superior to vancomycin for the endpoint of global cure or sustained cure up to three weeks after end of treatment. Based on our review findings, we recommend approval of fidaxomicin 200mg twice daily for 10 days for treatment of CDAD.

The applicant's main efficacy results in support of the two indications are from two multicenter, multinational, double blind, active controlled trials. The two trials have identical protocols using oral vancomycin 125mg, four times a day for ten days, the only FDA approved drug for treatment of CDAD (NDA 05606 approved in 1986), as the active control. The first trial (study 003) has centers in the US and Canada, whereas the second trial (study 004) has centers in the US, Canada and Western Europe. Subjects in the trials were stratified by CDAD history into two strata: no CDAD history stratum or one prior CDAD episode in the previous 3 months stratum.

The primary endpoint of clinical cure at end of treatment is a clinician's assessment of the need for no additional CDAD therapy within two days of the end of treatment (day 10). Conversely, the need for additional therapy is based on lack of resolution of signs and symptoms of CDAD. The key secondary endpoint of global cure at the end of treatment is a composite of clinical cure at the end of treatment with no recurrence until the end of the follow up period. Recurrence during the follow up period is assessed by the clinician as re-establishment of diarrhea, toxin positive for *C. difficile*, and the need for CDAD therapy.

Since our review found some subjects assessed as non-recurrent even though they died during the study or they received CDAD medication during follow up, we decided to explore different definitions of non-recurrence in sensitivity analyses. In our preferred sensitivity analysis (sensitivity 2) for the endpoint of global cure, all clinical failures at the end of treatment, deaths, and suspected recurrence of CDAD with diarrhea needing CDAD therapy are treated as failures.

The length of follow up for assessing non-recurrence is defined in the protocol to be at least 36 days from start of the study or 26 days after end of treatment. However, some subjects in the trial were assessed as non-recurrent prior to this day. Our preferred sensitivity analysis (sensitivity 2) uses study day 31 or 21 days after the end of treatment as the earliest protocol allowed day for assessing non-recurrence. The outcome of non-recurrence is then used to determine the global cure endpoint. Recurrence outcomes for subjects with missing recurrence assessment visits or with visits prior to study day 31 are considered missing in sensitivity 2 and are imputed using a multiple imputation method.

The statistical review supports the applicant's finding of non-inferiority of fidaxomicin to vancomycin for the endpoint of clinical cure rate among all mITT subjects. The non-inferiority margin of 10% proposed by the applicant is acceptable based on results from two large recent trials showing superiority of vancomycin to tolevamer. The results of the applicant for clinical cure rates are 88% for the fidaxomicin arm and 86% for the vancomycin arm in study 003 and 88% for the fidaxomicin arm and 87% for the vancomycin arm in study 004. The 95% confidence interval for the difference in cure rate between fidaxomicin and vancomycin is (-2.9%, 8.0%) in study 003 and (-4.8%, 6.8%) in study 004.

The statistical review supports the applicant's finding of superiority of fidaxomicin to vancomycin for the endpoint of global cure. The review of case report forms found a few possible inconsistencies with the investigator's assessment of non-recurrence such as death, early assessment, and CDAD concomitant medication during follow up. However, all FDA sensitivity analyses support the superiority of fidaxomicin to vancomycin for the endpoint of global cure.

The applicant's results for global cure rate among all mITT subjects is 74% for fidaxomicin and 64% for vancomycin in study 003 and 77% for fidaxomicin and 63% for vancomycin in study 004. The 95% confidence interval for the difference in global cure rates between fidaxomicin and vancomycin is (2.8%, 17.5%) for study 003 and (5.4%, 21.1%) for study 004. The FDA sensitivity analyses found lower global cure rates in both arms and both trials with sensitivity analysis 2 showing a global cure rate of 71% for fidaxomicin and 57% for vancomycin in study 003 and 72% for fidaxomicin and 59% for vancomycin in study 004. The 95% confidence interval for the difference in global cure rates between fidaxomicin and vancomycin from sensitivity 2 is (5.0%, 21.2%) for study 003 and (4.5%, 22.0%) for study 004.

The review finds the other secondary endpoint, recurrence among those cured, hard to interpret and explores the findings of recurrence among all mITT subjects. The difference in recurrence among those cured between two treatment arms compares the risk of recurrence at follow up among two different subsets of the mITT population, those cured by fidaxomicin in one hand to those cured in vancomycin on the other hand. For example, in study 003, those cured in the vancomycin arm were significantly older than those cured in the fidaxomicin arm. So, in study 003, the difference in recurrence among those cured is hard to interpret as it is comparing the risk of recurrence among younger subjects in fidaxomicin arm to risk of recurrence among older subjects in vancomycin arm. The review explored the endpoint of recurrence over all mITT subjects, and found that fidaxomicin is superior to vancomycin for this endpoint.

The treatment effect of fidaxomicin over vancomycin for the clinical cure and global cure endpoints is consistent across the subgroups of age, CDAD history, patient status (inpatient versus outpatient), and geographic region. One possible exception is treatment effect of fidaxomicin over vancomycin for the global cure rate in the different strain subgroups (virulent versus non-virulent).

There are concerns for global cure that the treatment effect of fidaxomicin relative to vancomycin was significantly decreased for subjects with the *C. Difficile* virulent strain in comparison to those with the non-virulent strain. At least a quarter of all *C. Difficile* strains are

virulent in each study, at least half of all *C. Difficile* strains are non-virulent, and about a quarter of all mITT subjects had missing information on their *C. Difficile* strain's virulence. In a logistic regression of global cure on treatment and virulence, the interaction between treatment effect and virulence is significant in study 003 (p-value=0.009). However, this effect modification was not replicated in study 004 (p-value=0.29). In the non-virulent subgroup, the estimate and 95% confidence interval of the difference between fidaxomicin and vancomycin for the endpoint of global cure are 16.9% (6.3%, 27.0%) in study 003 and 19.6% (8.7%, 30.0%) in study 004. In contrast, for the virulent subgroup, the estimate and 95% confidence interval of the difference between fidaxomicin and vancomycin for the endpoint of global cure are -5.5% (-20.3%, 9.5%) in study 003 and 12.9% (-4.2%, 29.2%) in study 004.

## 2 INTRODUCTION

This section provides the background and overview of the drug development process for this submission and the two pivotal studies submitted. The applicant conducted two pivotal clinical studies, 101-1-C-003 and 101-1-C-004, that we refer to as study 003 and study 004, respectively.

### 2.1 Overview

Optimer Pharmaceuticals, Inc. submitted New Drug Application NDA 201,699 for Dificid™ (fidaxomicin tablets) on November 29, 2010. Fidaxomicin is a macrolide antibacterial with an 18-membered ring that is microbiologically active against *Clostridium difficile*. It has a narrow spectrum antibacterial profile and has bactericidal activity against *Clostridium difficile*. In addition, it is poorly absorbed and exerts its activity in the gastrointestinal (GI) tract.

The Applicant's two proposed indications for fidaxomicin are: first, the treatment of adults with *Clostridium difficile* infection (CDI), also known as *Clostridium difficile*-associated diarrhea (CDAD); and second, reducing recurrences when used for initial CDI treatment.

The drug product is supplied as 200-mg tablets. The proposed dose regimen for fidaxomicin is 200 mg twice daily for 10 days.

### 2.2 History of Drug Development

The IND (number 64,435) application for fidaxomicin was filed on August 20, 2003. There were three main meetings where the design of the two Phase 3 studies and endpoints were discussed. The three meetings are summarized in Table 1.

**Table 1: Selected FDA/Industry IND Meetings about fidaxomicin**

Date	Meeting Type	Summary of Statistical Issues Discussed
July 13, 2005	FDA meeting to discuss Phase 3 program	FDA recommended a second Phase 3 study since it considered one pivotal study that showed non-inferiority (rather than superiority) not to be sufficient. Based on this recommendation, a second study (Study 004) was initiated.
September 18, 2009	Type C Meeting: Overview of non-clinical program and Phase 3 results	Results from the first Phase 3 study were discussed. Global Cure changed from exploratory to secondary endpoint (at the request of the applicant) for the ongoing Phase 3 study 004.
July 1, 2010	Type B Meeting: Nonclinical/Clinical Pre-NDA Meeting	Adequacy of 10% non-inferiority margin based on the proposed justification was agreed to. Specifics of the efficacy analysis to be performed, the dataset formats and the location of microbiology data were confirmed.

## 2.3 Specific Studies Reviewed

Table 2 below shows a description of the two pivotal clinical studies 003 and 004.

**Table 2: Description of the Two Pivotal Clinical Studies.**

<b>Trial</b>	<b>Description</b>	<b>Treatment Regimens</b>	<b>#Patients Randomized</b>	<b>#Patients Treated</b>
101-1-C-003	Randomized, double-blind, multicenter, comparator-controlled study in CDAD patients. Study Centers: 102 sites (23 Canada and 79 US) Conducted: 5/2006 – 8/2008	fidaxomicin 200 mg q12h for 10 days	302	300
		vancomycin 125 mg q6h for 10 days	327	323
101-1-C-004	Randomized, double-blind, multicenter, comparator-controlled study in CDAD patients Study Centers: 96 (11 Canada, 30 US, and 45 Europe) Conducted: 4/2007 – 12/2009	fidaxomicin 200 mg q12h for 10 days	265	264
		vancomycin 125 mg q6h for 10 days	270	260

The two trials 003 and 004 used identical protocols, although the total sample size and the number and location of investigative sites varied. Both trials used multi-national, multi-center, double-blind, randomized (1:1), parallel group designs. Both trials compared fidaxomicin 200 mg PO q12h with vancomycin 125 mg PO q6h in patients with *Clostridium difficile*-associated diarrhea. The dosing duration for both treatments was ten days in both trials.

The randomization was stratified by prior CDAD episode with two strata: (1) no prior CDAD episode in the last 3 months or (2) a single prior CDAD episode in the last 3 months.

## 2.4 Main Statistical Issues

Four statistical issues are identified. They are:

- 1- Interpretability of secondary endpoint of recurrence among cured
- 2- Inconsistencies between the investigator's assessments of non-recurrence and other available information in the CRF
- 3- Complexity of the language in the CRF to define clinical cure and recurrence. These definitions are composites and data on individual components of the composite are not collected in the CRF

- 4- Lack of homogeneity of data collection of number of unformed bowel movement during the treatment period

These issues are further described in Section 5.

## 2.5 Data Sources

The NDA was an electronic submission with electronic data sets. The material reviewed is

- (1) Clinical overview: <\\Cdsub1\evsprod\NDA201699\0002\m2\25-clin-over>
- (2) Clinical Summary: <\\Cdsub1\evsprod\NDA201699\0002\m2\27-clin-sum>
- (3) Clinical study reports for each study as well as the integrated summary of safety and integrated summary of efficacy <\\Cdsub1\evsprod\NDA201699\0005\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\cdi>
- (4) Original dataset at <\\Cdsub1\evsprod\NDA201699\0002\m5>
- (5) Documentation files (define.pdf) with more details were submitted as a response to an information request at <\\Cdsub1\evsprod\NDA201699\0005\m5\datasets>

The tabulation data is in SDTM format, although some of the variables in the tabulation folder were derived. Raw and derived datasets and codes were submitted.

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

There are some issues of data and analysis quality, but none of them is considered a major issue. The issues are: poor documented traceability of derived variables from tabulation data sets, poor documented traceability of tabulation data sets from case report forms, and complex and confusing language used in the Case Report Form for the two efficacy assessments of clinical cure and recurrence.

There is minimal derivation involved in the primary and two secondary endpoints. Clinical Cure and Recurrence are the two main efficacy outcomes, they are clinically reported outcomes directly captured in a CRF. These two assessments had very little missing values (1 missing value for Clinical Cure and 15 missing values for recurrence among cured) which were set to failures as pre-planned in protocol. Thus, these two assessments matched the data entry in the CRF most of the time and with minimal imputation of failures for missing values. There is minimal derivation for the endpoint of global cure, since it is a composite of clinical cure AND no-recurrence during follow up.

However, all pre-planned sensitivity analyses and exploratory variables relied on derived variables. Traceability of variable derivation from tabulation datasets to analysis datasets is fairly poor in the original submission. The sensitivity analysis based on the modified definition of cure

and the exploratory analyses on time to cure and time to recurrence relied on derived variables using daily number of unformed bowel movement or follow up information on diarrhea. Traceability is usually documented in the define.pdf files with the results of each study as well as the integrated summary of efficacy. After an information request was sent to applicant, new documentation with better information on traceability for the data was submitted in <\\Cdseub1\evsprod\NDA201699\0005\m5\datasets>.

The poor language used in the CRF is further discussed in Subsection 3.2.2.

Lastly, the recurrence assessment visit written in the CRF does not always correspond to the subject's visit time for the scheduled recurrence assessment visit. For instance, there are instances where the recurrence assessment visit date corresponds to either the date of death or the date of the last day of follow up prior to death. This had an impact on the analysis of global cure, since missing the scheduled recurrence assessment visit did not imply a missing value for either the recurrence assessment visit date or global cure outcome. The sensitivity analyses of global cure adjusted for this issue.

## **3.2 Evaluation of Efficacy**

This section describes the study design in Subsection 3.2.1, endpoints in Subsection 3.2.2 and statistical methodology in Subsection 3.2.4. This section also shows the results of the applicant and FDA sensitivity analyses in Subsection 3.2.5.

The efficacy assessments submitted by the applicant rely on three endpoints, clinical cure at the end of treatment, recurrence among cured subjects, and global cure or sustained cured at the end of follow up. The results subsection shows first the results for the primary endpoint of clinical cure as well as sensitivity analyses on this endpoint. Then, the subsection shows the results of the secondary endpoint of global cure with its sensitivity analyses. Because the endpoint of recurrence among cured subjects is hard to interpret, as discussed in Subsection 3.2.2, this review does not show the results on this endpoint.

### **3.2.1 Study Design**

The two trials, 003 and 004, used identical protocols, although the total sample size and the number and location of investigative sites varied. Both trials used multi-national, multi-center, double-blind, randomized (1:1), parallel group designs. Both trials compared fidaxomicin 200 mg PO q12h with vancomycin 125 mg PO q6h in patients with *Clostridium difficile*-associated diarrhea. The dosing duration for both treatments and in both trials is ten days.

#### **3.2.1.1 Scheduled Visits**

An End-of-Therapy (EOT) visit was conducted on Day 10-11 and clinical response (the primary outcome) was assessed. Weekly contacts with subjects were made thereafter (Day 17 ±1 day,

Day 24 ±1 day, Day 31 ±1 day) until recurrence or Post-study Visit [Days 36-40 (or at least 25 days after last dose of study medication)].

### 3.2.1.2 Analyses Population

The two main analyses sets for efficacy are the modified intent-to-treat (mITT) population and the Per Protocol (PP) population for cure. The sample sizes in each of these population is shown in each treatment and study in Table 3.

The mITT population is defined as the group of randomized subjects with CDAD confirmed by >3 unformed bowel movements in the 24 hours prior to randomization and a positive toxin assay and who received at least one dose of study medication.

The PP population is the set of subjects in the mITT population with the following criteria:

- Meet confirmed CDAD clinical diagnosis criteria
- Meet Inclusion criteria and meet no exclusion criteria (unless deviations to either of these are documented and approved by the Sponsor)
- Take sufficient course of therapy. That is, at least 3 complete days of treatment for failure and 8 complete days of treatment for cure; or equivalently, 6 active doses of fidaxomicin for a failure and 16 active doses of fidaxomicin for a cure and 12 active doses of vancomycin for a failure and 32 active doses of vancomycin for a cure.
- Have an EOT clinical evaluation
- Do not have significant protocol violations including: use of concomitant CDAD therapy or other drugs which could confound the assessment of efficacy and other significant protocol violations, as judged by a blinded assessment prior to study unblinding.

Note: Subjects with a positive toxin test within 96 hours (4 days) of randomization are accepted into the mITT population if they have not received more than 24 hours of *C. difficile* therapy as defined in the protocol and meet the other criteria for inclusion into these populations. Subjects who received more than 24 hours of *C. difficile* therapy (e.g. metronidazole failure subjects) must have a positive toxin test within the 48-hour window prior to randomization.

**Table 3: Analyses population**

Population	Trial 003		Trial 004	
	fidaxomicin	vancomycin	fidaxomicin	vancomycin
Randomized	302	327	265	270
Randomized and Treated	300	323	264	260
mITT	289	307	253	256
PP	268	280	217	234

### 3.2.2 Study Endpoints

There is one primary and two secondary endpoints in the trial. The primary endpoint is clinical cure at end of treatment, the two secondary endpoints are recurrence among those cured and global or sustained cure. Each of the endpoints is defined in the subsections below. In addition to the primary and secondary endpoint, the modified definition of cure is presented as it is used for a pre-planned sensitivity endpoint for clinical cure.

Note that clinical assessments (cure/failure, recurrence) were based on the investigator's judgment of subjects' clinical parameters, most importantly based on their diarrhea status.

#### 3.2.2.1 Clinical Cure Endpoint

Definition of Clinical response at the test-of-cure (TOC) assessment (10 days after starting treatment, i.e. EOT  $\pm$  2 days):

Clinical Cure:

- Subjects who, in the opinion of the Investigator, require no further CDAD therapy 2 days after completion of study medication will be considered cured.
- Subjects who have 3 or fewer unformed stools for 2 consecutive days and remain well prior to the time of study medication discontinuation will be considered cured.
- Subjects who at EOT have had a marked reduction in the number of unformed stools and who have residual and mild abdominal discomfort interpreted as recovering bowel by the Investigator may be tentatively considered cured at that time providing no new anti-infective CDAD therapy has been initiated. Subjects who are considered cured based on stabilization and improvement in CDAD signs and symptoms will be evaluated 2-3 days after the end of study medication. In the event that their signs or symptoms of CDAD worsen, they will be designated primary failures.
- Subjects who enter the study without signs or symptoms of CDAD, other than diarrhea, will be evaluated as failures on the basis of continued diarrhea alone as defined in this protocol.
- Subjects having a rectal collection device who are passing liquid stools periodically during the day will be considered to have resolution of diarrhea when the volume (over a 24 hour period) is decreased by 75% compared to admission or the subject is no longer passing liquid stools.

Clinical Failure:

- Subjects who, in the opinion of the Investigator, require additional CDAD therapy will be considered a failure.

The Investigator was to base his/her clinical impression on the need for additional CDAD therapy on the subject's CDAD status, inclusive of the presence of diarrhea and other signs/symptoms of CDAD including: fever  $>38.0^{\circ}\text{C}$ , elevated WBC  $>13,000/\text{mL}$ , or abdominal

pain of moderate severity or greater lasting one hour or more and/or abdominal tenderness of at least moderate severity, including any peritoneal signs.

The primary endpoint of Clinical Cure Rate is the proportion of subjects who were cured at end of treatment among all those in the mITT population.

*Reviewers' comment: The above definition of cure and failure is the one used in the Case Report Form (CRF). After this definition, an investigator can check whether the subject satisfies the cure definition or whether they satisfy the failure definition. Note that the language defining cure is long and complex and may cause confusion. Note also that the investigator does not have an opportunity to specify which of these composite conditions were satisfied to determine cure. As per ICH-E9 guidelines, for any composite endpoint, it is preferable to collect each component of the composite separately.*

### **3.2.2.2 Recurrence among Cured Endpoint:**

Subjects who remain in the study up to the Post-study visit (Study Day 36-40) or who recur prior to that are evaluated for recurrence and non-recurrence using the following definitions:

Recurrence is the re-establishment of diarrhea to an extent (frequency of passed unformed stools) that is greater than that noted on the last day of study medication with the demonstration of either toxin A or B or both of *C. difficile* and, in the Investigator's opinion, require retreatment with CDAD anti-infective therapy. Subjects designated as evaluable for recurrence must have positive toxin demonstrated in the stool. If a rapid screening test is used which fails to demonstrate toxin, then a confirmatory test using a non-rapid method must be used.

Non-recurrence is the maintenance of a non-diarrheal state up to and through the Post-study Visit. Subjects that develop other causes of diarrhea associated with a negative *C. difficile* stool toxin test will not be considered a recurrence.

The secondary endpoint of recurrence among those cured is the proportion of subjects who recurred during the follow up period among those cured at the end of treatment.

### **3.2.2.3 Global Cure Endpoint**

Global or sustained cure is defined as cure at the end of treatment with no recurrence at follow up, where no-recurrence is as defined in the subsection above. The endpoint of global cure rate is the proportion of subjects who were cured at the end of treatment with no recurrence at follow up among all mITT subjects. This endpoint is an exploratory endpoint in study 003 and a key secondary endpoint in study 004.

*Reviewers' comments: We have two general comments on the endpoints of recurrence among cured and global cure. The first comment concerns the assessment of recurrence and applies to both endpoints. The second comment is on the lack of interpretation of the endpoint of recurrence among cured compared to global cure.*

*First, we state our comment about recurrence assessment. As for the assessment of clinical cure at the end of treatment, the assessment of recurrence during the follow up period is a composite of (1) Diarrhea, (2) Positive Toxin, and (3) requiring CDAD medication. However, the investigator could only check recurrence/non-recurrence (all conditions satisfied) in a CRF and no opportunity to detail which of the signs and symptoms were observed. As per ICH-E9 guidelines, for any composite endpoint, it is preferable to collect each component of the composite separately.*

*Second, we state our comment about difficulty of interpretation of recurrence among cured endpoint to measure treatment benefit. Because the recurrence among cured endpoint is conditioning on cure, a post randomization variable, the difference between recurrence among cured for two treatment groups is hard to interpret. More specifically, recurrence among cured quantifies the risk to recur after a subject was cured in that treatment group. However, those cured in one treatment arm may be different than those cured in another treatment arm. Thus, the difference in recurrence among cured compares the risk of recurrence in completely different populations and is hard to interpret as a treatment benefit. By contrast, the difference in global cure rates between two treatment groups quantifies the difference in sustained cure between two groups who were nearly identical at baseline due to randomization.*

#### **3.2.2.4 Modified Definition of Cure**

The modified definition of cure is based on the patient reported outcome of number of unformed bowel movements collected daily during the treatment period. A subject meets the modified definition of cure if that subject has 3 or fewer unformed stools for 2 consecutive days maintained to the end of the end of therapy.

The modified definition of cure endpoint is the proportion of subjects who meet the modified definition of cure at the test of cure among all subjects in the mITT population.

#### **3.2.3 Patient Disposition, Demographic and Baseline Characteristics**

Baseline patient demographic data for Trials 003 and 004 are summarized in Table 4 and Table 5 below. A summary of reasons for discontinuation of study drug in the randomized population is provided in the following Table 6.

**Table 4: Baseline Patient Demographic Data (mITT population)**

	Trial 003			Trial 004		
	fidaxomicin (N=287)	vancomycin (N=309)	All subjects (N=596)	fidaxomicin (N=252)	vancomycin (N=257)	All subjects (N=509)
Sex, n (%)						
Female	164 (57.1)	169 (54.7)	333	148 (58.7)	162 (63.0)	310 (60.9)
Male	123 (42.9)	140 (45.3)	(55.9) 263 (44.1)	104 (41.3)	95 (37.0)	199 (39.1)
Race, n (%)						
White	252 (87.8)	267 (86.4)	519	232 (92.1)	238 (92.6)	470 (92.3)
Black	30 (10.5)	33 (10.7)	(87.1) 63	17 (6.7)	17 (6.6)	34 (6.7)
Asian	4 (1.4)	7 (2.3)	(10.6)	2 (0.8)	1 (0.4)	3 (0.6)
Other <sup>a</sup>	1 (0.3)	2 (0.6)	11 (1.8) 3 (0.5)	1 (0.4)	1 (0.4)	2 (0.4)
Age (yrs)						
N	287	309	596	252	257	509
Mean±SD	60.3±16.9	62.9±16.9	61.6±16.9	64.3±17.9	62.5±18.4	63.4±18.1
Median	61.0	64.0	63.0	67.5	65.0	66.0
Weight (kg)						
N	287	308	595	251	257	508
Mean±SD	78.1±24.2	76±21.3	77±22.8	71.44±20.7	70.88±19.8	71.15±20.2
Median	74.1	73.0	74.0	68.00	67.00	68.00
Range	36.4, 230.6	36, 242.3	36, 242.3	32.0, 231.6	32.8, 181.4	32.0, 231.6
Height (cm)						
N	287	308	595	251	256	507
Mean±SD	167.1±11.1	166.9±12.1	167±11.6	167.07±9.7	165.76±10.97	166.41±10.4
Median	167.0	167.6	167.6	166.00	165.00	165.10
Range	124, 193	129.5, 198	124, 198	146.0, 195.6	114.0, 208.0	114.0, 208.0
BMI(kg/m <sup>2</sup> ) <sup>b</sup>						
N	287	308	595	251	256	507
Mean±SD	27.9±8.1	27.3±7.4	27.6±7.8	25.5±6.30	25.7±6.7	25.6±6.3
Median	26.3	26.0	26.2	24.2	24.9	24.5
Range	15.9, 79.6	15.4, 83.6	15.4, 83.6	12.5, 63.8	12.8, 51.9	12.5, 63.8

<sup>a</sup> Other includes: American Indian and Alaska native.

<sup>b</sup> Calculated body mass index is defined as (weight in kg)/(height in meters)<sup>2</sup>.

BMI – body mass index; SD = standard deviation

Source: Applicant ISE Table 3.1-1

**Table 5: Additional baseline patient demographic data (mITT population)**

	101.1.C.003			101.1.C.004		
	Fidaxomicin (N=287)	Vancomycin (N=309)	All subjects (N=596)	Fidaxomicin (N=252)	Vancomycin (N=257)	All subjects (N=509)
Subject status, n (%)						
Inpatient	167 (58.2)	187 (60.5)	354 (59.4)	174 (69.0)	173 (67.3)	347 (68.2)
Outpatient	120 (41.8)	122 (39.5)	242 (40.6)	78 (31.0)	84 (32.7)	162 (31.8)
Stratum, n (%)						
No Prior Episode	239 (83.3)	255 (82.5)	494 (82.9)	212 (84.1)	221 (86.0)	433 (85.1)
Single Prior Episode	48 (16.7)	54 (17.5)	102 (17.1)	40 (15.9)	36 (14.0)	76 (14.9)
Daily Bowel Movements						
N	287	309	596	251	257	508
Mean ±SD	8.1±4.2	8.3±5.4	8.2±4.8	7.5±4.4	7.5±4.3	7.5±4.3
Median	7.0	6.0	7.0	6.0	6.0	6.0
Min, Max	4, 32	4, 50	4, 50	4, 30	4, 30	4, 30
Baseline disease severity <sup>a</sup> , n (%)						
Mild	64 (22.3)	80 (25.9)	144 (24.2)	77 (30.6)	95 (37.0)	172 (33.8)
Moderate	111 (38.7)	106 (34.3)	217 (36.4)	82 (32.5)	73 (28.4)	155 (30.5)
Severe	112 (39.0)	123 (39.8)	235 (39.4)	90 (35.7)	88 (34.2)	178 (35.0)
Missing	0	0	0	3 (1.2)	1 (0.4)	4 (0.8)
<i>C. difficile</i> Toxin, n (%)						
Positive	287 (100)	309 (100)	596 (100)	252 (100)	257 (100)	509 (100)
Negative	0	0	0	0	0	0
CDI Indication, n (%)						
Diarrhea Alone	49 (17.1)	68 (22.0)	117 (19.6)	188 (74.6)	192 (74.7)	380 (74.7)
Diarrhea and Other Symptoms	238 (82.9)	241 (78.0)	479 (80.4)	64 (25.4)	65 (25.3)	129 (25.3)
Prior Use of CDI Antibiotics, n (%)						
Prior Use	128 (44.6)	139 (45.0)	267 (44.8)	225 (89.3)	220 (85.6)	445 (87.4)
No Prior Use	159 (55.4)	170 (55.0)	329 (55.2)	27 (10.7)	37 (14.4)	64 (12.6)
Metronidazole Failure, n (%)						
Yes	13 (4.5)	17 (5.5)	30 (5.0)	12 (4.8)	8 (3.1)	20 (3.9)
No	274 (95.5)	292 (94.5)	566 (95.0)	240 (95.2)	249 (96.9)	489 (96.1)

<sup>a</sup> Baseline disease severity categories are defined as: Mild CDI = 4-5 UBM/day or WBC ≤ 12,000/mm<sup>3</sup>; Moderate CDI = 6-9 UBM/day or WBC 12,001-15,000 mm<sup>3</sup>; Severe CDI = ≥ 10 UBM/day or WBC ≥ 15,001/mm<sup>3</sup>

Source: Applicant ISE Table 3.1-2

**Table 6: Reasons for Discontinuation of Study Drug**

	101.1.C.003		101.1.C.004	
	Fidaxomicin (N=302)	Vancomycin (N=327)	Fidaxomicin (N=270)	Vancomycin (N=265)
Total who terminated early	22 (7.3)	32 (9.9)	45 (17.0)	34 (13.1)
Reason for early termination				
Adverse event	12 (4.0)	15 (4.6)	15 (5.6)	16 (6.0)
Subject choice	6 (2.0)	7 (2.1)	10 (3.7)	10 (3.8)
Clinical failure	NA	NA	8 (3.0)	3 (1.1)
Effective Concomitant CDI Therapy	0	5 (1.5)	0	0
Protocol violation	0	3 (0.9)	3 (1.1)	2 (0.8)
Non-compliance	2 (0.7)	1 (0.3)	8 (3.0)	3 (1.1)
Lost to follow-up	1 (0.3)	1 (0.3)	0	0
Treatment failure (less than 3 days of therapy)	1 (0.3)	0	0	0
Not having a robust enough response	NA	NA	1 (0.4)	0

NOTE: A subject can have multiple reasons for study termination. NA = not applicable (i.e. category was not included in the study as an option)

Source: Applicant ISE Table 3.1-3

### 3.2.4 Statistical Methodologies

There were three main endpoints in the trial, clinical cure rate, recurrence among cure rate and global cure rate as described in Subsection 3.2.2. This subsection describes the planned analyses on these endpoints as well as the planned gate keeping strategy for multiple testing.

#### 3.2.4.1 Primary Efficacy Analyses

The primary efficacy analysis compared the difference in clinical cure rates between treatment groups (fidaxomicin - vancomycin), using a two-sided 95% confidence interval (CI). Noninferiority of fidaxomicin to vancomycin is demonstrated if the lower limit of the CI was greater than the pre-specified non-inferiority margin of -10%. See Appendix A for the justification of the noninferiority margin.

A two-sided 95% CI was computed for the difference in treatment recurrence rates among cured as well as the difference in global cure rates.

*Reviewer's comment: As discussed in Subsection 3.2.2, the difference in recurrence among cured between two treatment arms is difficult to interpret since it is conditioning on two different subsets.*

All statistical analyses were performed on the mITT population and the PP population.

*Reviewer's comment: The review results shown in the results subsection (Subsection 3.2.5) are all on the mITT population. The size of the per protocol population in each study and treatment is shown in Table 3.*

In order to maintain the overall error rate for testing of secondary endpoints, the following gate-keeping strategy is used as the statistical testing approach for secondary endpoints:

- If the noninferiority of fidaxomicin to vancomycin is demonstrated in the mITT populations (1-sided  $\alpha=0.025$ ) and remain consistent in the PP population, the superiority comparison of treatments for recurrence rates will be made (two-sided  $\alpha = 0.05$ ).

-If the above treatment comparison for recurrence rates among cured is statistically significant in favor of fidaxomicin for both the mITT and PP populations, the superiority comparison of treatments for global cure rate will be made using both the mITT and PP populations (two-sided  $\alpha = 0.05$ ).

*Reviewer's comment: Both endpoints, recurrence rate among cured and global cure rate, contain information on recurrence. It is unclear why the applicant decided to test for superiority of fidaxomicin to vancomycin for the endpoint of recurrence among cured before testing for superiority of fidaxomicin to vancomycin for the endpoint of global cure.*

Efficacy endpoints were conducted in these predefined subgroups: age, sex, race, country, stratum (no prior episodes or single prior episode), CDI-prescribed antibiotic within 24 hours prior to study treatment (yes/no), Metronidazole Failure Prior to Study (yes/no), concomitant systemic antibacterial treatment over the course of the study (yes/no), baseline disease severity (mild/moderate/severe), patient status of inpatient or outpatient, and initial strain of CDI (virulent/non-virulent).

### **3.2.4.2 Handling missing values:**

Missing values in the investigator's classification of clinical cure or failure are replaced with the clinical failure classification.

Missing values in the investigator's classification of recurrence or non-recurrence are replaced with a recurrence classification. There is an exception for missing values for subjects who were followed for more than 25 days after date of cure with complete Day 17, Day 24, and Day 31 Subject Assessments (7, 14, and 21 days after therapy, respectively) without indication of re-establishment of diarrhea; these are classified as non-recurrence. Thus, study day 31 is the earliest protocol allowed day to assess non-recurrence.

The global efficacy variable is derived using the classification for cure and recurrence after any imputation for missing values.

*Reviewer's comment: Although study day 31 is the earliest protocol allowed day to assess non-recurrence, several subjects had their recurrence assessment visit earlier than that date. Outcomes of subjects who died during the study were not considered missing because their recurrence assessment visit date was imputed with either their day of death or last follow up visit. We do not recommend such imputations of the CRF.*

### 3.2.5 Results and Conclusions

The FDA review results support the Applicant's claims for the endpoint of clinical cure and the endpoint of global cure. Although the numbers we report are slightly different than those of the applicant, our final conclusions are in agreement with the Applicant regarding noninferiority of fidaxomicin to vancomycin for the endpoint of clinical cure and superiority of fidaxomicin to vancomycin for the endpoint of global cure.

This section provides the FDA results for clinical cure and global cure rates. When our numbers differ from those of the applicant we explain why. This section also presents results of additional sensitivity analyses motivated by differences in assessments. This section does not provide the results for the endpoint of recurrence among cured due to the difficulty of interpretation, which is further discussed in Subsection 3.2.2 and Subsection 5.1.2. However, we show the result of the exploratory endpoint of recurrence among all mITT subjects and explain how it relates to the result of clinical cure rate and global cure rate.

#### 3.2.5.1 The Reasons why Our Rates Differ from Those Presented by the Applicant

The difference between the Agency's results and the Applicant's is due to some inconsistencies that we have identified during the review between the assessment of clinical cure or global cure by the investigators in the trial and other available information relating to drop out and diarrhea in the sample case report forms (CRFs).

Review of a random sample of 118 CRFs<sup>1</sup> identified a few subjects who were declared as cures or global cures by the Applicant although one or several of the following conditions were true: (1) Death during the study, (2) Concomitant medication treating CDAD received during treatment period or follow up, or (3) Recurrence assessment visit occurred early (before study day 31)<sup>2</sup>.

The result from the sample of CRFs motivated a full search of all study subjects with similar possible inconsistencies. There are 13 subjects who were identified as cures by the Applicant with some inconsistencies and the breakdown by treatment and study is shown in Table 7. There are 85 subjects who were identified as global cures by the applicant with possible inconsistencies and the breakdown by treatment, study and reason of inconsistency is shown in Table 10. These inconsistencies motivated our sensitivity analyses described in the following subsections.<sup>3</sup>

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<sup>1</sup> The FDA's DAIOP division requested that the Applicant submit a 10% random sample of the case report forms (CRFs) from studies 003 and 004. The CRFs were requested for the purpose of establishing consistency among the investigators in their conduct of the study, interpretation of the protocol, and accuracy in reporting of results.

<sup>2</sup> The protocol defined window for recurrence assessment visit is study day 36. However, as shown in the handling of missing values subsection in the clinical development section, the protocol allows for imputing missing recurrence assessments as non-recurrence if subjects were diarrhea free up to study day 31. Thus, study day 31 is the earliest protocol defined day to assess non-recurrence.

<sup>3</sup> Although our sensitivity analyses were not pre-planned in the protocol, they were developed after noticing the inconsistencies in the random sample and before the total tally of the inconsistencies across all subjects in the study.

### 3.2.5.2 Results for Cure

Table 7 shows the results for the endpoint of clinical cure at day 10. This table shows the Applicant's results as well as the results of the FDA analysis. The FDA analysis changed the few observations with inconsistencies to failures. Identified inconsistencies consisted of subjects considered cured by applicant although they either died before the end of treatment or had received concomitant medication treating CDAD during the treatment period. These were identified as possible inconsistencies with the Applicant's assessment of cure because they could indicate treatment failure.

**Table 7: Clinical Cure Rates at End of Treatment Visit**

<b>Applicant's Results</b>				
<b>Study</b>	<b>003</b>		<b>004</b>	
<b>Treatment (mITT)</b>	<b>fidaxomicin (N= 289)</b>	<b>vancomycin (N = 307)</b>	<b>fidaxomicin (N = 253)</b>	<b>vancomycin (N = 256)</b>
<b>Cure n/N (%)</b>	255/289 (88%)	263/307 (86%)	222/253 (88%)	222/256 (87%)
<b>Difference<sup>1</sup> 95% CI<sup>2</sup></b>	2.6% (-2.9%, 8.0%)		1.0% (-4.8%, 6.8%)	
<b>FDA's Results (Sensitivity 1)</b>				
<b>Study</b>	<b>003</b>		<b>004</b>	
<b>Treatment (mITT)</b>	<b>fidaxomicin (N= 289)</b>	<b>vancomycin (N = 307)</b>	<b>fidaxomicin (N = 253)</b>	<b>vancomycin (N = 256)</b>
<b>Inconsistencies with Applicant's assessment of cure<sup>3</sup></b>	0	5	5	3
<b>Cure n/N (%)</b>	255/289 (88%)	258/307 (84%)	217/253 (86%)	219/256 (85%)
<b>Difference<sup>1</sup> 95% CI<sup>2</sup></b>	4.2% (-1.4%, 9.7%)		0.2% (-5.9%, 6.4%)	

1. Difference = Cure Rate fidaxomicin treatment arm – Cure Rate of vancomycin treatment arm
2. 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)
3. Inconsistencies with applicant's assessment of cure are those subjects with outcome of cure by the applicant although these subjects died before day 10, or had taken concomitant medication treating CDAD during treatment period.

### 3.2.5.3 Modified Definition of Cure Results and Differences with Definition of Cure

The analysis of the modified definition of cure endpoint is the Applicant's pre-defined sensitivity analysis of the primary endpoint of cure. The results of this sensitivity analysis support the

noninferiority claim of fidaxomicin to vancomycin, although the estimate for the treatment effect is lower with this endpoint.

The cure rates using the modified definition of cure in the mITT population are 79% in fidaxomicin arm and 80% in the vancomycin arm in trial 003 and 79% in both arms in trial 004. The 95% confidence for the difference in treatment effect (fidaxomicin – vancomycin) is (-8%, 4.9%) in trial 003 and (-6.9%, 7.2%) in trial 004. Since the lower bound of the confidence interval in both studies is higher than -10%, this endpoint meets the non-inferiority margin as well.

There are some data quality concerns with the endpoint of modified definition of cure because the patient reported outcome data of number of unformed bowel movement was not collected in a standardized way in all clinical studies. That is, how the data was collected and who was collecting it varied at the discretion of each site. This dataset has also > 10% of missing values starting at study day 10 and about 18% of missing value by study day 11 (See Table 9).

As shown in Table 8, the outcome of the modified cure endpoint agreed with the outcome of the cure endpoint for most subjects in both arms although the modified cure endpoint is more conservative. There is more agreement of outcomes from these two endpoints in study 003 (about 91% in both arms) than in study 004 (about 88% in both arms). Almost all of the differences between the outcomes from these two endpoints are for outcomes identified as clinical cure based on investigator's assessment but identified as non-cures by the modified definition of cure based on number of unformed bowel movement.

Those identified as non-cures for the endpoint of modified definition of cure included subjects with missing values for the number of unformed bowel movements in at least one of the two days prior to test of cure. About 3% of those identified as non-cures for the modified definition of cure and as clinical cure by investigator had missing values on number of unformed bowel movements in at least one of the two days prior to test of cure. The remaining 6-7% of disagreements between the modified definition of cure and clinical cure were due to the modified definition of cure not being met.

**Table 8: Differences between Cure and Modified Definition of Cure**

<b>Study 003</b>				
<b>Treatment (mITT)</b>	<b>fidaxomicin (N = 289)</b>		<b>vancomycin (N = 307)</b>	
Mod. Cure	Modified Cure No	Modified Cure Yes	Modified Cure No	Modified Cure Yes
Cure-No	34	0	38	6
Cure-Yes	27	228	22	241
<b>Agreement n/N (%)</b>	<b>262/289 (91%)</b>		<b>279/307 (91%)</b>	
<b>Study 004</b>				
<b>Treatment (mITT)</b>	<b>fidaxomicin (N = 253)</b>		<b>vancomycin (N = 256)</b>	
Mod. Cure	Modified Cure No	Modified Cure Yes	Modified Cure No	Modified Cure Yes
Cure-No	28	3	27	7
Cure-Yes	24	198	26	196
<b>Agreement n/N (%)</b>	<b>226/253 (89%)</b>		<b>223/256 (87%)</b>	

**Table 9: Percent of Missing Values of Unformed Bowel Movements for Study days 8 to 11**

Study Day	8	9	10	11
% missing	10%	12%	14%	18%

### 3.2.5.4 Results for Global Cure

We first present the breakdown of identified inconsistencies by trial, treatment, and reason for inconsistency. We then describe sensitivity analyses conducted by the Agency to address these inconsistencies.

The first sensitivity analysis treats all inconsistencies as failures. In the two other sensitivity analyses, we break the inconsistencies into two groups. The first group is the set of global failures from the agency’s perspective and the second group is the set of cases with some doubt on whether global cure would have been achieved. The outcome of global cure for this second group of subjects is then considered “missing”. The method used to classify inconsistencies into these two groups differed between sensitivity analysis 2 and 3. However, the two last sensitivity analyses use the same set of covariates to impute the missing values in the second group.

### 3.2.5.4.1 Identified Possible Inconsistencies

Three reasons for inconsistencies with Applicant’s assessment of global cure were identified by the FDA review of the random sample of CRFs. The first reason is subject’s death prior to study day 31. This is an inconsistency with assessment of global cure because the subject would have missed the earliest protocol allowed day for assessing non-recurrence. The second reason is subject’s taking of concomitant medication treating CDAD either during the treatment phase or during the follow-up phase for recurrence. This is an inconsistency with assessment of global cure because the subject could have been prescribed this additional therapy due to treatment failure or suspected recurrence. The last reason is the recurrence assessment visit occurring before study day 31. This is an inconsistency with the assessment of global cure because subjects were followed for fewer days than the earliest protocol allowed day for assessing non-recurrence.

The breakdown of these inconsistencies by treatment group and trial is shown in Table 10. Note that the total number of inconsistencies is not the sum of each individual inconsistency since there is overlap in these categories. We see that the total number of inconsistencies with global cure is higher in the vancomycin group in both trials. This has an impact on our sensitivity analyses as we will see that our sensitivity analyses show a larger estimated treatment effect of fidaxomicin compared to vancomycin.

**Table 10: Potential Inconsistencies with Assessment of Global Cure**

Study	003		004	
	fidaxomicin (N= 215)	vancomycin (N = 197)	fidaxomicin (N = 194)	vancomycin (N = 162)
Total Inconsistencies with Applicant’s Assessment of Global Cure	18 (8%)	26 (13%)	18 (9%)	23 (14%)
Inconsistency due to death before study day 31	4	6	8	4
Inconsistency due to CDAD Concomitant Med during trt or follow up	12	18	12	13
Inconsistency due to recurrence visit before day 31	10	13	6	9

### 3.2.5.4.2 Sensitivity Analysis 1, Treating Inconsistencies as Failures

In this sensitivity analysis, we treat all inconsistencies as failures. Results are shown in Table 11. Because the inconsistencies occurred more often in the vancomycin arm, the estimate of treatment effect using this sensitivity analysis is larger than the one derived by applicant. Results of this sensitivity analysis demonstrate the superiority of fidaxomicin to vancomycin for Global Cure assessed at day 31.

**Table 11: Global Cure Rate- Sensitivity Analysis 1, Treating Inconsistencies as Failures**

Study	003			004		
	fidaxomicin (N= 289)	vancomycin (N = 307)	<b>Difference<sup>1</sup></b> <b>(95% CI)<sup>2</sup></b>	fidaxomicin (N = 253)	vancomycin (N = 256)	<b>Difference<sup>1</sup></b> <b>(95% CI)<sup>2</sup></b>
Global Cure (Applicant's results)	215/289 (74%)	197/307 (64%)	<b>10.2%</b> <b>(2.8, 17.5)</b>	194/253 (77%)	162/256 (63%)	<b>13.4%</b> <b>(5.4, 21.1)</b>
Inconsistencies Total	18/289 (6%)	26/307 (8%)		18/253 (7%)	23/256 (9%)	
Global Cure (FDA- Sensitivity 1)	197/289 (68%)	171/307 (56%)	<b>12.5%</b> <b>(4.7, 20)</b>	176/253 (70%)	139/256 (54%)	<b>15.3%</b> <b>(6.8, 23.4)</b>

1. Difference = Cure Rate fidaxomicin treatment arm – Cure Rate of vancomycin treatment arm
2. 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

### 3.2.5.4.3 Sensitivity Analyses Using Multiple Imputation

In Sensitivity Analysis 2 and 3, the set of inconsistencies identified in Table 10 is split into two subsets. In the first subset, the agency disagrees with the investigator assessment's of global cure. This group includes those taking concomitant medication treating CDAD together with evidence of diarrhea in the CRF (sensitivity analysis 2 and 3) and those who died during the study (sensitivity 2). In the second subset, the agency considers the outcome of global cure missing. The set of missing outcome in both sensitivity analysis 2 and sensitivity analysis 3 is different. The breakdown of what are considered global cure by the Applicant but failures by the FDA is shown in Table 12 for sensitivity analysis 2 and in Table 14 for sensitivity analysis 3.

The missing outcomes in each sensitivity analysis are imputed using the multiple imputation method. We used the chained equation algorithm (van Buuren and Oudshoorn 2000, Raghunathan et al 2001) implemented in library MI in R (see Su et al (2009) and Gelman et al (2008)) to conduct the imputation and generate 25 imputed datasets. The estimate of the treatment effect as well as the confidence interval is derived from these imputed datasets.

In the imputation step, missing global cure rate outcomes are imputed using a logistic model predicting the probability of global cure with covariates of baseline characteristics, follow-up information for diarrhea and timing variables such as length of treatment. More specifically, we included the following variables in the logistic model: treatment assignment, study, study center,

sex, race, age, weight, height, BMI, subject status (inpatient/outpatient), prior CDAD episodes, daily bowel movement at baseline or baseline disease severity, Diarrhea alone or other symptoms, prior use of CDAD antibiotics, metronidazole failure, number of study days in treatment phase, diarrhea at follow up visits after cure, serum albumin concentration (below 2.5 dl or not).

#### **3.2.5.4.4 Sensitivity Analysis 2**

In this sensitivity analysis (see Table 12), the global cure outcome of subjects who died before study day 31 or who had diarrhea during follow up period and received concomitant medication treating CDAD was changed to failure. All other inconsistencies identified in Table 10 were changed to missing. In addition, the outcome of global cure was changed to missing for all subjects who were cured at TOC and had a missing outcome for recurrence. Thus, this analysis corresponds to treating all non-cure at the end of treatment, suspected CDAD recurrence or death as failures, whether or not the toxin is positive at the recurrence assessment. This analysis also sets all outcomes with incomplete information related to suspected CDAD recurrence as missing.

Results of this sensitivity analysis are shown in Table 13. We see that these results demonstrate superiority of fidaxomicin to vancomycin for global cure. The treatment effect estimate is higher for study 003 and about the same as the one reported by the Applicant for study 004. The confidence intervals in this sensitivity analysis account for the uncertainty in the estimate due to missingness. The percent of variation due to missingness is small; it is in the range of 2.8%-4.1% in each study.

**Table 12: Missing Values and Disagreements in Sensitivity Analysis 2**

Treatment	fidaxomicin (N= 289)	vancomycin (N = 307)	fidaxomicin (N = 253)	vancomycin (N = 256)
<b>Disagreement: Applicant's Global Cure Success and FDA Global Cure Failure</b>				
Total Disagreements	8	12	12	10
Deaths before study day 31	4	6	8	4
Concomitant Med to treat CDAD and Diarrhea	4	6	4	6
<b>Missing Values: Applicant's Global Cure Success and FDA Global Cure Missing</b>				
Total <sup>1</sup>	10	14	6	13
<b>Missing Values: Applicant's Global Cure Failures and FDA Global Cure Missing<sup>2</sup></b>				
Clinical cure and missing recurrence <sup>3</sup>	3	1	3	7

1: The total includes those subjects with inconsistencies who are alive at study day 31 and either did not receive concomitant medication to treat CDAD or received concomitant medication to treat CDAD but did not have documented diarrhea.

2: These observations were cure but had missing information for recurrence and were assessed as global cure failure by applicant. Note that the only observation missing from clinical cure was a failure

3: These observations were set to recurrence by applicant because of the missingness of the recurrence assessment visit.

**Table 13: Global Cure Rate in Sensitivity Analysis 2**

Study	003		004	
<b>Global Cure Rate Sensitivity 2</b>	fidaxomicin 71%	vancomycin 57%	fidaxomicin 72%	vancomycin 59%
<b>Difference<sup>1</sup> 95% CI<sup>2</sup></b>	13.1% (5.0% , 21.2%)		13.3% (4.5%, 22.0%)	
<b>Percent Total Variability Due to Missingness<sup>3</sup></b>	2.8%		4.1%	

1. Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm

2. 95% CI accounts for within imputed samples variability W and between imputed samples variability B

3. Percent of total variability due to missingness is the ratio  $(1+1/25)*B/ V$ , where  $V = W + (1+1/25)*B$ , B is the between imputed samples variation and W is the within imputed samples variation.

### 3.2.5.4.5 Sensitivity Analysis 3

The difference between this sensitivity analysis and sensitivity analysis 2 is that global cure outcomes of subjects who died before study day 31 are set to missing and imputed in this analysis whereas they are set to failures in sensitivity analysis 2.

In this sensitivity analysis (see Table 14), the global cure outcome of subjects identified as global cure by the Applicant although they had diarrhea during follow up period and received concomitant medication treating CDAD was changed to failure. All other inconsistencies identified in Table 10 are set to missing. In addition, the outcome of global cure was set to missing for all subjects who were cured at test of cure and had a missing outcome for recurrence. This analysis corresponds to treating all non-cures and all suspected CDAD recurrences to failures, whether or not the toxin is positive at the recurrence assessment. This analysis also sets all outcomes with incomplete information related to suspected CDAD recurrence as missing, including those subjects who died before study day 31.

Results of this sensitivity analysis are shown in Table 15. We see that these results support the superiority of fidaxomicin to vancomycin for global cure. The treatment effect estimate is higher for study 003 and study 004 compared to the results reported by the Applicant. The confidence intervals in this sensitivity analysis account for the uncertainty in the estimate due to missingness. The percent of variation due to missingness is small; it is in the range of 3.8%-6.1% in each study.

**Table 14: Disagreement and Missing Values in Sensitivity Analysis 3**

Treatment	fidaxomicin (N= 289)	vancomycin (N = 307)	fidaxomicin (N = 253)	vancomycin (N = 256)
<b>Disagreement: Applicant's Global Cure Success and FDA Global Cure Failure</b>				
Concomitant Med to treat CDAD and Diarrhea	4	6	4	6
<b>Missing Values: Applicant's Global Cure Success and FDA Global Cure Missing</b>				
Total <sup>1</sup>	<b>14</b>	<b>20</b>	<b>14</b>	<b>17</b>
<b>Missing Values: Applicant's Global Cure Failures and FDA Global Cure Missing</b>				
Cure and missing recurrence (set to global cure failure by applicant)	<b>3</b>	<b>1</b>	<b>3</b>	<b>7</b>

1: The total include those subjects with inconsistencies who did not receive concomitant medication or received concomitant medication but did not have documented diarrhea

**Table 15: Global Cure Rates in Sensitivity Analysis 3**

Study	003		004	
<b>Global Cure Rate Sensitivity 3</b>	fidaxomicin 71%	vancomycin 58%	Fidaxomcin 73%	vancomycin 59%
<b>Difference<sup>1</sup> 95% CI<sup>2</sup></b>	13.1% (5.0%, 21.2%)		14.3% (5.5%, 23.0%)	
<b>Percent Total Variability Due to Missingness<sup>3</sup></b>	3.8%		6.1%	

1. Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm
2. 95% CI accounts for within imputed samples variability W and between imputed samples variability B
3. Percent of total variability due to missingness is the ratio  $(1+1/25)*B/ V$ , where  $V = W + (1+1/25)*B$ , B is the between imputed samples variation and W is the within imputed samples variation.

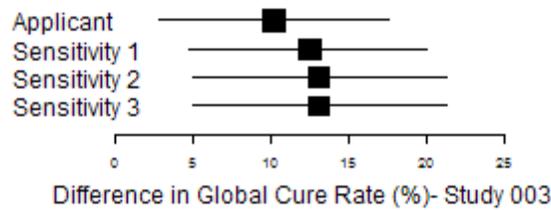
### 3.2.5.4.6 Summary of results for Global Cure

In summary (Table 16), the three sensitivity analyses show a lower global cure rate in both the fidaxomicin arm and the vancomycin arm and in both trials than in the Applicant’s analysis.

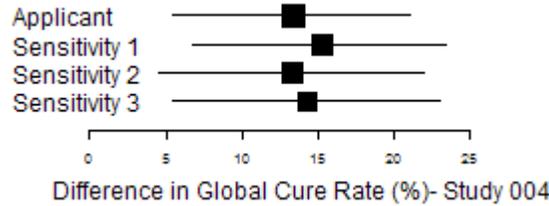
**Table 16: Summary of Global Cure Rates by Study and Treatment**

Study	Study 003		Study 004	
Treatment	fidaxomicin (N= 289)	vancomycin (N = 307)	fidaxomicin (N = 253)	vancomycin (N = 256)
Global Cure n (n/N)	215 (74%)	197 (64%)	194 (77%)	162 (63%)
Inconsistencies n (n/N)	18 (6%)	26 (8%)	18 (7%)	23 (9%)
Sensitivity 1	68%	56%	70%	54%
Sensitivity 2	71%	57%	72%	59%
Sensitivity 3	71%	58%	73%	59%

However, conclusion of the superiority of fidaxomicin to vancomycin is maintained in the three sensitivity analyses. The point estimate and confidence interval for the difference in global cure rate between the fidaxomicin arm and the vancomycin arm are shown in Figure 1 for Study 003 and Figure 2 for Study 004. We see that the difference in Global Cure rate between fidaxomicin and vancomycin is higher with the three sensitivity analyses than in the applicant’s results in study 003 and comparable to those of the applicant in study 004. Note that the confidence interval with sensitivity analyses 2 and 3 are wider than those of the applicant since they account for uncertainty due to missing values. All these confidence intervals are above 0 which supports the superiority of fidaxomicin to vancomycin.



**Figure 1: Applicant's and FDA three sensitivity Analysis Results for the Endpoint of Global Cure in Study 003**



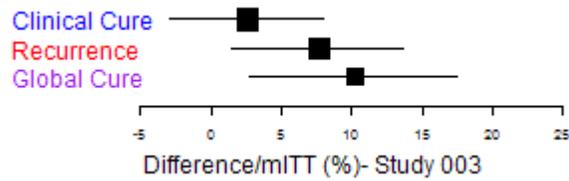
**Figure 2: Applicant's and FDA Sensitivity Analysis Results for the Endpoint of Global Cure in Study 004**

### 3.2.5.5 Results for Difference in Recurrence over all mITT Subjects

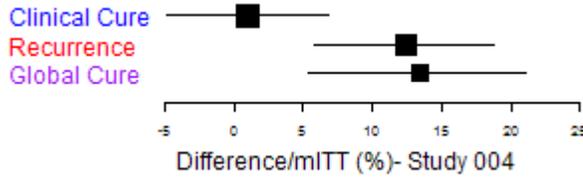
The results for the secondary endpoint of recurrence among those cured are not presented in this review because of the difficulty in interpreting this endpoint, as discussed in Subsection.3.2.2. However, we show here the results of the exploratory endpoint of recurrence among all mITT subjects.

Note that the difference in global cure rates between the two treatment arms quantifies an overall *benefit* of the drug through the end of follow up. This overall benefit can be decomposed into two components: benefit during the treatment period quantified by the difference in clinical cure rate at end of therapy, and benefit during the follow up period after the end of therapy quantified by the difference in recurrence rate among all mITT subjects.

Thus, as illustrated in Table 17, the difference in recurrence rate over all mITT subjects between two treatments can be derived from the difference in global cure rate and the difference in cure rate between the two treatments. More precisely, the difference in recurrence rate is simply the difference of global cure rate from which we subtract the difference in clinical cure rate. The results in Table 17 use the applicant's results for clinical cure and global cure to derive the recurrence rate over all mITT subjects. As we see in this table and the corresponding figures (Figure 3 and Figure 4), these results support the superiority of fidaxomicin to vancomycin for recurrence during the follow up period. They also show that most of the overall benefit captured by the global cure endpoint is due to benefit during the follow up period captured by recurrence over all mITT subjects.



**Figure 3: Results of Difference of Recurrence over all mITT subjects, study 003 (see text)**



**Figure 4: Results of Difference of Recurrence over all mITT subjects, study 004 (see text)**

**Table 17: Results for Difference in Recurrence over all mITT subjects by Treatment and Study**

Applicant's Results				
Study	003		004	
Treatment (mITT)	fidaxomicin (N= 289)	vancomycin (N = 307)	fidaxomicin (N = 253)	vancomycin (N = 256)
Difference in Clinical Cure Rates <sup>1</sup> 95% CI <sup>2</sup>	2.6% (-2.9%, 8.0%)		1.0% (-4.8%, 6.8%)	
Difference in Recurrence Rates (mITT) <sup>3</sup> 95% CI <sup>2</sup>	7.7% (1.5%, 13.7%)		12.4% (5.8%, 18.8%)	
Difference in Global Cure Rates (applicant) <sup>4</sup> 95% CI <sup>2</sup>	10.2% (2.8%, 17.5%)		13.4% (5.4%, 21.1%)	

1. Difference = Cure Rate fidaxomicin treatment arm – Cure Rate of vancomycin treatment arm
2. 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)
3. Recurrence Rates in this table is proportions of subjects cured at end of treatment and recurred at follow up among all mITT subjects. Difference = recurrence rate in vancomycin arm - recurrence rate in fidaxomicin arm.
4. Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm

### 3.3 Evaluation of Safety

We refer to the Clinical Review for evaluation of safety.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The treatment effect for cure and global cure was consistent in most subgroups including different age groups and CDAD history subgroups. The only possible exception is for virulent (BI) versus non-virulent (non BI) initial strains of *C. difficile*. Results for this subgroup are shown in Table 24 for cure and Table 25 for global cure.

### 4.1 Sex, Race, Age, and Geographic Region

As we see in the last column of Table 18 and the last column of Table 19, the treatment effect of fidaxomicin relative to vancomycin is similar for the endpoint of clinical cure rate at the end of treatment in subgroups of sex, race, age and geographic region.

As we see in the last column of Table 20 and the last column of Table 21, the treatment effect of fidaxomicin relative to vancomycin is similar for the endpoint of global cure rate (applicant's results) in subgroups of sex, race, age and geographic region.

Clinical cure rates at the end of treatment and global cure rates at the end of follow up (1) decrease with increasing age in both treatment groups and in both studies; (2) are slightly higher in Canada than in the USA in both treatment arms and both studies with European rates falling in between Canada and the USA in study 004; (3) do not differ between male and females in both treatments and both studies. The large majority of subjects in both studies were white, the other racial subgroups are too small in these studies to make an inference for these racial groups.

**Table 18: Clinical Cure Rate by Treatment and Study in the Subgroups of Sex, Race and Region (mITT)**

Study	Factor	Subgroups	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference <sup>1</sup> (95% CI) <sup>2</sup>
Study 003	Overall		255 / 289 ( 88%)	263 / 307 ( 86%)	3% ( -2.9% , 8.0%)
	sex	Female	148 / 164 ( 90%)	144 / 169 ( 85%)	5% ( -2.1% , 12.2%)
		Male	107 / 125 ( 86%)	119 / 138 ( 86%)	-1% ( -9.3% , 7.8%)
	race	White	223 / 254 ( 88%)	229 / 265 ( 86%)	1% ( -4.5% , 7.2%)
		Black	27 / 30 ( 90%)	27 / 33 ( 82%)	8% ( -10.1% , 25.7%)
		Other	5 / 5 ( 100%)	7 / 9 ( 78%)	22% ( -24.0% , 54.7%)
	region	Canada	113 / 124 ( 91%)	112 / 121 ( 93%)	-1% ( -8.6% , 5.8%)
		USA	142 / 165 ( 86%)	151 / 186 ( 81%)	5% ( -3.0% , 12.5%)
Study 004	Overall		222 / 253 ( 88%)	222 / 256 ( 87%)	1% ( -4.8% , 6.9%)
	sex	Female	130 / 149 ( 87%)	142 / 161 ( 88%)	-1% ( -8.5% , 6.4%)
		Male	92 / 104 ( 88%)	80 / 95 ( 84%)	4% ( -5.4% , 14.1%)
	race	White	203 / 233 ( 87%)	204 / 237 ( 86%)	1% ( -5.2% , 7.3%)
		Black	16 / 17 ( 94%)	16 / 17 ( 94%)	0% ( -21.6% , 21.6%)
		Other	3 / 3 ( 100%)	2 / 2 ( 100%)	0% ( -56.1% , 65.8%)
	region	Canada	70 / 79 ( 89%)	75 / 82 ( 91%)	-3% ( -12.7% , 6.8%)
		Europe	89 / 100 ( 89%)	82 / 98 ( 84%)	5% ( -4.4% , 15.1%)
USA		63 / 74 ( 85%)	65 / 76 ( 86%)	0% ( -12.0% , 11.1%)	

(1) Difference = Cure Rate fidaxomicin treatment arm – Cure Rate of vancomycin treatment arm

(2) 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

**Table 19: Clinical Cure Rates by Treatment and Study for Age Subgroups (mITT)**

Study	Factor	Subgroups	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference <sup>1</sup> (95% CI) <sup>2</sup>
Study 003		Overall	255 / 289 ( 88%)	263 / 307 ( 86%)	3% ( -2.9% , 8.0%)
	Age Groups*	[18 yrs to 50 yrs]	71 / 76 ( 93%)	56 / 65( 86%)	7% ( -2.9% , 18.3%)
		[50 yrs to 64 yrs]	74 / 81 ( 91%)	70 / 83 ( 84%)	7% ( -3.2% , 17.3%)
		[64 yrs to 77 yrs]	63 / 73 ( 86%)	73 / 82 ( 89%)	-2.7% ( -13.7% , 7.8%)
		[77 yrs to 94 yrs]	47 / 59 ( 80%)	64 / 77 ( 83%)	-3.4% ( -17.1% , 9.4%)
Study 004		Overall	222 / 253 ( 88%)	222 / 256 ( 87%)	1% ( -4.8% , 6.9%)
	Age Groups*	[18 yrs to 50 yrs]	48 / 52 ( 92%)	59 / 62 ( 95%)	-3% ( -13.8% , 6.8%)
		[50 yrs to 64 yrs]	47 / 53 ( 89%)	52 / 60( 87%)	2% ( -10.9% , 14.4%)
		[64 yrs to 77 yrs]	61 / 71 ( 86%)	51 / 63 ( 81%)	5% ( -7.7% , 17.9%)
		[77 yrs to 94 yrs]	66 / 77 ( 86%)	60 / 71 ( 84%)	1% ( -10.4% , 13.1%)

\* Age groups were determined based on the quartiles of the study population

(1) Difference = Cure Rate fidaxomicin treatment arm – Cure Rate of vancomycin treatment arm

(2) 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

**Table 20: Global Cure Rate by Treatment and Study in the Subgroups of Sex, Race and Region (mITT)**

Study	Factor	Subgroups	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference <sup>1</sup> (95% CI) <sup>2</sup>
Study 003	Overall		215/289 (74%)	197/307 (64%)	10% (2.8%, 17.5%)
	sex	Female	125/164 (76%)	109/169 (64%)	12% (1.9%, 21.2%)
		Male	90/125 (72%)	88/138 (64%)	8% (-3.1%, 19.2%)
	race	White	189/254 (74%)	166/265 (63%)	12% (3.8%, 19.5%)
		Black	22/30 (73%)	24/33 (73%)	1% (-21.0%, 21.7%)
		Other	4/5 (80%)	7/9 (78%)	2% (-43.1%, 38.6%)
	region	Canada	99/124 (80%)	83/121 (69%)	11% (0.3%, 21.9%)
		USA	116/165 (70%)	114/186(61%)	9% (-0.9%, 18.6%)
Study 004	Overall		194/253 (77%)	162/256 (63%)	13% (5.4%, 21.1%)
	sex	Female	115/149 (77%)	106/161 (66%)	11% (1.3%, 21.0%)
		Male	79/104 (76%)	56/95 (59%)	17% (4.0%, 29.4%)
	race	White	177/233 (76%)	148/237 (62%)	14% (5.2%, 21.6%)
		Black	14/17 (82%)	12/17 (71%)	12% (-16.6%, 38.1%)
		Other	3/3 (100%)	2/2 (100%)	0% (-56.1%, 65.8%)
	region	Canada	58/79 (73%)	51/82 (62%)	11% (-3.2%, 25.0%)
		Europe	81/100 (81%)	63/98 (64%)	17% (4.3%, 28.5%)
USA		55/74 (74%)	48/76 (63%)	11% (-3.7%, 25.3%)	

(1) Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm

(2) 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

**Table 21: Global Cure Rates by Treatment and Study for Age Subgroups (mITT)**

Study	Factor	Subgroups	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference <sup>1</sup> (95% CI) <sup>2</sup>
Study 003		Overall	215/289 (74%)	197/307 (64%)	10% (2.8%, 17.5%)
	Age Groups*	[18 yrs to 50 yrs]	60/ 76 ( 79%)	47 / 65( 72%)	7% ( -7.4% , 20.8%)
		[50 yrs to 64 yrs]	67 / 81 ( 83%)	53 / 83 ( 64%)	19% ( 5.3% , 31.5%)
		[64 yrs to 77 yrs]	52 / 73 ( 71%)	54 / 82 ( 66%)	5% ( -9.2% , 19.5%)
		[77 yrs to 94 yrs]	36/ 59 ( 61%)	43 / 77 ( 56%)	5% ( -11.4% , 21.1%)
Study 004		Overall	194/253 (77%)	162/256 (63%)	13% (5.4%, 21.1%)
	Age Groups*	[18 yrs to 50 yrs]	44 / 52 ( 85%)	44 / 62 ( 71%)	14% ( -1.9% , 27.9%)
		[50 yrs to 64 yrs]	40 / 53 ( 75%)	38 / 60 ( 63%)	12% ( -4.9% , 28.0%)
		[64 yrs to 77 yrs]	54 / 71 ( 76%)	36 / 63 ( 57%)	19% ( 3.0% , 33.8%)
		[77 yrs to 94 yrs]	56 / 77 ( 73%)	44 / 71 ( 62%)	11% ( -4.3% , 25.3%)

\* Age groups were determined based on the quartiles of the study population

(1) Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm

(2) 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

## 4.2 Other Special Subgroup Populations

### 4.2.1 Inpatient/Outpatient, Disease Severity at Baseline and CDAD history

As we see in the last column of Table 22, the treatment effect of fidaxomicin relative to vancomycin is similar for the endpoint of clinical cure rate at the end of treatment in subgroups of patient status (inpatient/outpatient), CDAD history and, CDAD baseline severity.

As we see in the last column of Table 23, the treatment effect of fidaxomicin relative to vancomycin is similar for the endpoint of global cure rate (applicant's results) in subgroups of patient status (inpatient/outpatient), CDAD history and, CDAD baseline severity.

Clinical cure rates at the end of treatment and global cure rates at the end of follow up are higher for outpatients than for inpatients in both studies and both treatments. Global cure rates at the end of follow up are higher for patients with no CDAD history in both studies and both

treatments and are higher for non-severe CDAD at baseline compared to severe CDAD at baseline.

**Table 22: Clinical Cure Rates by Study and Treatment for Special Subgroups (mITT)**

Study	Factor	Subgroups	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference <sup>1</sup> (95% CI) <sup>2</sup>
Study 003	Overall		137 / 168 ( 82%)	145 / 186 ( 78%)	4% ( -4.9% , 11.9%)
	Patient Status	Inpatient	118 / 121 ( 98%)	118 / 121 ( 98%)	0% ( -4.8% , 4.8%)
		Outpatient	213 / 241 ( 88%)	215 / 253 ( 85%)	3% ( -2.7% , 9.4%)
	CDAD history	No Prior Episodes	42 / 48 ( 88%)	48 / 54 ( 89%)	-1% ( -14.9% , 11.5%)
		Single Prior Episode in the past 3 months	162 / 176 ( 92%)	155 / 185 ( 84%)	8% ( 1.5% , 15.0%)
	CDAD at baseline	Non severe	93 / 113 ( 82%)	108 / 122 ( 89%)	-6% ( -15.5% , 2.9%)
		Severe	255 / 289 ( 88%)	263 / 307 ( 86%)	3% ( -2.9% , 8.0%)
Study 004	Overall		155 / 175 ( 86%)	142 / 172 ( 83%)	4% ( -4.0% , 11.4%)
	Patient Status	Inpatient	71 / 78 ( 91%)	80 / 84 ( 95%)	-4% ( -13.1% , 4.0%)
		Outpatient	185 / 213 ( 87%)	190 / 220 ( 86%)	0% ( -6.0% , 7.0%)
	CDAD history	No Prior Episodes	37 / 40 ( 93%)	32 / 36 ( 89%)	4% ( -10.5% , 18.6%)
		Single Prior Episode in the past 3 months	148 / 164 ( 90%)	149 / 167 ( 89%)	1% ( -5.7% , 7.7%)
	CDAD at baseline	Non severe	74 / 89 ( 83%)	73 / 89 ( 82%)	1% ( -10.1% , 12.4%)
		Severe	222 / 253 ( 88%)	222 / 256 ( 87%)	1% ( -4.8% , 6.9%)

(1) Difference = Cure Rate fidaxomicin treatment arm – Cure Rate of vancomycin treatment arm

(2) 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

**Table 23: Global Cure Rates by Study and Treatment for Special Subgroups (mITT)**

Study	Factor	Subgroups	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference <sup>1</sup> (95% CI) <sup>2</sup>
Study 003		Overall	215 / 289 ( 74%)	197 / 307 ( 64%)	10% ( 2.8% , 17.5%)
	Patient Status	Inpatient	112 / 168 ( 67%)	106 / 186 ( 57%)	10% ( -0.5% , 19.5%)
		Outpatient	103 / 121 ( 85%)	91 / 121 ( 75%)	10% ( -0.2% , 19.8%)
	CDAD history	No Prior Episodes	182 / 241 ( 76%)	164 / 253 ( 65%)	11% ( 2.6% , 18.6%)
		Single Prior Episode in the past 3 months	33 / 48 ( 69%)	33 / 54 ( 61%)	8% ( -10.8% , 25.1%)
	CDAD at baseline	Non severe	134 / 176 ( 76%)	118 / 185 ( 64%)	12% ( 2.9% , 21.5%)
		Severe	81 / 113 ( 72%)	79 / 122 ( 65%)	7% ( -5.0% , 18.5%)
Study 004		Overall	194 / 253 ( 77%)	162 / 256 ( 63%)	13% ( 5.4% , 21.1%)
	Patient Status	Inpatient	132 / 175 ( 75%)	106 / 172 ( 62%)	14% ( 4.0% , 23.2%)
		Outpatient	62 / 78 ( 79%)	56 / 84 ( 67%)	13% ( -0.9% , 25.8%)
	CDAD history	No Prior Episodes	164 / 213 ( 77%)	141 / 220 ( 64%)	13% ( 4.3% , 21.2%)
		Single Prior Episode in the past 3 months	30 / 40 ( 75%)	21 / 36 ( 58%)	17% ( -4.4% , 36.1%)
	CDAD at baseline	Non severe	132 / 164 ( 80%)	110 / 167 ( 66%)	15% ( 5.1% , 23.8%)
		Severe	62 / 89 ( 70%)	52 / 89 ( 58%)	11% ( -2.8% , 24.7%)

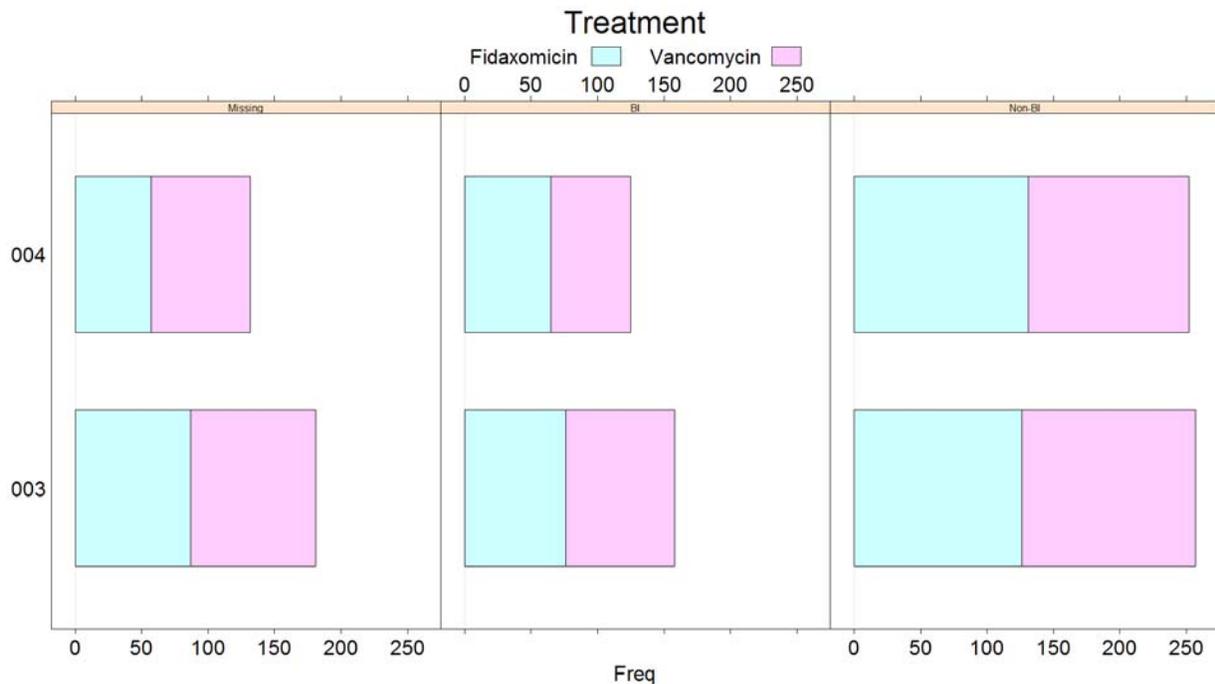
(1) Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm

(2) 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

#### 4.2.2 Virulent and non-virulent strains of *C. difficile*

The applicant tested all baseline *C. difficile* isolates by restriction endonuclease analysis to determine whether they were part of the BI group. This is one of the testing methods used to identify the epidemic strain of *C. difficile* (027/NAP1/BI) that has been increasing in the US and Canada, and is associated with more severe infection. About a quarter of the mITT strains were

virulent, about a half of the mITT strains were non-virulent and about a quarter of the mITT strains had missing assessment on virulence (counts in each study and treatment arm are shown in Figure 5)



**Figure 5: Frequency of Missing, Virulent and Non-virulent strains by Study and by Treatment Arm**

As we see in the second and third column of Table 24 and Table 25, clinical cure rates at the end of treatment and global cure rates at the end of follow up are higher for non-virulent strain than for virulent strains in both studies and both treatments. Although the fidaxomicin cure rates for the missing subgroup are similar to those in the overall population, the vancomycin cure rates are higher in this subgroup than in the overall population in both studies, and especially in study 004.

As we see in the last column of Table 24 and in Figure 6, the treatment effect of fidaxomicin relative to vancomycin in each study is similar for the endpoint of clinical cure rate at the end of treatment in subgroups of virulence (virulent/non-virulent/missing).

As we see in the last column of Table 25 and in Figure 7, the treatment effect of fidaxomicin relative to vancomycin vary by subgroups of virulence (virulent/non-virulent/missing) for the endpoint of global cure rate at the end of treatment. More precisely, there is a concern that there is a reduction of treatment effect of fidaxomicin relative to vancomycin in the virulent subgroup compared to the non-virulent subgroup as seen in study 003.

To explore the treatment effect in the different virulent strains, we fit a logistic model of global cure rate by treatment and virulence subgroup. The main effect of virulence was significant in both studies (pvalue: 0.0001 in study 003 and p-value of 0.004 in study 004). The interaction effect between treatment and virulence was significant in study 003 (p-value of 0.009) and not significant in study 004 (pvalue=0.29). The main effect of virulence and the interaction between

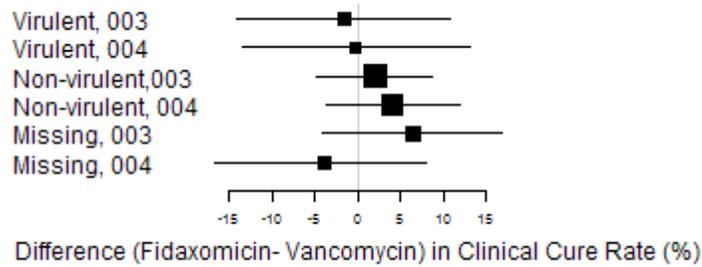
virulence and treatment remain significant in study 003 after accounting for factors of age, patient status (inpatient/outpatient), stratum (no prior CDAD/one prior CDAD in the past three months) and baseline CDAD severity with p-values of 0.005 for the main effect and 0.004 for the interaction effect.

It may not be appropriate to pool the data from the two studies for this subgroup analysis. Strains' virulence varies geographically, and study 004 includes European sites (1/3 of subjects in the mITT population) in addition to sites in the USA and Canada whereas study 003 has sites only in USA and Canada. Note also that there is a large amount of missing information on virulence in each study (1/4 of the data), and the mixture of virulent and non-virulent strains in this subgroup may be different in study 003 than study 004 because of the differences in sites between the two studies. The efficacy results on the missing subgroup further suggest that the missing subgroup in study 003 is different from the missing subgroup in study 004.

**Table 24: Cure Rates for Different Initial Strains of C. difficile**

<b>Study 003</b>			
	<b>fidaxomicin</b>	<b>vancomycin</b>	<b>Difference<sup>1</sup> (95% CI)<sup>2</sup></b>
Missing	77/87 (88%)	77/94 (82%)	6.6% (-4.0%, 16.9%)
Virulent (BI)	60/76 (79%)	66/82 (80%)	-1.5% (-14.2%, 10.9%)
Non-virulent (non BI)	118/126 (94%)	120/131 (92%)	2.0% (-4.7%, 8.8%)
<b>Study 004</b>			
	<b>fidaxomicin</b>	<b>vancomycin</b>	<b>Difference<sup>1</sup> (95% CI)<sup>2</sup></b>
Missing	48/57 (84%)	66/75 (88%)	-3.8% (-16.6%, 8.0%)
Virulent (BI)	54/65 (83%)	50/60 (83%)	-0.2% (-13.4%, 13.2%)
Non-virulent (non BI)	120/131 (92%)	106/121 (88%)	4.0% (-3.6%, 11.9%)

1. Difference = Cure Rate fidaxomicin treatment arm – Cure Rate of vancomycin treatment arm
2. 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

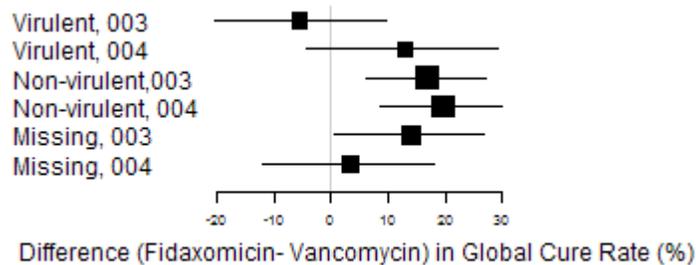


**Figure 6: Forest plot for Difference in Clinical Cure Rate Between fidaxomicin and vancomycin in Different Strain Virulence Subgroups**

**Table 25: Global Cure Rates for Different Initial Strains of CDI**

Study 003			
Initial Strain of CDI	fidaxomicin	vancomycin	Difference <sup>1</sup> (95% CI) <sup>2</sup>
Missing	66/87 (76%)	58/94 (61%)	14.1% (0.6%, 26.9%)
Virulent (BI)	44/76 (58%)	52/82 (63%)	-5.5% (-20.3%, 9.5%)
Non-virulent (non BI)	105/126 (83%)	87/131 (66%)	16.9% (6.3%, 27.0%)
Study 004			
Initial Strain of CDI	fidaxomicin	vancomycin	Difference <sup>1</sup> (95% CI) <sup>2</sup>
Missing	43/57 (75%)	54/75 (72%)	3.4% (-11.9%, 17.9%)
Virulent (BI)	42/65 (65%)	31/60 (52%)	12.9% (-4.2%, 29.2%)
Non-virulent (non BI)	109/131 (83%)	77/121 (64%)	19.6% (8.7%, 30.0%)

1. Difference = Cure Rate fidaxomicin treatment arm – Cure Rate of vancomycin treatment arm
2. 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)



**Figure 7: Forest plot for Difference in Global Cure Rate Between fidaxomicin and vancomycin in Different Strain Virulence Subgroups**

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

#### 5.1.1 Main Results

The collective evidence is that (1) fidaxomicin is non-inferior to vancomycin for the endpoint of clinical cure at the end of treatment (2) fidaxomicin is superior to vancomycin for the endpoint of global or sustained cure at the end of follow up (study day 31), and (3) the treatment effect at the end of treatment and end of follow up is consistent in most subgroups with the possible exception of the virulent strain subgroup showing no significant benefit of fidaxomicin compared to vancomycin at the end of follow up.

The 95% confidence interval for the difference in clinical cure rates at the end of treatment between fidaxomicin and vancomycin is (-2.9%, 8.0%) in trial 003 and (-4.8%, 6.8%) in trial 004. The lower bound is above -10%, the non-inferiority margin for the active control comparator of vancomycin.

The 95% confidence interval for the difference in global cure rates at the end of follow up (study day 31) between fidaxomicin and vancomycin is (5.0%, 21.2%) for study 003 and (4.5%, 22.0%) for study 004 using the preferred sensitivity analysis (sensitivity analysis 2). In this sensitivity analysis, a clinical failure in global cure is either a failure at the end of treatment, suspected recurrence at follow up (diarrhea and CDAD concomitant medication), or death. In addition in this sensitivity analysis, missing recurrence assessments prior to study day 31 are imputed using multiple imputations (25 imputations using a logistic model with all baseline covariates, follow up for diarrhea and length of treatment as covariates).

There are concerns for global cure that the treatment effect of fidaxomicin relative to vancomycin is significantly decreased for subjects with the *C. Difficile* virulent strain in comparison to those with the non-virulent strain. At least a quarter of all *C. Difficile* strains are virulent in each study, at least half of all *C. Difficile* strains are non-virulent, and about a quarter of all mITT subjects had missing information on their *C. Difficile* strain's virulence. In a logistic regression of global cure on treatment and virulence, the interaction between treatment effect and virulence is significant in study 003 (p-value=0.009). However, this effect modification was not replicated in study 004 (p-value=0.29). In the non-virulent subgroup, the estimate and 95% confidence interval of the difference between fidaxomicin and vancomycin for the endpoint of global cure are 16.9% (6.3%, 27.0%) in study 003 and 19.6% (8.7%, 30.0%) in study 004. In contrast, for the virulent subgroup, the estimate and 95% confidence interval of the difference between fidaxomicin and vancomycin for the endpoint of global cure are -5.5% (-20.3%, 9.5%) in study 003 and 12.9% (-4.2%, 29.2%) in study 004.

## 5.1.2 Some statistical issues

### 5.1.2.1 Secondary endpoint of Recurrence among Cured

Recurrence among those cured is a key secondary endpoint used to support the indication of reducing recurrence sought by the applicant. This endpoint quantifies the risk of recurrence of a subject during the follow up period given that this subject has been cured in that treatment arm at the end of treatment.

It is hard to interpret the difference in recurrence among those cured between two treatment arms as those cured in one treatment arm may be different than those who are cured in the other treatment arm. Thus, the difference in recurrence among those cured may be comparing the risk of recurrence at follow up among very different subsets of the mITT population. For example, those cured in the vancomycin arm in study 003 were significantly<sup>4</sup> older (mean age is 63 years old and median age is 64 years) than those cured in the fidaxomicin arm in study 003 (mean age 59 years and median age is 60 years). Interpreting the difference in risk of recurrence of younger subjects in fidaxomicin arm to older subjects in vancomycin arm is problematic.

Instead of using this endpoint to quantify recurrence, the review focused on the other secondary endpoint: global cure defined in the next subsection. The review also explored the endpoint of recurrence rate among all mITT subjects.

### 5.1.2.2 Inconsistencies with the Assessment of Global Cure

Global or sustained cure is another key secondary endpoint used to support the indication of reducing the recurrence sought by the applicant. This endpoint is a composite of clinical cure at the end of treatment together with non-recurrence during the follow up period after the test of cure.

The review found some inconsistencies with the investigator's assessment of global cure. The reasons for these inconsistencies are at least one of the following (1) death before the end of follow up period (2) receipt of concomitant medication treating CDAD during treatment or follow up, or (3) early recurrence assessment visit.

To correct for these inconsistencies, the review presents the results of three sensitivity analyses. The first sensitivity analysis treats all inconsistencies as failures. The two other sensitivity analyses treat some inconsistencies as failures and some inconsistencies as missing values and use multiple imputation methods to impute the missing values. The sensitivity analyses results showed lower global cure rates in both treatment groups and both trials. However, all sensitivity analyses showed superiority of fidaxomicin to vancomycin for the endpoint of global cure.

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<sup>4</sup> P-value for testing for difference in age between the two treatment arm is 0.02 using t-test.

### **5.1.2.3 Language in the CRF**

The two efficacy assessments: clinical cure at the end of treatment and recurrence during follow up period are clinician reported outcome or assessed by clinical investigators. Each definition is a composite of signs and symptoms.

The definition of cure in the CRF is long and confusing. The definition of recurrence and more specifically re-establishment of diarrhea during the follow up period is not precise. For all composite endpoints, ICH-E9 recommends assessing each item in the composite separately. Thus, a preferred method is to assess each sign and symptom separately before assessing the composite. We also prefer to have precise definition of each sign and symptom.

It is impossible to quantify the possible effect of the poor CRF language on the endpoint of clinical cure in these trials. However, we note that the modified definition of cure at the end of treatment, a symptom based definition of resolution of diarrhea, showed lower cure rates at the end of treatments in both arms and both studies than the investigator's assessment of cure at the end of treatment. Although the modified definition of cure rates are lower than the investigator assessed cure rates, both endpoints show non-inferiority of fidaxomicin to vancomycin.

Similarly, it is impossible to quantify the possible effect of the poor CRF language for recurrence on the endpoint of global cure. However, the sensitivity analyses on this endpoint try to use information on concomitant CDAD therapy to assess recurrence. The sensitivity analyses results showed lower global cure rates in both treatment groups and both trials. However, all sensitivity analyses showed superiority of fidaxomicin to vancomycin for the endpoint of global cure.

### **5.1.2.4 Data collection of number of unformed bowel movement**

The number of unformed bowel movement is a patient reported outcome collected every day during the 10 day treatment period. Who collected the data and how it was collected varied from site to site and was at the discretion of each clinical site. Thus, there are some concerns of variability in this dataset representing heterogeneity in method of data collection.

## **5.2 Conclusions and Recommendations**

Based on the efficacy results of this drug, we recommend approval of fidaxomicin 200 mg twice daily for 10 days for the treatment of CDAD. The clinical studies section of the label can include:

- (1) Results of clinical cure rate at end of treatment (applicant's results)
- (2) Results of global cure rate at study day 31 (FDA sensitivity analysis 2)
- (3) Results for the virulent subgroup compared to the non-virulent subgroup

As for the statistical issues for the endpoint of recurrence among cured, language in the CRF and data collection of unformed bowel movements:

- (1) We do not recommend using the endpoint of recurrence among those cured to assess treatment efficacy
- (2) We recommend that each component of the composite endpoint of cure and recurrence be collected and that the language defining clinical cure and recurrence be simplified in the future
- (3) We recommend that the patient reported outcome of number of unformed bowel movement be collected in a uniform way across centers

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## 6 Appendix A: Justification for a Noninferiority Margin for the Active Comparator vancomycin in Treatment of CDAD

The pre-planned noninferiority margin of 10% proposed by the Applicant for the active comparator of vancomycin<sup>5</sup> is justifiable. This section describes the FDA's rationale for accepting this margin. Both our and the Applicant's rationales use the results of vancomycin versus tolevamer<sup>6</sup> trial as the basis for deriving the treatment effect of vancomycin. The applicant's rationale uses only the published results from the review by Weiss 2009. Our comparison of the trials in this document is more extensive and it relies on publications by Louie et al 2006, Louie et al 2007, Bouza et al 2008, Weiss 2009 and summary of the trials in clinicaltrials.gov. In addition to the derivation of the treatment effect, our comparison includes a discussion of similarities and differences between the historical trials and current trials as well as a discussion of evidence from vancomycin placebo trials.

First, we describe the available historical evidence to estimate the treatment effect of vancomycin against placebo and the reasons for choosing the two trials of vancomycin compared to tolevamer to derive the margin. Then, the plausibility of the constancy assumption is discussed by comparing the historical trials to the current trials with respect to the patient characteristics, endpoints and main inclusion criteria. Finally, we discuss the process of derivation of the non-inferiority margin.

### 6.1 Historical Evidence of Sensitivity to vancomycin in Treatment of CDAD

Placebo-controlled studies provide the most direct estimate of an active comparator's drug treatment effect. However, there is limited information on effect of vancomycin compared to placebo for treatment of CDAD. The Cochrane review (Nelson 2007) identified only two randomized studies comparing vancomycin to placebo for treatment of *C. difficile* infection: Keighley 1978 and Johnson 1992. Johnson's 1992 study is not appropriate for our NI derivation because while the patient population in that trial was stool positive for *C. difficile*, they did not have diarrhea and diarrhea is an important symptom of CDAD. Keighley's 1978 study was originally used to derive the noninferiority margin because it was the more relevant vancomycin-placebo trial available when current trial 003 was planned. A discussion of characteristics and results of this study are shown in the next two sections.

More recently, results of two large randomized, double blind, and controlled studies demonstrating the superiority of vancomycin to tolevamer have been published (Louie et al 2007, Bouza et al 2008 and Weiss 2009). We use the results of these two later trials, referred to 301 and 302 for the purposes of this appendix, to estimate vancomycin's treatment effect while considering tolevamer as putative placebo. It is assumed that the efficacy of tolevamer is no worse than placebo. However, as the poster by Louie et al. (2007) indicates for trial 301, tolevamer's efficacy may not be much better than placebo since 48% of subjects in the tolevamer arm did not complete treatment and the main reason for dropping out of the study was non-

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<sup>5</sup> That is oral vancomycin 125mg, 4 times a day, for 10 days.

<sup>6</sup> That is tolevamer 3g, three times a day, for 14 days

response to treatment (28% of subjects in tolevamer arm). Details of the design of trials 301 and 302 and how they compare to the current trials is provided in the next section.

## 6.2 Comparison of Historical Trials to Current Trial

Comparison of historical studies to current trials is important to establish the validity of the constancy assumption. That is, there is reliable data that vancomycin's effect would not differ between studies conducted today and the historical studies.

There is little support for the constancy assumption between the Keighley 1978 trial and the current CDAD trials. First, susceptible populations to CDAD and *C. difficile* strains have changed over time (see Aslam et al 2005), so results from Keighley 1978, a > 30 year old study, may not apply to the current CDAD population. Moreover, Keighley's 1978 design varied substantially from current CDAD trials with the most important difference being the duration of treatment of vancomycin (4 times a day for 5 days compared to 4 times a day for 10 days in current trials.) Additionally, there are several major quality concerns with this study including inadequate follow-up, and mislaid or missing specimens. When the poor quality of the trial and the small size are taken into consideration, the study results should be used with caution.

The constancy assumption between trials 301, 302 and current trials is plausible as trials 301 and 302 have similar design characteristics, inclusion criteria, and clinical trial populations compared to the two current studies under review. We describe in the remainder of this section the similarities and differences between trials 301, 302 and current trials 003 and 004. Design characteristics are summarized in Table 26, clinical trial subjects' characteristics are summarized in Table 27, and main inclusion criteria are shown in at the end of the Appendix.

Similarities in the design characteristics include the following (see Table 26): first, all studies are randomized, double blind, parallel arm with an active control comparator of vancomycin 125 mg every 6 hours for 10 days; second, studies 301 and 302 are contemporaneous to the current trials 003 and 004 with similar geographic distributions of multinational sites. Thus, the strains of *C. difficile* and susceptible populations are likely to be similar. Most of the sites in the historical studies and the current studies are in the United States and Canada, with some sites in Europe. Finally, the key inclusion criteria and definition of CDAD are similar although not identical.

One subtle difference in study design between trials 301, 302 and current trials 003 and 004 is the difference in definition of clinical cure and its assessment. In study 301 (Louie et al 2007), clinical cure was defined as resolution and the absence of severe abdominal discomfort due to CDAD for two contiguous days including Day 10. Resolution was not defined in detail for the Phase 3 trial in Louie et al 2007, however it is defined in detail for the Phase 2 trial in Louie et al 2006. In Louie et al 2006, resolution is defined as 2 consecutive days on which the patient had any number of stools with an average consistency classified as hard or formed, or  $\leq 2$  stools with an average consistency of loose or watery. In addition, stool counts and average consistency were patient reported outcomes recorded daily (on days 1–14) by the clinical trial's nurse and/or investigator team after direct assessment and interview of hospitalized patients, and by daily telephone interview of outpatients on nonclinic days. In the current trial, clinical cure is a clinician reported outcome relying on whether continuation of CDAD therapy is indicated based

on resolution of diarrhea. More precisely, under the cure checkbox, clinicians could see the following definition for cure:

- Subjects who, in the opinion of the Investigator, require no further CDAD therapy 2 days after completion of study medication will be considered cured.
- Subjects who have 3 or fewer unformed stools for 2 consecutive days and remain well prior to the time of study medication discontinuation will be considered cured. Alternatively, subjects who at the end of treatment have had a marked reduction in the number of unformed stools but who have residual and mild abdominal discomfort interpreted as recovering bowel by the Investigator may be considered cured at that time, providing no new anti-infective CDAD therapy is required.
- Subjects who are considered cured based on stabilization and improvement in CDAD signs and symptoms will be evaluated 2-3 days after study medication. In the event that their signs or symptoms of CDAD worsen, they will be designated primary failures. If they remain stable and are not considered to require further CDAD therapy to maintain their stable state, they will be followed for recurrence as cures.
- Subjects having a rectal collection device who are passing liquid stools periodically during the day will be considered to have resolution of diarrhea when the volume (over a 24-hour period) is decreased by 75% compared to admission or the subject is no longer passing liquid stools.
- Subjects who enter the study without signs or symptoms of CDAD, other than diarrhea will be evaluated as failures on the basis of continued diarrhea alone as defined in the protocol.

A review of the baseline characteristics of population in studies 301, 302 compared to the population in current trials 003 and 004 (see Table 27) shows a largely similar clinical trial population in terms of age, baseline severity of the disease determined by number of stools, white blood count, and CDAD history (first episode or a re-infection).

**Table 26: Main Design Characteristics of two historical trials and the two current trials**

<b>Trials</b>	<b>Tolvamer Studies</b>	<b>Current Studies</b>
General	Randomized, double blind, parallel arms	
Multinational sites	Study 301: 91 sites in US and Canada (Louie et al 2007 and clinicaltrial.gov)	Study 003: 75 sites in United States, 23 sites in Canada
	Study 302: sites in Australia, Canada, and Europe. Total of 135 sites listed in clinicaltrial.gov.	Study 004: 30 sites enrolled subjects in the US, 11 sites enrolled subjects in Canada, and 45 sites enrolled subjects in Europe.
Treatment arms Randomization Total number of subjects	1- vancomycin 2- Tolvamer 3- Metronidazole 1:2:1 randomization scheme Total number of subjects in ITT: 1420	1- vancomycin 2- fidaxomicin 1:1 randomization scheme Total number of subjects in mITT: 1105
Start date-end date	301: March 2005 to February 2007	003: 09 May 2006 to 21 August 2008
	302: May 2005 to August 2007	004: 19 April 2007- 11 December 2009
Duration of treatment	10 days	10 days
Number of visits	Daily Assessments	Daily Assessments
Assessment of cure	Day 10	EOT to day 12

**Table 27: Clinical Trial Subject Characteristics**

Trials	Tolvamer Studies Pooled 301 and 302	Current Studies Pooled 003 and 004
Age (years) Mean (SD) Min, Max	64 (17) <sup>1</sup> Not available	62 (17) 18-94
CDAD severity <sup>2</sup> Mild Moderate Severe	Mild (31%), Moderate (43%) Severe (25%)	Mild (28%) Moderate (34%) Severe (37%)
CDAD history First occurrence Recurrent	First occurrence (83%) Recurrent (17%)	First occurrence (84%) Recurrent (16%)

1. Age mean and standard deviation for the 301 trial (see poster by Louie et al 2007) , no data on age was available from publications for trial 302.
2. In tolvamer studies, the definitions are the following (see poster by Louie et al 2007) (1) Mild: 3-5 bowel movements per day, WBC less or equal to 1500 mm<sup>3</sup> and no abdominal pain (2) Moderate: 6-9 bowel movements per day, WBC 1501-2000 mm<sup>3</sup> and no, mild or moderate abdominal pain (3) Severe: 10 or more bowel movements per day, WBC greater or equal to 20001 mm<sup>3</sup> and severe abdominal pain. In current studies, the definitions are the following (1) Mild: 4-5 unformed bowel movements per day and WBC less or equal to 12000 mm<sup>3</sup> (2) Moderate: 6-9 unformed bowel movements per day and WBC between 1201-1500 mm<sup>3</sup> (3) Severe: 10 or more unformed bowel movements per day and WBC greater than 1500 mm<sup>3</sup>

### 6.3 Determination of the Non-Inferiority Margin for vancomycin in the treatment of CDAD

The results for clinical cure on the intent to treat population for studies 301 and 302 are shown in Table 28. A meta analysis of the results using the DerSimonian and Laird approach (random effect model) gives an estimate of the treatment effect of 37% with **95% CI of (30%, 43%)**.

**Table 28: Summary of Clinical Success Rate of Historical Trials (from Louie et al (2007) and Bouza et al (2008)): Intent-to-Treat Analysis**

Study	Agent	Clinical Cure rate		Treatment Difference (95% CI) <sup>2</sup>
301	Tolvamer	124/266	46.44%	
	vancomycin	109/134	80.74%	35% (25% -43%)
302	Tolvamer	112/268	41.64%	
	vancomycin	101/125	80.16%	39% (29%- 47%)

1. Intent to Treat Set: includes all randomly assigned patients who received at least 1 dose of study drug, with any post dosing Investigator Evaluation data.
2. Confidence interval was derived using method recommended in Newcombe 1998 and Agresti and Caffo (2000).

Keighley's 1978 study shows that 9 out of 12 subjects in the vancomycin group had a resolution of diarrhea compared to 1 out of 9 subjects in the placebo group which gives a 95% confidence interval for the difference in proportion of (21% - 82%)<sup>7</sup>. However, as explained in the previous section, the results of this trial should be considered with caution as the constancy assumption does not hold, trial conduct was poor, and sample sizes are small.

In summary, the overall data supporting a reliable and reproducible treatment effect was estimated only from the two studies outlined in Table 3. On one hand, this estimate may be conservative as tolevamer may have higher antimicrobial activity than placebo. On the other hand, there are uncertainties in the consequences of departing from the constancy assumption for vancomycin treatment effect and uncertainties in the generalizability of the results. These departures from the constancy assumption and generalizability issues include the following:

1. Potential difference in prognostic factors and inclusion/exclusion criteria
2. Differences in the definition of clinical cure compared to that used in current trials
3. Differences in disease severity at baseline
4. Limited historical data
5. Inter-trial variability of the estimate of active control treatment effect

To account for these uncertainties, the treatment effect estimate from the meta-analysis is discounted to estimate M1. We propose a discounting of 10%-15% and an M1 in the range of 26%-27%. This amount of discounting is based on our evaluation of the potential effect of the sources of uncertainties 1-5 above on the estimated treatment effect of vancomycin. In our derivation, the 10-15% discounting is applied to 30%, the lower limit of the 95% CI of the treatment effect of vancomycin over tolevamer from meta-analysis above. We acknowledge that the true treatment effect of vancomycin over placebo is probably larger than the estimate from the meta-analysis considering that tolevamer may have some antimicrobial activity.

In conclusion, the historical evidence supports the Applicant's proposed margin of 10% while still preserving over 60% of the treatment effect based on clinical judgment.

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<sup>7</sup> Confidence interval was derived using the method recommended in Newcombe 1998 and Agresti and Caffo (2000).

## References:

Aslam S, Hamill RJ, Musher DM (2005). Treatment of *Clostridium difficile*-associated disease: old therapies and new strategies. *Lancet Infect Dis* 2005; 5:549-57.

Bouza E., Dryden M., Mohammed R., Peppe J., Chasan-Taber S., Donovan J., Davidson D., Short G. (2008). Results of a phase III trial comparing tolevamer, vancomycin and metronidazole in patients with *Clostridium difficile*-associated diarrhea. Poster Abstract Number: O464. 18th European Congress of Clinical Microbiology and Infectious Diseases Barcelona, Spain, 19–22 April 2008

Keighley MR, Burdon DW, Arabi Y, Williams JA, Thompson H, Youngs D, et al. Randomised controlled trial of vancomycin for pseudomembranous colitis and postoperative diarrhoea. *Br Med J* 1978; 2(6153):1667–9.

Johnson S, Homann SR, Bettin KM, Quick JN, Clabots CR, Peterson LR, et al. Treatment of asymptomatic *Clostridium difficile* carriers (fecal excretors) with vancomycin or metronidazole. A randomized, placebo-controlled trial. *Ann Intern Med* 1992;117(4):297–302.

Louie T, Peppe J, et al (2006). Tolevamer, a novel nonantibiotic polymer, compared with vancomycin in the treatment of mild to moderately severe *Clostridium difficile*-associated diarrhea. *Clin Infect Dis* 2006;43:411-420.

Louie TJ, Gerson M, Grimard D, Johnson S, Poirier A, Weiss K, et al. (2007). Results of a phase III study comparing tolevamer, vancomycin and metronidazole in *Clostridium difficile*-associated diarrhea (CDAD). In: Program and Abstracts of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 17–20 September 2007; Chicago, IL. Washington, DC:ASM Press; 2007. Abstract K-4259.

Nelson, Richard L (2007). "Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults". *Cochrane Database Syst Rev* (3): CD004610. doi:10.1002/14651858.CD004610.pub3.

Weiss K. Toxin-binding treatment for *Clostridium difficile*: a review including reports of studies with tolevamer. *Int J Antimicrob Agents*. 2009;33(1):4-7.

## **7 SIGNATURES/DISTRIBUTION LIST**

Primary Statistical Reviewer: Rima Izem, PhD

Date: April 15, 2011

Concurring Reviewer(s): Scott Komo, PhD

cc:

Project Manager: Fariba Izadi

Medical Officer: Dmitri Iarikov

Medical Team Leader: John Alexander

Deputy Director of DAIOP: Katherine Laessig

Acting Division Director of DAIOP: Wiley Chambers

Primary Statistical Reviewer: Rima Izem

Statistical Team Leader: Thamban Valappil

Biometrics Division Director: Mohammad Huque

Biometrics Division Deputy Director: Daphne Lin

Immediate Office: Lillian Patrician

## 8 CHECK LIST

Number of Pivotal Studies: 2

### Trial Specification

The two trials had identical protocols

**Protocol Number (s):** 003 and 004

**Phase:** 3

**Control:** Active Control

**Blinding:** Double-Blind

**Region(s) (Country):** US, Canada, Western Europe

**Duration:** 40 days

**Treatment Arms:** fidaxomicin, vancomycin

**Treatment Schedule:** fidaxomicin 200mg administered orally twice a day for 10 days, vancomycin 125mg administered orally four times a day for 10 days

**Randomization:** Yes

Ratio: 1:1

Method of Randomization: stratification by number of prior CDAD episodes

**Primary Endpoint:** Clinical Cure at end of treatment (day 10)

**Primary Analysis Population:** (e.g., ITT, mITT, Per-Protocol...)

**Statistical Design:** Non-Inferiority

Non-inferiority margin of 10% calculated based on historical data

**Primary Statistical Methodology:** CI for difference in rates uses the method recommended by Agresti and Caffo

**Interim Analysis:** No

**Sample Size:** 1105 total in both trials

**Sample Size Determination:** based on primary variable

- Changes in protocol: implementation of gate-keeping strategy for multiple testing in study 004 and Global cure rate changed from exploratory endpoint in study
- **Covariates (subgroup and strata)** are pre-specified in the protocol
- Applicant performed **Sensitivity Analyses** on primary and secondary endpoints
- There were few **Missing Data**. They were imputed as failures.
- **Multiple Secondary Endpoints** are included in the label with gate-keeping strategy.
- **Subgroup Analyses are Performed**

- No **Discrepancies** between the protocol/statistical analysis plan vs. the study report are found
- Overall, the study results are positive

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RIMA IZEM  
04/15/2011

SCOTT S KOMO  
04/15/2011

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 201699**

**Applicant: Optimer  
Pharmaceuticals, Inc.**

**Stamp Date: 11/30/2010**

**Drug Name: Fidaxomicin  
Tablet**

**NDA/BLA Type:  
NME**

**Indication: treatment of *C. difficile*  
bacterial infection**

**Priority review**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).		X		Define.pdf files are poorly documented. An information Request was sent to applicant.

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

### Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Main Endpoints	Sponsor's findings
<b>101.1.C.003</b>	A Multi-national, Multi-center, Double-Blind, Randomized, Non-inferiority Study	(1) 200 mg fidaxomicin q12h for 10 days (300 subjects)  (2) 125 mg Vancomycin Taken q6h for 10 days (323 subjects)	<b>Primary: Clinical Cure at end of therapy</b>	95% CI in mITT population: (1) Fidaxomicin: (84%, 91%) (2) Vancomycin: (81%, 89%)  95% CI in mITT for difference in treatment: Vancomycin -- Fidaxomicin (-8.0, 2.9)
			<b>Secondary: Recurrence</b>	Difference 95% CI Vancomycin-Fidaxomicin (-16.2, -2.5) pvalue=0.008
			<b>Secondary: Global cure (clinical cure and no recurrence)</b>	Difference 95% CI Vancomycin-Fidaxomicin (-17.5, -2.8) pvalue=0.007
<b>101.1.C.004</b>	A Multi-national, Multi-center, Double-Blind, Randomized, Non-inferiority Study	(1) 200 mg fidaxomicin q12h for 10 days (270 subjects)  (2) 125 mg Vancomycin Taken q6h for 10 days (265 subjects)	<b>Primary: Clinical Cure at end of therapy</b>	95% CI in mITT population: (1) Fidaxomicin: (83%, 91%) (2) Vancomycin: (82%, 90%)  95% CI in mITT for difference in treatment: Vancomycin -- Fidaxomicin (-6.8, 4.8)
			<b>Secondary: Recurrence</b>	Difference 95% CI Vancomycin-Fidaxomicin (-21.6, -7) pvalue<0.001
			<b>Secondary: Global cure (clinical cure and no recurrence)</b>	Difference 95% CI Vancomycin-Fidaxomicin (-21, -5.4) pvalue=0.001

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

## Statistical Issues:

- Derivation of the non-inferiority margin. Data from two pivotal trials showing superiority of Vancomycin to tolevamer is used to derive the non-inferiority margin for Vancomycin. This assumes tolevamer is a putative placebo. These two historical trials were conducted by (b) (4) as part of (b) (4). The data from these trials was submitted to FDA in NDA 50-606 on 4/23/10 to support label change for Vancocin. The results from these trials seem to support a non-inferiority margin of 10% proposed by the applicant.
- Comparison of historical trial design to current design. There are slight differences in the definition of clinical cure between the two historical trials and the two current trials. A detailed discussion of the differences in the endpoint as well as comparison of the clinical study population between historical and current trial will be discussed in the review.
- Handling of missing values. There was very little assessment of missing values and ways in which they were handled in the Statistical Analysis Plan and analyses submitted by the applicant. This is of special concern for the daily collected bowel movement dataset. This data was collected by phone for outpatients.

Rima Izem

12-20-2010

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Reviewing Statistician

Date

Scott Komo/ Thamban Valappil

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Supervisor/Team Leader

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RIMA IZEM  
12/20/2010

THAMBAN I VALAPPIL  
12/20/2010