

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-506**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/Serial Number:** 21-506/N\_000 Re-Submission

**Drug Name:** Mycamine™ (micafungin sodium) for Injection 50 mg

**Indication(s):** Prophylaxis of *Candida* Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT).

**Applicant:** Fujisawa Healthcare, Inc.

**Date(s):** Application: 8/24/04  
Received: 8/24/04  
Goal Date: 3/14/05  
User Fee: 2/25/05 (3-month extension 5/25/05)

**Review Status:** Resubmission (6 months)

**Biometrics Division:** Division of Biometrics III (HFD-725)

**Statistical Reviewer:** LaRee Tracy, M.A.

**Concurring Reviewers:** Karen Higgins, Sc.D.

**Medical Division:** Division of Special Pathogen and Immunologic Drug Products (HFD-590)

**Clinical Team:** Team Leader: Eileen Navarro, M.D.  
Medical Reviewer: Joette Meyer, Pharm.D.

**Project Manager:** Christina Chi, Ph.D.

**Keywords:** NDA review, clinical studies, anti-fungal, prophylaxis of *Candida* infections

**TABLE OF CONTENTS**

**TABLE OF TABLES** ..... 3

**1. EXECUTIVE SUMMARY** ..... 4

    1.1 CONCLUSIONS AND RECOMMENDATIONS ..... 4

    1.2 BRIEF OVERVIEW OF CLINICAL STUDIES ..... 4

    1.3 STATISTICAL ISSUES AND FINDINGS ..... 5

**2. INTRODUCTION** ..... 5

    2.1 OVERVIEW ..... 5

    2.2 DATA SOURCES ..... 7

**3. STATISTICAL EVALUATION** ..... 7

    3.1 EVALUATION OF EFFICACY ..... 7

        3.1.1 Analysis Methods ..... 7

        3.1.2 Primary Efficacy from Original Submission ..... 8

        3.1.3 Blinded Review of Investigator-Reported Proven and Probable Fungal Infections ..... 9

        3.1.4 Sponsor’s Additional Analysis of Breakthrough *Candida* Fungal Infections ..... 10

        3.1.5 Study 98-0-050 Efficacy Results by Primary Reason for Failure ..... 11

    3.2 EVALUATION OF SAFETY ..... 13

**4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS** ..... 13

    4.1 GENDER, RACE AND AGE ..... 13

    4.2 OTHER SPECIAL/SUBGROUP POPULATIONS ..... 14

**5. SUMMARY AND CONCLUSIONS** ..... 14

    5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE ..... 14

    5.2 CONCLUSIONS AND RECOMMENDATIONS ..... 15

**SIGNATURES/DISTRIBUTION LIST** ..... 16

**REFERENCE** ..... 17

---

**TABLE OF TABLES**

**Table 3.1 Study 98-0-050 Primary Efficacy Results from Original Submission ..... 8**  
**Table 3.2 Proven or Probable Fungal Infections by Organism as Assessed by the Investigator ..... 9**  
**Table 3.3 Proven or Probable Fungal Infections by Organism as Assessed by Blinded Committee. 10**  
**Table 3.4 Sponsor’s Results of Study 98-0-050 for Proven *Candida* Infections ..... 10**  
**Table 3.5 Study 98-0-050 Efficacy Results by Primary Reason for Failure ..... 13**

Appears This Way  
On Original

## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

Based on primary efficacy results from study 98-0-050 and results from two studies (Phase 2 study FG463-21-09 and Phase 3 study 03-7-005 submitted under NDA 21,754/N\_000) that evaluated micafungin for treatment of esophageal candidiasis there is sufficient evidence demonstrating prophylactic activity of micafungin 50 mg/day against *Candida* infection in patients undergoing hematopoietic stem cell transplantation.

### 1.2 Brief Overview of Clinical Studies

This re-submission is in response to the Division's January 2003 approvable letter for NDA 21-506/N\_000, micafungin for 'prophylaxis of \_\_\_\_\_ in patients undergoing HSCT'. The Division granted an approvable action for the original NDA concluding that study 98-0-050 was not robust enough to demonstrate superiority of micafungin over fluconazole for prevention of \_\_\_\_\_ in patients undergoing HSCT. Additionally the data failed to provide sufficient evidence demonstrating micafungin's activity in the treatment of documented invasive *Candida* \_\_\_\_\_ infections. Following the approvable action, Fujisawa Healthcare, Inc. (Sponsor) requested to pursue a narrower indication of 'prophylaxis of *Candida* infection in patients undergoing HSCT' based on study 98-0-050 results and supportive evidence of micafungin's activity against *Candida* infections from a Phase 2 dose ranging study and a Phase 3 confirmatory study in EC. This amendment contains a re-submission of study 98-0-050 focusing on the incidence and comparison of breakthrough *Candida* infections between micafungin and fluconazole. Additionally it contains a thorough literature review and meta-analyses of relevant studies to determine an appropriate non-inferiority margin for which to test micafungin against fluconazole.

Study 98-0-050 was designed to compare the rate of prophylactic success between micafungin 50 mg/day and fluconazole 400 mg/day in patients undergoing HSCT. The protocol defined primary endpoint of treatment success was defined as the composite of the absence of a proven, probable, or suspected fungal infection through the end of therapy and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period. The Sponsor's reported treatment success rates were 80.0% and 73.5% for micafungin and fluconazole respectively resulting in a p-value of 0.023. Analyses by the original statistical reviewer demonstrated a lack of robustness in the Sponsor's results. Furthermore, the difference between success rates was mainly driven by the rate of possible or suspected fungal infections and no difference was noted in the rate of breakthrough (probable and proven) fungal infections. These results were not considered to be robust enough to demonstrate superiority of micafungin over fluconazole for the Sponsor's initial indication of prophylaxis of \_\_\_\_\_ in patients undergoing HSCT. However, for the narrower indication of prophylaxis of *Candida* infections in patients undergoing HSCT, an indication for which fluconazole is currently approved; these results sufficiently demonstrate non-inferiority of micafungin to fluconazole.

The Sponsor's re-analysis of a new efficacy endpoint of breakthrough *Candida* infections is considered statistically invalid. Re-defining the primary endpoint as well as treating all non-*Candida* fungal infections and deaths during study as successes is inappropriate. The reviewer therefore concludes that the original protocol defined analysis of study 98-0-050 comparing the absence of fungal infections remains

the primary analysis for concluding non-inferiority of micafungin to fluconazole. All other analyses are considered supportive and descriptive in nature. This review will summarize the primary efficacy results based on a new review of the data performed during this review cycle.

### 1.3 Statistical Issues and Findings

This submission relies on a re-submission of a previously submitted clinical study 98-0-050 as basis for a prophylaxis indication for *Candida* infection. The Sponsor conducted a re-analysis focusing solely on the incidence of breakthrough *Candida* infections, an endpoint different from the originally studied primary endpoint of incidence of proven, probable, or suspected fungal infections. Additionally, this analysis treats all other breakthrough infections and deaths as positive outcomes. Given these issues, this new analysis by the Sponsor is considered statistically inappropriate by the reviewer. Statistically, the original analysis of the pre-defined primary endpoint is the most appropriate and any additional analyses of these data are considered secondary or post-hoc.

The primary result of study 98-0-050 based on the protocol defined endpoint and analysis, demonstrated the superiority of micafungin over fluconazole; however this result was not robust (lower bound of the 95% CI of difference between micafungin and fluconazole just above zero) and was driven mainly by the incidence of suspected infections rather than breakthrough proven or probable infections. Although the results of superiority are marginal, conclusions of non-inferiority of micafungin to fluconazole can be drawn and are considered robust. The results are further strengthened when considered along with results from a Phase 2 dose ranging, active controlled EC treatment study and a Phase 3 active controlled non-inferiority study for EC treatment. In total, these results support the conclusion of micafungin's non-inferiority to fluconazole for prophylaxis of *Candida* infections in patients undergoing HSCT, an indication for which fluconazole is currently approved and marketed.

## 2. INTRODUCTION

### 2.1 Overview

The Sponsor is requesting approval of Mycamine (micafungin sodium) 50 mg/day for prophylaxis against *Candida* infections in patients undergoing HSCT. Currently, fluconazole (Diflucan®) is the only FDA approved and marketed antifungal for prophylaxis against *Candida* infection in bone marrow transplant patients. The use of fluconazole has been shown to reduce the incidence of *Candida* infections thus reducing the number of deaths due to fungal infection in bone marrow transplant patients, neutropenic cancer patients and patient with acute leukemia.

Mycamine (micafungin sodium) is the second (the first is caspofungin) in a new class of antifungals known as echinocandins. Echinocandins are semisynthetic lipopeptides with potent and broad-spectrum antifungal activity. Their activity is due to the presence of a synthetic cell-wall enzyme complex  $\beta$ -1,3-D-glucan synthase, which acts by inhibiting the large polysaccharide  $\beta$ -1,3-D-glucan (an essential component of the fungi cell wall providing rigidity and osmotic and structural integrity) leading to cell and eventual fungal death [Denning, 2003]. Unlike fungal cells, human cells lack in a cell-wall thus making echinocandins good targets for fungal infections in humans.

In April 2002, the Sponsor submitted NDA 21-506/N\_000 for micafungin 50 mg/day for the indication of 'prophylaxis of *Candida* in patients undergoing hematopoietic stem cell transplantation'. This

submission was based on one Phase 3 study, study 98-0-050 that compared the rate of treatment success, defined as the absence of proven, probable or suspected fungal infection through the end of therapy and the absence of proven or probable fungal infection through the end of study, between micafungin 50 mg/day and fluconazole 400 mg/day. Results of this study were not shown to be robust enough to demonstrate superiority of micafungin over fluconazole, a necessary requirement since fluconazole is not approved for the [redacted]. Specifically, the results of this study were mainly driven by the number of suspected or possible fungal infections as opposed to proven or probable fungal infections. Additionally, prior to approval for prophylaxis of [redacted] s in patients undergoing HSCT, it was also necessary for the Sponsor to demonstrate that micafungin had activity against invasive *Candida* s infections. [redacted] 98-0-047, failed to fully demonstrate such activity.

In January 2003, the Division took an approvable action on NDA 21-506/N\_000 stating the following:

*"The one study submitted in support of prophylaxis of [redacted] in patients undergoing hematopoietic stem cell transplantation, Study 98-0-050, alone did not provide sufficiently robust statistical evidence of superiority of micafungin over fluconazole, a comparator not approved for this indication. Specifically, the results of this analysis were largely determined by patients with "possible" as opposed to probable or proven fungal infection. In addition, prior to approval for prophylaxis of [redacted] in patients undergoing hematopoietic stem cell transplantation, it is expected that micafungin sodium should demonstrate activity in the treatment of documented invasive *Candida* s infections. Studies [redacted] 98-0-047 failed to provide sufficient information to demonstrate such activity. Thus, the results from Study 98-0-050 alone do not provide substantial evidence of efficacy. In order for this indication to be approved, it will be necessary to provide data from additional controlled clinical trials.*

In March 2003, the Sponsor requested that the indication of prophylaxis of [redacted] be narrowed down to only prophylaxis of *Candida* infections in patients undergoing HSCT based on data from study 98-0-050. Additionally, they requested Division concurrence that study FG-463-21-09 (a Phase II dose ranging study of micafungin for the treatment of EC with a fluconazole control group) addresses the Division's request for additional clinical trial data to support approval of micafungin for the treatment of *Candida* infections. The Division agreed that this approach is acceptable given that the results from study FG-463-21-09 demonstrate both safety and efficacy of micafungin for the treatment of EC. The Division further noted that administratively the prophylaxis for *Candida* infections and treatment of EC indications would need to be submitted under two separate NDAs.

To demonstrate prophylaxis activity of micafungin against *Candida* specific fungal infections, the Sponsor proposed re-submitting study 98-0-050 along with a new analysis comparing the incidence of breakthrough (proven or probable) *Candida* infections between micafungin and fluconazole. Since

fluconazole is currently labeled for the prevention of *Candida*, or more specifically, 'to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy', it is only necessary for the Sponsor to demonstrate that micafungin is non-inferior to fluconazole for a narrower prophylactic indication. This Division accepted this proposal and noted however that the results of the originally defined primary endpoint are still considered primary.

In August, 2004, the Sponsor submitted the new analysis of study 98-0-050 along with a meta-analysis of published clinical studies that compared fluconazole versus placebo for the prevention of fungal infections. Based on this meta-analysis the Sponsor proposed a non-inferiority margin as basis to determine micafungin's non-inferiority in study 98-0-050.

## 2.2 Data Sources

The NDA Amendment submission is located in the Electronic Document Room at path: \\Cdsub1\21506\N\_000\2004-08-24. Additional tables and summaries requested during the review cycle can be located at \\Cdsub1\21506\N\_000.

Original NDA submitted on 04/29/2002 is located at: \\Cdsub1\21506\N\_000\2002-04-29.

During the review cycle, the Division requested additional datasets of patients who met the primary endpoint as defined in the study protocol. These datasets are located at \\Cdsub1\21506\N\_000\2005-02-09\21506\050209\CRT

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 Analysis Methods

This submission relies on the previously submitted clinical study 98-0-050 as basis for a prophylaxis indication for invasive *Candida* infection. The Sponsor conducted a re-analysis that focused solely on the incidence of breakthrough *Candida* infections, an endpoint different from the originally designed endpoint of incidence of proven, probable, or suspected fungal infection. Additionally, this analysis inappropriately treats all other breakthrough infections and deaths as positive or successful outcomes. Given these issues, this new analysis is considered statistically inappropriate by the reviewer. Statistically, the original analysis of the pre-defined primary endpoint is the most appropriate. Any additional analyses of these data are considered post-hoc and secondary.

To accurately account for all treatment failures in Study 98-0-050, especially cases of suspected fungal infection, the Division requested from the Sponsor a detailed breakdown of all patients in the full analysis set. The breakdown of failures was according to severity while applying the strict protocol criteria for proven, probable and suspected fungal infection. This is discussed in detail in section 3.1.5.

### 3.1.2 Primary Efficacy from Original Submission

*Study 98-0-050 was previously reviewed during the first submission cycle. For details of this review, including efficacy conclusions, study design, patient demographics and safety, please refer to original statistical review by Qian Li, Sc.D. dated 1/31/2003 in DFS. This current review will focus on new analyses of study 98-0-050 performed during this review cycle.*

Primary support for the prophylaxis of *Candida* in the original NDA was study 98-0-050, which was a randomized, double-blind, comparative Phase 3 study of micafungin 50 mg/day (1 mg/kg/day for patients weighing < 50 kg) vs. fluconazole at the recommended approved dose of 400 mg/day (8 mg/kg for patients weighing < 50 kg). This study included adult and pediatric subjects who were scheduled to undergo an autologous or syngeneic or allogenic hematopoietic stem cell transplant putting them at high risk for fungal infection. This study was designed with the primary endpoint of treatment success, defined as the composite of the absence of a proven, probable, or suspected fungal infection through the end of therapy and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period.

The Sponsor's primary efficacy results of the full analysis set (same as MITT=all randomized patients who received at least one dose of study drug) of study 98-0-050 resulted in a treatment success rate of 80.0% and 73.5% in the micafungin and fluconazole groups respectively. This yielded a treatment difference (micafungin-fluconazole) of +6.5%, and a 95% confidence interval around the difference of 0.9% to 12.0%. The incidence of proven and probable fungal infections in this analysis was based on investigator-reported rates. The following table presents these results along with the breakdown of treatment failures. Note that the incidence of suspected fungal infections was the primary failure outcome. *Note: Discussed later in this review are the rates of proven and probable infections as determined by independent committee.*

**Table 3.1 Study 98-0-050 Primary Efficacy Results from Original Submission**

	Micafungin N=425	Fluconazole N=457
Success	340 (80%)	336 (73.5%)
Failure	78 (18.4%)	112 (24.5%)
<i>Reason for failure</i>		
Proven (on therapy)	4	5
Probable (on therapy)	9	6
Suspected (on therapy)	64	98
Proven (post therapy)	1 <sup>2</sup>	3
Probable (post therapy)	1	0
N/A <sup>1</sup>	7 (1.6%)	9 (2.0%)

<sup>1</sup> N/A: For Micafungin: 5 lost to follow-up, 1 systemic fungal infection at enrollment, 1 death without post-treatment assessment. For Fluconazole: 6 deaths (3 on drug, 3 post-treatment), 1 systemic fungal infection at enrollment, 2 lost to follow-up.

<sup>2</sup> One subject (0572528) had a suspected fungal infection on therapy and a proven infection post-therapy

Source: Sponsor's tables 13.4.4.1, 13.4.7.1, and 13.4.8.1

Population includes all randomized subjects who received at least one dose of study drug

The original statistical reviewer disagreed with the Sponsor's primary analysis (see original review for details). Of major concern was a change in the study protocol to no longer require patients to be alive at the end of study to be considered a success. From the original statistical review, "*Such changes in the primary endpoint were not considered appropriate since patients who were not alive at the end of the study should not be considered as treatment successes by default, even if no proven, probable or suspected fungal infections were identified.*"

There were six patients in each treatment group who died during study counted as treatment successes in the Sponsor's analysis because they did not have a proven, probable or suspected fungal infection up to time of death. When including these 12 patients as treatment failures, the rates of treatment success becomes 334 (78.6%) and 330 (72.2%) for micafungin and fluconazole respectively resulting in a difference (micafungin-fluconazole) of 6.4%, 95% CI around the difference of {0.71, 12.0}.

**Reviewer's Comment:** *The reviewer considers these results as the primary efficacy results and all other results presented are considered supportive.*

Total deaths during study were 18 and 26 for micafungin and fluconazole respectively resulting in a difference of 1.0%, 95% CI [-3.8, 1.8].

The breakdown of proven and probable investigator-reported fungal infections is presented below in Table 3.2. Note that more *Aspergillus* infections were reported in the fluconazole group, which were likely due to the presumed *Aspergillus* resistance to fluconazole.

**Table 3.2 Proven or Probable Fungal Infections by Organism as Assessed by the Investigator**

Organism	Micafungin N=425		Fluconazole N=457	
<b>Proven</b>	<b>5</b>	<b>(1.18%)</b>	<b>8</b>	<b>(1.75%)</b>
<i>Aspergillus</i> species	0	(0.00%)	4	(0.88%)
<i>Candida</i> species	3	(0.71%)	2	(0.44%)
<i>Fusarium</i> species	1	(0.24%)	2	(0.44%)
<i>Zygomycetes</i> species	1	(0.24%)	0	(0.00%)
<b>Probable</b>	<b>10</b>	<b>(2.35%)</b>	<b>6</b>	<b>(1.31%)</b>
<i>Aspergillus</i> species	2	(0.47%)	4	(0.88%)
<i>Candida</i> species	4	(0.94%)	1	(0.22%)
Unknown <sup>1</sup>	4	(0.94%)	1	(0.22%)

<sup>1</sup> Including one probable CNS for each treatment  
MITT Population

The Sponsor's analysis of the primary endpoint in the Per Protocol population was similar to that in the MITT population. The rate of treatment success was 81.1% and 74.1% in the micafungin and fluconazole groups respectively resulting in a treatment difference (micafungin-fluconazole) of +7.0%, and a 95% confidence interval around the difference of 1.3% to 12.6%.

### 3.1.3 Blinded Review of Investigator-Reported Proven and Probable Fungal Infections

The case report forms of all patients with an investigator-reported proven or probable fungal infection were reviewed by a blinded independent committee prior to data analysis using the protocol-specific diagnostic criteria. The committee confirmed all 13 investigator-reported proven fungal infections. Of the 16 (10 micafungin and 6 fluconazole) investigator-reported probable fungal infections, the independent committee confirmed four as probable and considered one as proven [Table 3.3]. There were six total breakthrough *Candida* infections of which four were in the micafungin group.

**Reviewer's Comment:** *The original primary efficacy results for study 98-0-050 are based on the numbers of proven and probable investigator-reported fungal infections.*

**Table 3.3 Proven or Probable Fungal Infections by Organism as Assessed by Blinded Committee**

Organism	Micafungin (N=425)		Fluconazole (N=457)	
<b>Proven</b>	<b>6</b>	<b>(1.4%)</b>	<b>8</b>	<b>(1.8%)</b>
<i>Aspergillus</i> species	0	(0.0%)	4	(0.9%)
<i>Candida</i> species	4	(0.9%)	2	(0.4%)
<i>Fusarium</i> species	1	(0.2%)	2	(0.4%)
<i>Zygomycetes</i> species	1	(0.2%)	0	(0.0%)
<b>Probable</b>	<b>1</b>	<b>(0.2%)</b>	<b>3</b>	<b>(0.7%)</b>
<i>Aspergillus</i> species	1	(0.2%)	3	(0.7%)

**MITT Population:** all randomized patients who received at least 1 dose of study drug

**Proven:** includes biopsy-proven (with or without culture) invasive or disseminated fungal infection

**Probable:** includes patients with the characteristic clinical or radiologic (chest x-ray, CT scan, other) picture of pulmonary aspergillosis plus a positive BAL specimen.

**Source:** Table 18 in the applicant's original report for Study 98-0-050

### 3.1.4 Sponsor's Additional Analysis of Breakthrough *Candida* Fungal Infections

The Sponsor's new analysis of the rate of breakthrough *Candida* fungal infections in study 98-0-050 is presented below in Table 3.4. This analysis considers breakthrough *Candida* infections as treatment failures while all other breakthrough infections and deaths during study are considered treatment successes. This analysis therefore is statistically inappropriate as a method to determine non-inferiority of micafungin to fluconazole. Additionally, the Sponsor's re-defining of the primary endpoint from absence of fungal infections during study to incidence of *Candida* infections is also statistically invalid.

**Table 3.4 Sponsor's Results of Study 98-0-050 for Proven *Candida* Infections**

Micafungin	Fluconazole	Difference (Micafungin - Fluconazole)	95% Confidence Interval†	99% Confidence Interval†
4/425 (0.94%)	2/457 (0.44%)	0.5%	(-0.6%, 1.6%)	(-0.9%, 1.9%)

† Difference = micafungin - fluconazole (CI using normal approximation)

Source: Study 98-0-050

Table obtained from Sponsor's 040824.pdf document in amendment submission, page 39

The Sponsor's re-submission provides a detailed literature review of published clinical studies that evaluated fluconazole versus placebo for prophylaxis against *Candida* infections in patients undergoing HSCT. Although this summary is useful to better estimate an appropriate non-inferiority margin for future prophylaxis studies for this indication, the proposed margin and analysis are irrelevant for the study 98-0-050 efficacy analysis. Study 98-0-050 was originally designed with the primary endpoint of absence of fungal infections. This primary endpoint, and primary analysis based on reviewer's adjustments appropriate to protocol design issues, remains the primary analysis for this submission.

### 3.1.5 Study 98-0-050 Efficacy Results by Primary Reason for Failure

To accurately account for all treatment failures in Study 98-0-050, especially cases of suspected fungal infection, the Division requested from the Sponsor a detailed breakdown of all patients in the full analysis set according to the following process:

1. All deaths and patients lost to follow-up, regardless of causality
2. Of the remaining patients (minus deaths and LTFs), all patients diagnosed (by the blinded, independent committee) as having a proven or probable infection  
*Note: Though the results from the blinded committee were not considered primary by the study protocol (site investigators results served as primary), they were preferred by the Division since the criteria used by the committee more closely matched those defined in the protocol.*
3. Of the remaining patients (minus deaths, LTFs and patients with proven/probable fungal infections), all patients who met the protocol definition for suspected fungal infection, regardless of whether or not they received systemic antifungal therapy

The original protocol definition of suspected fungal infection consisted of three components:

- Patients with neutropenia ( $ANC < 500/mm^3$ ) AND
- Persistent fever of  $\geq 100.4^\circ F$  ( $\geq 38^\circ C$ ) for which there is no known etiology OR a recurrent fever of  $> 100.4^\circ F$  ( $> 38^\circ C$ ) on two measurements of temperature at least 3 hours apart or a single measurement of  $\geq 101.3^\circ F$  ( $\geq 38.5^\circ C$ ) AND
- Failed to respond to 96 hours of adequate broad spectrum antibacterial therapy

For this analysis, the applicant re-reviewed all patients who received empirical antifungal therapy and the applied the protocol definition of suspected fungal infection. The applicant also further clarified the criteria of persistent/recurrent fever, for the purposes of reducing patient ambiguity, as follows:

A persistent fever was defined as four consecutive days of fever greater than  $38^\circ C$ . A recurrent fever was defined as either having at least one day with a temperature  $\geq 38.5^\circ C$  after having at least one prior temperature  $> 38^\circ C$ ; or having two days of temperatures  $> 38^\circ C$  after having at least one prior temperature  $> 38^\circ C$ .

Additionally, all patients who did not receive empirical antifungal therapy (and who did not die, or have a proven/probable infection) and had at least one day of fever  $\geq 38^\circ C$  during neutropenia, were re-reviewed applying the protocol criteria of suspected fungal infection, as detailed above.

4. Of the remaining patients (minus deaths, patients with proven/probable/suspected infection), all patients who received systemic antifungal therapy. *Note: These patients were not included in the calculation of treatment failure, based on the protocol defined primary endpoint.*

**Results of this analysis are as follows and presented below in Table 3.5:**

1. Death during study: **18 micafungin, 26 fluconazole**  
Patients Lost to Follow-up: **5 micafungin, 3 fluconazole**
2. Proven/probable infections (as assessed by independent blinded committee): **6 micafungin, 8 fluconazole**
3. Suspected fungal infections: **53 micafungin, 83 fluconazole\***
  - a. 53 micafungin (of those 43 received systemic antifungal therapy and 10 who did not, but met the protocol criteria for a suspected fungal infection)
  - b. 83 fluconazole (of those 73 received systemic antifungal therapy and 10 who did not, but met the protocol criteria for a suspected fungal infection.)

\*1 micafungin, 4 fluconazole patients were included as suspected fungal infections, although they were initiated on empirical systemic antifungal therapy after 72-96 hours, rather than at least 96 hours as defined by the protocol. These patients met the other protocol criteria and therefore, the Clinical Reviewer agrees with including these patients as having a suspected fungal infection.

4. Use of systemic antifungal therapy post-treatment

	Micafungin n=178	Fluconazole n=192
<b>Reasons</b>		
<b>Prophylaxis</b>	160	174
Empirical	19	27
Treatment	9	6
Maintenance	3	1

The overall reported treatment success rates [Table 3.5] were **80.7% (343/425)** and **73.7% (337/457)** in the micafungin and fluconazole groups respectively resulting in a difference of **7.0%**, **95% CI [1.5, 12.5]**. These results, based on application of the protocol criteria of suspected fungal infection, are similar to previously reported results sufficiently demonstrating non-inferiority (and marginal superiority) of micafungin over fluconazole.

*Reviewer's Comment: These results are considered supportive by the reviewer. The primary efficacy results, including death as failure, from the original submission [section 3.1.2] are still considered primary by this reviewer.*

**Table 3.5 Study 98-0-050 Efficacy Results by Primary Reason for Failure**

	Micafungin (N=425)	Fluconazole (N=457)
<b>Treatment Success</b>	<b>343 (80.7%)</b>	<b>337 (73.7%)</b>
	<b>+7.0% treatment difference [95% CI=1.5%, 12.5%] *</b>	
Treatment Failure	82 (19.3%)	120 (26.3%)
<i>All Deaths</i>	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/Probable fungal infection (not resulting in death)	6 (1.4%)	8 (1.8%)
Suspected fungal infection	53 (12.5%)	83 (18.2%)
Lost to Follow-up	5 (1.2%)	3 (0.7%)

*\*95% CI around the difference (micafungin-fluconazole) using the Normal Approximation to the Binomial Method without continuity correction*

Previously discussed in section 3.1.3, there were 12 investigator-reported probable infections determined by the blinded committee review to not be probable fungal infections. Based on this re-review of patients per Division request, the final outcome of these 12 patients are as follows:

- 2 deaths: patients 1253104 (fluconazole), 4181001 (fluconazole)
- 1 proven infection: patient 0323003 (micafungin)
- 6 suspected infections: patients 0082502, 0203505, 0321009, 0352504, 0523101, 1252103 (all in the micafungin group)
- 3 received systemic therapy: patients 0311006 (micafungin), 0892001 (fluconazole), 1233502 (micafungin)

This re-review of data, which strictly applied protocol criteria for suspected fungal infection resulted in re-classification of three patients who were originally considered treatment failures (by investigator) now classified as treatment successes. If these patients were to be treated as failures in a sensitivity analysis, the overall treatment success rates in the micafungin and fluconazole groups respectively would be 341/425 (80.2%) and 336/457 (73.5%) resulting in a difference of 6.7%, 95% CI [1.2, 12.3]. These results only slightly differ from results presented above.

### 3.2 Evaluation of Safety

Refer to original statistical review (dated 1/31/03) and clinical reviews of NDA 21-506/N\_000 and NDA 21-754/N\_000 for detailed safety reviews.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

See original statistical review (dated 1/31/03) of NDA 21-506/N\_000.

#### 4.2 Other Special/Subgroup Populations

See original statistical review (dated 1/31/03) of NDA 21-506/N\_000.

### 5. SUMMARY AND CONCLUSIONS

#### 5.1 Statistical Issues and Collective Evidence

In this re-submission of study 98-0-0505, the primary efficacy endpoint was modified by the Sponsor from absence of a proven, probable or suspected fungal infection through the end of therapy and the absence of a proven or probable fungal infection through the end of study to the *incidence of breakthrough (proven or probable) Candida fungal infections during study*. This re-analysis is statistically invalid for the following reasons:

- This new analysis treats all non-*Candida* proven or probable fungal infections and suspected fungal infections as treatment successes. Given that this study was designed and powered to detect a difference in the absence of all fungal infections this new analysis lacks in statistical validity and rigor and thus is consider post-hoc.
- This analysis treats all deaths during study as treatment successes. It is statistically inappropriate to consider death, regardless of causality, as success in an intent-to-treat analysis.

**The reviewer considers the originally defined primary efficacy endpoint and analysis as primary. Results from the primary analysis, including all deaths as failures, yielded observed treatment success rates of 334/425 (78.6%) and 330/457 (72.2%) for micafungin and fluconazole respectively. This resulted in a difference (micafungin-fluconazole) of 6.4%, 95% CI around the difference of [0.71, 12.0].**

These results demonstrate marginal superiority of micafungin over fluconazole; however these results are not sufficiently robust and were mainly driven by the incidence of suspected (use of empiric therapy) infections rather than breakthrough proven or probable fungal infections. Although the results for superiority are marginal, conclusions regarding non-inferiority of micafungin to fluconazole can be drawn. Given that the current indication is for prophylaxis of *Candida* infections, an indication for which fluconazole is approved; there is only a need for micafungin to show non-inferior results to fluconazole. Though the non-inferiority margin was not defined ahead of time, given that the confidence interval excludes zero, this implies that it would exclude any negative valued non-inferiority margin. Therefore, these results demonstrate that micafungin is non-inferior to fluconazole. These results are further strengthened by findings from two randomized, active-controlled studies (FG 463-21-09 and 03-7-005) for the treatment of esophageal candidiasis (see statistical review of NDA 21-754/N\_000 for treatment of esophageal candidiasis). *Demonstration of activity against Candida infection is a requirement pre-specified by the Division (see section 2.1)*. In total, these results support the conclusion of micafungin's non-inferiority to fluconazole for prophylaxis of *Candida* infections in patients undergoing HSCT.

## 5.2 Conclusions and Recommendations

Based on primary efficacy results from study 98-0-050 and results from two studies (Phase 2 study FG463-21-09 and Phase 3 study 03-7-005 submitted under NDA 21,754/N\_000) that evaluated micafungin for treatment of esophageal candidiasis there is sufficient evidence demonstrating prophylactic activity of micafungin 50 mg/day against *Candida* infection in patients undergoing hematopoietic stem cell transplantation.

**APPEARS THIS WAY  
ON ORIGINAL**

**SIGNATURES/DISTRIBUTION LIST**

**Primary Statistical Reviewer: LaRee Tracy, M.A.**  
**Date: March 8, 2005**

**Concurring Reviewers:**  
**Statistical Team Leader: Karen Higgins, Sc.D.**

**cc:**  
**HFD-590/Christina Chi, Ph.D.**  
**HFD-590/Joette Meyer, PharmD**  
**HFD-590/Eileen Navarro Almario, M.D.**  
**HFD-590/Renata Albrecht, M.D.**  
**HFD-725/Mohammad Huque, Ph.D.**  
**HFD-700/Charles Anello, Sc.D.**

#### Reference

Denning, D.W., 2003, "Echinocandin antifungal drugs", *Lancet*, 362: 1142-51.

**Appears This Way  
On Original**

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

LaRee Tracy  
3/8/05 09:35:23 AM  
BIOMETRICS

Karen Higgins  
3/8/05 01:14:33 PM  
BIOMETRICS



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF BIOSTATISTICS

## Statistical Review and Evaluation CLINICAL STUDIES

NDA: 21-506

Name of drug: Micafungin Sodium (FK463) for injection. — .50 mg

Applicant: Fujisawa Healthcare, Inc.

Indication: Prophylaxis of — in patients undergoing  
hematopoietic stem cell transplantation

Documents reviewed: Summary, Statistical sections for Study 50 and CRT for  
Study 50 from electronic submission received on May 2,  
2002 (\\Cdsesub1\n21506\N\_000\2002-04-29)

Project manager: Susan Peacock

Clinical reviewer: Ekopimo Ibia, M.D.

Dates: Received 4/29/2002; user fee (priority plus 3 month  
extension) 1/29/03

Statistical reviewer: Qian Li, Sc.D.

Statistics team leader: Karen Higgins, Sc.D.

Biometrics division director: Mohammad Huque, Ph.D.

Keywords: NDA review, clinical studies, one study application,  
robustness of evidence

1 Executive Summary of Statistical Findings	3
1.1 Conclusions and Recommendations	3
1.2 Overview of Clinical Program and Studies Reviewed	3
1.3 Principal Findings	3
2 Statistical Review and Evaluation of Evidence	4
2.1 Introduction and Background	4
2.2 Data Analyzed and Sources	4
2.3 Statistical Evaluation of Evidence on Efficacy / Safety	5
2.3.1 <i>Sponsor's Results and Conclusions</i>	5
2.3.2 <i>Statistical Methodologies</i>	7
2.3.3 <i>Detailed Review of Study 050</i>	7
2.3.3.1 <i>Study design</i>	7
2.3.3.2 <i>Efficacy and Safety Endpoints</i>	7
2.3.3.3 <i>Patient Populations</i>	8
2.3.3.4 <i>Statistical Methods</i>	8
2.3.3.5 <i>Patient Accounting Information</i>	9
2.3.3.6 <i>Demographic Information and Baseline Information</i>	10
2.3.3.7 <i>Study Duration and Concomitant Medication</i>	11
2.3.3.8 <i>Reviewer's Efficacy Analysis</i>	12
2.3.3.9 <i>Safety Analysis</i>	15
2.3.4 <i>Statistical Reviewer's Findings</i>	16
2.4 Findings in Special/Subgroup Populations	16
2.5 Statistical and Technical Issues	17
2.6 Statistical Evaluation of Collective Evidence	17
2.7 Conclusions and Recommendations	18

---

## 1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

---

### 1.1 CONCLUSIONS AND RECOMMENDATIONS

The one study submitted for the indication of prophylaxis of \_\_\_\_\_ in patients undergoing hematopoietic stem cell transplantation failed to provide robust evidence of the efficacy of FK463. It was recommended that the sponsor should provide further supporting evidence, such as an additional study focusing on special patient population.

### 1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

One multi-center, randomized, double blinded and controlled phase III study was conducted to evaluate the efficacy and safety of FK463 for prophylactic treatment of \_\_\_\_\_ in patients undergoing hematopoietic stem cell transplantation. Fluconazole was used as the control. The primary efficacy endpoint was the treatment success at the end of study. Treatment success was defined as the absence of a proven, probable or suspected fungal infection through the end of the therapy, absence of a proven or probable fungal infection through the end of study. Note that this control is not approved for this specific indication.

### 1.3 PRINCIPAL FINDINGS

In the full analysis set which consisted of 882 patients, 425 in the FK463 treatment arm and 457 in the fluconazole arm, according to the sponsor's analysis on the primary efficacy endpoint, the overall success rate for FK463 (80.0%) was statistically significantly higher than that for fluconazole (73.5%) at 0.05 level ( $p=0.023$  two-sided). However, it is the reviewer's opinion that this study did not provide robust statistical evidence to support FK463 for the indication of prophylaxis of \_\_\_\_\_. The reviewer had many concerns regarding the analysis of the study, for instance, issues in the definition of the primary efficacy endpoint and the duration of prophylaxis therapy. Adjusting issues identified in this review, the reviewer's analysis on the primary efficacy endpoint yielded a p-value of 0.087 for the difference of success rates between the two treatment groups.

In addition, there is no supporting evidence to strengthen this marginal efficacy result observed in this single phase III study. No difference was observed in breakthrough of fungal infections (probable and proven) between FK463 and fluconazole. No difference was observed in failure which consisted of investigator identified probable, proven, and suspected fungal infections between the two treatment groups. The difference in the suspected fungal infections between the two treatment groups was marginally significant at 0.05 level for two-sided p-values ( $p=0.046$ ) by the reviewer's analysis.

---

## 2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

---

### 2.1 INTRODUCTION AND BACKGROUND

This NDA submission pursues market approval of FK463 for the following indications:

1) Prophylaxis of \_\_\_\_\_ in patients undergoing hematopoietic stem cell transplantation.

2)

3)

The three indications were divided into three NDA pieces, NDA 21-506 for the indication of prophylaxis of \_\_\_\_\_

\_\_\_\_\_ This statistical review covers the efficacy and safety evaluation of FK463 for the indication of prophylaxis of \_\_\_\_\_ in patients undergoing hematopoietic stem cell transplantation.

For the indication of prophylaxis of \_\_\_\_\_, a phase III randomized double-blinded study (98-0-050/NIAID MSG 46, referred to as Study 50) and three dose response studies (97-0-041, 98-0-043 and FG463-21-03) were conducted in support of the use of FK463 for prophylaxis of \_\_\_\_\_. However, the dose response studies were different from the phase III studies in many aspects: different dose levels, different study duration, different patient populations, and smaller sample size relative to the phase III study. Because of these, only the phase III study will be reviewed in-depth. The three dose response studies will be reviewed briefly in the section of evaluating collective evidence.

For the other two treatment indications, \_\_\_\_\_, the sponsor submitted two uncontrolled studies with a literature review as control. Though this review will not discuss these two indications, the efficacy of a drug in treating fungal infections is important in understanding its efficacy as a prophylactic treatment. In medical officer's review of NDA \_\_\_\_\_ it was determined that there was insufficient evidence for the determination of efficacy for these two indications.

### 2.2 DATA ANALYZED AND SOURCES

Thirty-one SAS data sets for Study 50 were submitted (including ANTFMED requested by the reviewer). The following data sets were used during the review: ACCT, ADV, ANTFMED, COM, DEM, FORMATS, FUNGLDX, LABCHEM1, LABCHEM2, LABHEMA1, LABHEMA2, MEDS, OUTCOME, and RISK.

In general, we found that the data sets were in good quality. However, there were a few problems with the submitted data. Firstly, the sponsor did not provide all the formats that variables were associated with in the FORMATS data sets. Secondly, the sponsor did not provide adequate labels for certain variables. For example, the variable "STARTDT" in the FUNGLDX data set was labeled as "date of onset fungal infection". By checking the case report forms, we found that this variable was actually the starting date of empirical therapy for suspected fungal infections, which should have been at least 4 days after the date of onset of fungal infections. Since the sponsor used "STARTDT" to define if the suspected fungal infection occurred during the therapy or post-therapy period, many of the suspected fungal infections that occurred during therapy were mislabeled by the sponsor as occurring in post-therapy period in the FUNGLDX data sets. The sponsor seemed to have corrected this error in the OUTCOME data set.

### 2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

#### 2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

In the full analysis set (MITT population), according to the sponsor's analysis, the overall success rate for FK463 (80.0%) was statistically significantly higher than that for fluconazole (73.5%). The analysis results for the primary efficacy endpoint are listed in Table 1. The analysis based on per protocol population generated similar results.

Table 1: Primary efficacy response rates in different patient populations

	FK463 (n=425)	Fluconazole (n=457)	FK463 – Flucon.	95% CI for the difference
MITT	340 (80.0%)	336 (73.5%)	6.5%	(0.9%, 12.0%)
Per-protocol	322/397 (81.1%)	321/433 (74.1%)	7.0%	(1.3%, 12.6%)

Source: Table 12 from study report and Table 13.4.4.2 from the end-of-text table and listings.

*Reviewer's comments: The overall response rates in both treatment arms are much higher than the projected response rates used in the determination of the sample size. The rate of treatment success for fluconazole was expected to be 40% based on previous prophylactic trials in adult bone marrow transplant patients.*

A secondary endpoint was the comparison of the number of proven and probable fungal infections during the study. Based on a strict interpretation of the protocol-specified diagnostic criteria for proven and probable invasive fungal infection, the sponsor reported 7 breakthrough infections in the FK463 treatment arm as compared with 11 breakthrough infections in the fluconazole treatment arm. The overall difference of breakthrough invasive fungal infections was 0.8% between the two treatment arms, which was not statistically significant. All 18 patients who developed confirmed proven or probable systemic fungal infections had received allogeneic transplants. Table 2 presents detailed information about those infections by treatment groups, type of fungal infections, and treatment period. Table 3 presents the counts of infections by organism.

Table 2: Proven and probable fungal infection counts by treatment arms, type of infections and period

Presence of Systemic Fungal Infection	FK463 (n=425)	Fluconazole (n=457)
<i>During Entire Study (Treatment and Posttreatment)</i>		
<b>Overall</b>	7 (1.6%)	11 (2.4%)
<b>Proven</b>	6 (1.4%)	8 (1.8%)
<b>Probable</b>	1 (0.2%)	3 (0.7%)
<i>During Prophylactic Treatment</i>		
<b>Proven</b>	4 (0.9%)	5 (1.1%)
<b>Probable</b>	1 (0.2%)	3 (0.7%)
<i>During 4-Week Posttreatment</i>		
<b>Proven</b>	2 (0.5%)	3 (0.7%)
<b>Probable</b>	0 (0.0%)	0 (0.0%)

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).  
 Proven: includes biopsy-proven (with or without culture) invasive or disseminated fungal infection  
 Probable: includes patients with the characteristic clinical or radiologic (chest x-ray, CT scan, other) picture of pulmonary aspergillosis plus a positive BAL specimen.  
 Source: Appendix 14.7

Table 3: List of proven or probable fungal infections during the study by organism

Organism	FK463 (n=425)	Fluconazole (n=457)
<b>Proven</b>	6 (1.4%)	8 (1.8%)
<i>Aspergillus species</i>	0 (0.0%)	4 (0.9%)
<i>Candida species</i>	4 (0.9%)	2 (0.4%)
<i>Fusarium species</i>	1 (0.2%)	2 (0.4%)
<i>Zygomycetes species</i>	1 (0.2%)	0 (0.0%)
<b>Probable</b>	1 (0.2%)	3 (0.7%)
<i>Aspergillus species</i>	1 (0.2%)	3 (0.7%)

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).  
 Proven: includes biopsy-proven (with or without culture) invasive or disseminated fungal infection  
 Probable: includes patients with the characteristic clinical or radiologic (chest x-ray, CT scan, other) picture of pulmonary aspergillosis plus a positive BAL specimen.  
 Source: Appendix 14.7

An additional secondary endpoint was regarding suspected fungal infections. The sponsor reported that a total of 64/425 (15.1%) FK463 patients and 98/457 (21.4%) fluconazole patients received empirical antifungal therapy (p=0.024) during prophylaxis for a suspected fungal infection. Ten patients in each treatment group had suspected fungal infection during post treatment period.

The reviewer had some concerns regarding the sponsor's efficacy analysis. These concerns are addressed in Section 2.3.3.8.

### 2.3.2 STATISTICAL METHODOLOGIES

See Section 2.3.3.4. Detailed Review of Study 050

### 2.3.3 DETAILED REVIEW OF STUDY 050

#### 2.3.3.1 Study design

Study 050 was a multicenter, randomized, double-blinded, comparative Phase III study conducted to evaluate the efficacy and safety of FK463 50 mg in comparison to fluconazole 400mg for prophylaxis of \_\_\_\_\_ in patients undergoing a hematopoietic stem cell transplant. Both FK463 and fluconazole were administered intravenously once daily. It was planned to recruit 800 evaluable patients, 400 in each arm, from ages 6 months and older undergoing an autologous (for hematologic malignancies) or allogeneic hematopoietic stem cell transplant. FK463 was administered at 50mg/day (1.0 mg/kg/day for patients weighing <50 kg) and fluconazole was administered at 400 mg/day (8 mg/kg/day for patients weighing <50 kg). Study drug was initiated at the time when the transplant-conditioning regimen was initiated or within 48 hours of initiating the transplant-conditioning regimen. Study drugs were administered until patients had neutrophil recovery to a post nadir ANC of  $\geq 500$  cells/mm<sup>3</sup> for three consecutive days. At the investigator's discretion, study drug could be continued for up to 5 days following recovery from neutropenia. Patients might receive study drugs for a maximum of 42 days after transplant. A post treatment evaluation was conducted 4 weeks after the last dose.

#### 2.3.3.2 Efficacy and Safety Endpoints

Fungal infection assessments were made twice weekly during the treatment period and at 4 weeks following discontinuation of study drug. The primary efficacy variable was treatment success at the end of study. Treatment success was defined as the absence of a proven, probable or suspected fungal infection through the end of the therapy, absence of a proven or probable fungal infection through the end of study.

A suspected systemic fungal infection was established if all of the following criteria were met for at least 96 hours: neutropenia (ANC < 500 cells/mm<sup>3</sup>); persistent or recurrent fever ( $\geq 100.4^\circ\text{F}$ ,  $\geq 38.0^\circ\text{C}$ ) for which there was no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy.

*Reviewer's comment: In the original version of the study protocol, treatment success was defined including two additional conditions, that the patient did not discontinue study drug due to an adverse event related study drug and that the patient was alive at the end of study. These conditions were removed in the revised version of study protocol (dated 10/12/99, prior to the initiation of the study). Such changes in the primary endpoint were not considered appropriate since patients who were not alive at the end of the study should not be considered as treatment success by default, even if no proven, probable or suspected fungal infections were*

identified. Analysis based on an endpoint with deaths considered non-evaluable will be assessed in this review (see Section 2.3.3.8).

Other efficacy endpoints were:

1. the incidence of proven or probable systemic fungal infections during the study (treatment through 4 weeks post treatment);
2. the incidence of proven, probable or suspected systemic fungal infections through the end of therapy;
3. the incidence of proven or probable systemic fungal infections during the post treatment period for patients who did not have a systemic fungal infection through the end of therapy;
4. the incidence of proven or probable systemic fungal infections during the study by organism.
5. the incidence of the use of systemic antifungal agents during the post treatment period;
6. the time to treatment failure during the study;
7. the time to suspected fungal infection;
8. the incidence of superficial fungal infections through the end of therapy;
9. the incidence of fungal colonization at baseline and at the end of therapy.

Safety assessment was based upon adverse events, laboratory profile, and vital signs.

#### *2.3.3.3 Patient Populations*

Two analysis populations were defined in this protocol. They were full analysis set (also known as safety analysis set or modified intent to treat population -- MITT) and per protocol set.

The full analysis set included those patients who received at least 1 dose of study drug. The primary efficacy analysis was performed on the full analysis set.

The per protocol set included all randomized patients who received at least one dose of study drug and who were deemed evaluable following patient classification criteria. Patient classification criteria were determined by the sponsor prior to unblinding the study. The criteria can be found in the Analysis Plan in the Statistical Method section of Appendix III of the study report. Analysis based on the per protocol set was a confirmatory analysis.

#### *2.3.3.4 Statistical Methods*

Randomization was stratified by study center, age (6 months to 12 years of age or 13 years of age and older), and type of transplant (autologous, matched-sibling allogeneic or any other allogeneic transplant). Patients receiving an allogeneic transplant was further stratified by risk of transplant related mortality (low risk or high risk).

The sample size estimation was based on the primary endpoint, treatment success at the end of the study. The rate of treatment success for fluconazole was estimated to be 40% based on previous prophylactic trials in adult bone marrow transplant patients with fluconazole. It

was estimated that 400 patients per treatment group would provide at least 80% power at a one-sided 2.5% significance level to demonstrate that FK463 is not inferior to fluconazole using a 10% non-inferiority margin, i.e., that FK463 is not more than 10% worse than fluconazole.

The sponsor's defined primary analysis was to construct a two-sided 95% confidence interval for the difference of success rates and test for non-inferiority using a 10% non-inferiority margin, i.e., testing that FK463 is not more than 10% worse than fluconazole. If the lower bound exceeded 0, the sponsor would conclude FK463 was statistically superior to fluconazole.

*Reviewer's comments: Since fluconazole does not have the indication studied in this trial, superior treatment difference for FK463 over fluconazole was required to show clinical benefit of FK463 for the prophylaxis of \_\_\_\_\_ in patients undergoing hematopoietic stem cell transplant.*

Chi-square tests or Cochran-Mantel-Hanszel (CMH) tests stratified by randomization strata, gender, and age were used in the analyses of secondary endpoints. The weighted test defined in sponsor's original statistical analysis plan will also be performed.

#### 2.3.3.5 Patient Accounting Information

A total of 1267 patients were screened from 70 sites in the United States and Canada and 889 were randomized into the study. A total of 426 patients were randomized to FK463 and 463 to fluconazole. The full analysis set comprised of 882 patients; 425 in the FK463 treatment arm and 457 in the fluconazole arm. The study was conducted between the period of Nov. 23, 1999 and Dec. 12, 2000. Patient accounting information is given in Table 4.

Table 4: Patient Accounting Information for Study 050

	FK463	Fluconazole	Total
All randomized patients	426	463	889
Completed Study	402 (94.4%)	428 (92.4%)	
Death	18 (4.2%)	27* (5.8%)	
Lost to follow-up	5 (1.2%)	3 (0.6%)	
Never received therapy	1 (0.2%)	5 (1.1%)	
Full analysis set	425 (99.8%)	457 (98.7%)	882 (99.2%)
Completed study	319 (75.1%)	310 (67.8%)	
Discontinued therapy	106 (24.9%)	147 (32.2%)	
Adverse event	18 (4.2%)	33 (7.2%)	
Lack of efficacy	75 (17.6%)	107 (23.4%)	
Administrative	13 (3.1%)	7 (1.5%)	
Per protocol set	397 (93.2%)	433 (93.5%)	830 (93.4%)

\* One patient (0203614) died before the administration of the study drug;  
 Sources: Table 2, Table 3 & Table 4 from Study Report for Protocol No. 98-0050.

Two patients in the FK463 treatment arm, Patient numbers 0572502 and 0793001, received study drug but never underwent transplants. The sponsor has classified the two patients as successes and included them in the MITT analysis. In the reviewer's analysis, the outcomes of the two patients were changed to non-evaluable in the MITT analysis (see Section 2.3.3.8).

In the category of discontinued therapy, the difference of withdrawal due to lack of efficacy between the two treatment groups was driven by the institution of empirical antifungal therapy for suspected fungal infections (see Table 5 below): 61(14.4%) in the FK463 treatment group and 94 (20.6%) in the fluconazole treatment. Issues regarding empirical therapy use and suspected fungal infections are discussed in Section 2.3.3.8.

Table 5: Patient withdrawal due to lack of efficacy.

	FK463 (N=425)	Fluconazole (N=457)
Total	75 (17.6%)	107 (23.4%)
Empirical antifungal therapy instituted	61 (14.4%)	94 (20.6%)
Probable fungal infection	8 (1.9%)	6 (1.3%)
Proven fungal infection	6 (1.4%)	7 (1.5%)

Source: Table 13.1.2 from Study Report for protocol No. 98-0050.

*2.3.3.6 Demographic Information and Baseline Information*

The majority of the patients were Caucasian (FK463 91.1%, fluconazole 89.9%). Approximately 60% of patients in both treatment arms were male. The study comprised 84/882 (9.5%) pediatric patients (<16 years of age) and 56/882 (6.3%) elderly patients (≥65 years of age). There were no statistically significant differences between the two treatment arms in terms of gender, race, age and weight.

The types of transplant that patients received were slightly imbalanced across the two arms. There were more allogeneic patients in fluconazole arm than that in FK463 arm, 256/457 (56.0%) in fluconazole and 220/425 (51.8%) in FK463. Table 6 gives the patient distribution by type of transplant and age. Numerically, there were more patients in high risk of transplant related mortality in fluconazole treatment group, 152/457 (33.3%), compared to that in the FK463 treatment group, 127/425 (29.9%).

**APPEARS THIS WAY  
 ON ORIGINAL**

Table 6: Patient distribution among types of transplant by treatment

Type of Transplant	FK463 (n=425)	Fluconazole (n=457)
<i>All Patients</i>		
Autologous or Syngeneic	203 (47.8%)	201 (44.0%)
Allogeneic	220 (51.8%)	256 (56.0%)
Matched Sibling	131 (30.8%)	160 (35.0%)
Other Donor	89 (20.9%)	96 (21.0%)
None	2 (0.5%)†	0 (0.0%)
<i>Adult Patients (≥16 years of age)</i>		
Autologous or Syngeneic	201 (47.3%)	199 (43.5%)
Allogeneic	183 (43.1%)	213 (46.6%)
Matched Sibling	117 (27.5%)	148 (32.4%)
Other Donor	66 (15.5%)	65 (14.2%)
None	2 (0.5%)†	0 (0.0%)
<i>Pediatric Patients (&lt;16 years of age)</i>		
Autologous or Syngeneic	2 (0.5%)	2 (0.4%)
Allogeneic	37 (8.7%)	43 (9.4%)
Matched Sibling	14 (3.3%)	12 (2.6%)
Other Donor	23 (5.4%)	31 (6.8%)

Patient base: patients who received at least 1 dose of study drug (full analysis set).

† Patient Numbers 0572502 and 0793001 received study drug but never received a transplant.

Source: Table 13.2.5.1 from the end-of-text tables and listings

The two treatment arms were comparable in terms of underlying disease and the disease status (active, remission, and relapse). The use of antifungal therapy prior to study drug administration was similar between treatment groups.

#### 2.3.3.7 Study Duration and Concomitant Medication

In the adult group, the mean duration of therapy was similar between the two treatment arms. The median duration was 18 days. The median duration of therapy for patients receiving an autologous or syngeneic transplant was 16 days for both treatment arms. The median duration for patients receiving an allogeneic transplant was 21 days for patients in the FK463 treatment arm and 20 days for patients in the fluconazole arm.

The duration of therapy was slightly higher in the pediatric patient population, comprised primarily of allogeneic transplant patients, but was still similar between treatment arms. The median duration was 22 days and 21 days for the FK463 arm and the fluconazole arm, respectively.

The use of immunosuppressant medication was similar across treatment arms during therapy. The use of both cyclosporine and/or tacrolimus during the treatment period for prevention or treatment of GVHD was similar between treatment arms.

2.3.3.8 Reviewer's Efficacy Analysis

There were a number of concerns regarding the sponsor's efficacy analysis. This section will review these concerns. The concerns on the secondary endpoints will be addressed first as they will have direct impact on the analysis of the primary endpoint. The re-analysis of the primary endpoint is given at the end, which reflects the cumulative effect of the issues identified in this study.

Probable and proven fungal infections:

Note that of the 12 investigator-reported probable invasive fungal infections not confirmed by a blinded assessment from an independent reviewer, 9 of the 12 patients were in the FK463 treatment group and 3 were in the fluconazole group.

The medical reviewer's assessment agreed with the assessment of the independent reviewer in majority of the cases. They only differed in three cases. Patient 0052505 from the FK463 group should be changed to non-evaluable from a confirmed probable fungal infection. Patient 0133502 from the fluconazole treatment group should be changed to non-evaluable from a confirmed proven fungal infection in the full analysis data set and removed from the per protocol data set. Patient 0572528 in FK463 should be changed to probable fungal infection from proven fungal infection. Details of these cases are explained in the medical officer's review.

Suspected fungal infections:

By examining the cases of suspected fungal infections identified by the sponsor, it can be seen that many cases had received only 4 days or less of empirical therapy for their suspected fungal infections. There were 18 patients in the FK463 treatment arm and 30 such cases in fluconazole arm. There were about equal number of patients in both treatment arms who had treatment duration longer than 9 days. The distribution on the duration of empirical therapy for the suspected fungal infections is listed in Table 7.

Table 7: Distribution on the duration of empirical therapy for suspected fungal infections by treatment.

	Missing n (%)	≤4days n (%)	5-8 days n (%)	≥9 days n (%)
FK463	2 (3%)	18 (28%)	11(17%)	32 (50%)
Fluconazole	5 (5%)	30 (31%)	28(29%)	35 (36%)

\*As percentage of all suspected fungal infections

There were 39 patients (provided by the medical reviewer instead of 40 patients reported in the study report) who started empirical therapy before the 96-hour protocol specified waiting period. Fifteen of those patients were from the FK463 arm and 24 from the fluconazole arm. Because of such violations, the outcomes of the 39 patients are changed to non-evaluable in the MITT population, but were removed from the per protocol analysis. If

these patients are removed from the suspected fungal infection count, the rates of suspected fungal infections become 49/425 (11.5%) for FK463 and 74/457 (16.2%) for fluconazole (p=0.046, two-sided).

Failures:

Patients who developed probable, proven, or suspected fungal infections were classified as failure. The analysis for failures was also re-analyzed due to the adjustment in the suspected fungal infections. The adjustments of the numbers in proven and probable fungal infection are discussed above regarding proven/probable fungal infections. The result of the analysis was presented in Table 8. Note the difference in failure between treatment groups was not statistically significant at level of 0.05 for two-sided p-value (p= 0.140 by chi-square test).

Table 8: Failure counts

	FK463 (425)	Fluconazole (457)
Proven	5	7
Probable	10	6
Suspected fungal infection on therapy	49	74
Total	64 (15.1%)	87 (19.0%)

Primary efficacy endpoint:

The primary endpoint in the original protocol also included in the definition of success that the patient did not discontinue study drug due to an adverse event related to study drug and that the patient did not die during the study. However, in a protocol amendment the sponsor removed these criteria for determining success. We believe that it is not appropriate to consider deaths as successes. Since the true outcomes were censored by the death, we performed an analysis by classifying the patients as non-evaluable in the MITT population and removing these patients from the per protocol population. Of the 18 FK463 deaths, 6 were considered successes. Of the 26 fluconazole deaths, 8 were considered successes. Two of these 8 patients died outside of the 4 week post therapy window and will therefore not be changed to non-evaluable in the following analysis.

During the review, it was found that many patients discontinued the prophylaxis therapy prematurely after a very short duration of treatment. Some patients received treatment for less than 8 days. The clinical relevance of such length of antifungal prophylaxis is uncertain according to the medical reviewer. Most of these patients also took other systemic antifungal therapy after the discontinuation of test drugs. Yet those patients were classified as treatment success. There were 9 such patients in the FK463 arm and 6 in the fluconazole arm. In the reviewer's analysis, the outcomes of these patients were changed to non-evaluable.

Based on the previous discussion, the following tables give re-analyses of the primary endpoint for both the MITT analysis (Table 9) and the per protocol analysis (Table 10). The columns of results in both tables are cumulative effect of the problems adjusted. The problems and data adjustments are explained in detail at the end of each table.

Table 9: MITT analyses for the primary endpoint:

Problems	# of success removed		Results		p-value
	FK463	Fluco.	FK463	Fluconazole	
			(425)	(457)	
Original success rates <sup>(1)</sup>			340 (80.0%)	336 (73.5%)	0.023
Patients without transplant <sup>(2)</sup>	2	0	338 (79.5%)	336 (73.5%)	0.036
Death during study <sup>(3)</sup>	6	6	332 (78.1%)	330 (72.2%)	0.043
On-therapy duration ≤7 days <sup>(4)</sup>	9	6	323 (76.0%)	324 (70.9%)	0.087

- (1) Original success rates: reported by the sponsor in the full analysis data set;
- (2) Patient without transplant: Patients 0572502 and 0793001 never underwent transplant. The outcomes of the two patients were changed from success to non-evaluable (N/A);
- (3) Death during study: For patients who died during study period (on therapy + 4 weeks post therapy), the patients should not be classified as successes since the patient's outcome was censored by the death. There were 6 patients who died during study and classified as success by the sponsor in each treatment group. The outcomes of those patients were changed to N/A;
- (4) On-therapy duration ≤7 days: 9 patients in FK463 and 6 in fluconazole discontinued therapy in 7 days or less without meeting the study criteria for successful stopping of antifungal prophylaxis (i.e., recovery from neutropenia). They then took other systemic antifungal therapy. Those patients were classified as successes in the primary efficacy variable by the sponsor. In this re-analysis, the outcomes of those patients are changed from success to N/A;

The 95% CI for the difference of success rates (FK463-fluconazole =5.1%) after the corrections discussed above was [-0.7%, 10.9%].

Table 10: Per protocol analysis for the primary endpoint.

Problems	# of success removed/ # removed from PP		Results		p-value
	FK463	Fluco.	FK463	Fluconazole	
Original success rates <sup>(1)</sup>			322/397 (81.1%)	321/433 (74.1%)	0.016
Death during study <sup>(2)</sup>	6/6	6/6	316/391 (80.8%)	315/427 (73.8%)	0.017
On-therapy duration ≤7 days <sup>(3)</sup>	4/4	1/1	312/387 (80.6%)	314/426 (73.7%)	0.019
Started empirical therapy early <sup>(4)</sup>	0/13	0/23	312/374 (83.4%)	314/403 (77.9%)	0.053
Removing one patients <sup>(5)</sup>	0/0	0/1	312/374 (83.4%)	314/402 (78.1%)	0.061

- (1) Original success rates: reported by the sponsor in the per protocol analysis data set;
- (2) Death during study: For patients died during study period (on therapy + 4 weeks post therapy), the patients should not be classified as success since the patient's outcome was censored by the death. There were 6 patients who died during study and classified as success by the sponsor in each treatment group. These patients are removed from the per protocol population.
- (3) On-therapy duration ≤7 days: 4 patients in FK463 and 1 in fluconazole discontinued therapy in 7 days or less. They then took other systemic antifungal therapy. Those patients were classified as success in the primary efficacy variable by the sponsor. In this re-analysis, those patients are removed from per protocol population.

- (4) In per protocol data sets, 13 patients from FK463 and 23 from fluconazole violated protocol to receive empirical therapy early. Those patients are removed from the per protocol population.
- (5) Remove two patients: Patient 0133502 are removed from the per protocol population. Patient 0133502 from fluconazole was removed from denominator since this patient was a failure. The details of the three cases were discussed in the proven/probable fungal infection section above.

The 95%CI for the difference of success rates (FK463-fluconazole =5.3%) was [-0.3%, 10.8%] after the corrections.

As can be seen from both Tables 9 and 10, adjusting all the problems identified, the analysis for the primary efficacy variable based on the MITT population yielded a p-value of 0.087 and a p-value of 0.061 based on the per protocol population. Stratified analyses (CMH and weighted tests) based on the stratification factors, age groups and types of transplant were also performed, no striking difference from the unstratified analyses was observed. The reviewer's sensitivity analyses suggested that the treatment difference between FK463 and fluconazole was not robustly large. The statistical evidence for FK463 prophylactically treating fungal infections with patients undergoing hematopoietic stem cell transplant was not convincing.

#### *2.3.3.9 Safety Analysis*

Requested by the medical reviewer, two sets of analyses on safety endpoints were conducted.

One set was to compare the adverse event rates for those patients who received study drugs concomitantly with the following drug families: corticosteroids, cyclosporine, tacrolimus, and midazolam versus that for those who did not take concomitant medicine. The adverse event rates were compared by treatment groups and body systems. Reviewed by the medical reviewer, the majority of the results from the analyses did not reveal clinical meaningful differences in AE rates between patients who took those concomitant medications and who did not. However, less patients in the FK463 arm experienced adverse events in metabolic system (47/60, 78.3%) compared to that in fluconazole arm (62/67, 92.5%) in patients who did not take the above mentioned concomitant medications. Analysis by preferred terms for this body system did not reveal important difference.

Another set of analyses was also performed to compare the rates of out of range laboratory values between treatment groups during therapy and during the entire study period. Those laboratory parameters includes hemoglobin less than 8, reticulocyte count greater than 4%, bilirubin greater than 5, SGOT>200, SGPT>200, alkaline phosphatase >400, and serum creatinine >3. All the values are in domestic units. Again those analyses did not show any safety signal for FK463 per the medical reviewer.

Please see the medical review for a complete discussion of safety.

### 2.3.4 STATISTICAL REVIEWER'S FINDINGS

The reviewer had many concerns regarding the analysis of the study. The definition of the primary endpoint which considered some deaths as successes, the early discontinuations, and the protocol violations all weakened the overall results of the trial.

### 2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor had conducted several subgroup analyses on the primary efficacy endpoint in the MITT population, including allogeneic versus autologous/syngeneic, present versus absent of GVHD, <16 years old versus ≥16 years, <65 years old versus ≥65 years, male versus female, and colonized versus not colonized. The results of the subgroup analyses are displayed in Table 11.

Table 11: Subgroup analyses in MITT population.

Subsets in ITT	FK463 (n=425)	Fluconazole (n=457)	FK463 -Flucon.
Allogeneic	157/220 (71.4%)	175/256 (68.4%)	3.0%
Autologous/syn	181/203 (89.2%)	161/201 (80.1%)	9.1%
GVHD Present	65/96 (67.7%)	58/102 (56.9%)	10.8%
GVHD Absent	275/329 (83.6%)	278/355 (78.3%)	5.3%
<16 years	27/39 (69.2%)	24/45 (53.3%)	15.9%
≥16 years	313/386 (81.1%)	312/412 (75.7%)	5.4%
<65 years	308/392 (78.6%)	320/434 (73.7%)	4.9%
≥65years	32/33 (97.0%)	16/23 (69.6%)	27.4%
Male	203/253 (80.2%)	205/274 (74.8%)	5.4%
Female	137/172 (79.7%)	131/183 (71.6%)	8.1%
Colonized	211/266 (79.3%)	183/241 (75.9%)	3.4%
Not colonized	129/159 (81.1%)	153/216 (70.8%)	10.3%

Source: Tables 13-16 from the study report.

As can be seen from the table, several subgroups showed large treatment differences. The large treatment differences were observed in the subgroups who had autologous/syngeneic transplant, who presented GVHD, who were younger than 16 or older than 65 years old, and who did not have colonized fungal infections.

As the primary analysis on the efficacy endpoint was not robust, it is necessary to explore which subgroups drive the treatment difference in the MITT population. In turn, these analyses can provide guidance for future study design. However, bear in mind that those exploratory analyses can not be used for confirmatory purposes in this NDA submission, as the primary analyses did not show convincing statistical evidence. The convincing statistical evidence is discussed in the section of collective evidence (see Section 2.6).

## 2.5 STATISTICAL AND TECHNICAL ISSUES

No statistical and technical issue is addressed in this review.

## 2.6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

The sponsor is required to provide substantial evidence for an efficacy claim according to regulatory requirement. The substantial evidence is usually interpreted to provide statistically significant results from two well-controlled phase III trials at the level of 0.025 for one-sided p-values. When only one trial is conducted without any supporting evidence, the statistical significance level should be at  $0.025^2$  so that the evidence from a single trial is equivalent to that obtained from two trials. In addition, this single trial should also provide reasonable consistent treatment effect among subgroups. Clearly, the only phase III trial in this NDA, Study 50, failed to provide convincing evidence alone since the significance level for this single trial is marginally around 0.05 for a two-sided p-value. Furthermore, the efficacy of FK463 as an antifungal treatment has not yet been determined based on the reviews of NDAs. It became necessary to collect all possible evidence to see if the results observed in Study 50 can be strengthened from other studies. For this purpose, the study design and results of the three dose-response studies (97-0-41, 98-0-043, and FG463-21-03) are briefly summarized in here.

Study 97-0-41 is a double blinded and randomized Phase I/II study to determine the maximum tolerated dose and pharmacokinetics of FK 463 in combination with fluconazole for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. Only 79 patients were recruited in this study. The dose of FK 463 was from 12.5, 25, 50, 75, 100, 150, to 200 mg/day. In the full analysis set, 41.7% (5/12) of control patients compared with 22.6% (14/62) of FK463 treated patients had a suspected fungal infection by the end of treatment. One patient (Patient Number 063109, 12.5 mg/day dose level) was discontinued due to a suspected fungal infection during treatment and was diagnosed with a probable fungal infection (histoplasmosis) on Day 20 (post-treatment). Two patients developed proven fungal infections that were detected in the post-treatment period: Patient Number 085403 (75 mg/day dose level) developed a pulmonary *Cunninghamella bertholletia* infection and Patient Number 063410 (75 mg/day dose level) had evidence of intestinal candidiasis on autopsy which was not confirmed by microscopic evaluation.

Study 98-0-043 is an open label, sequential group, dose-escalation Phase I study to determine the safety and pharmacokinetics of FK463 in febrile neutropenic pediatric patients age 2-7 years. The dose level of FK 463 was from 1.0 to 4.0 mg/kg per day. A total of 78 patients were enrolled in this study. A total of 27.3% (21/77) patients had a suspected systemic infection by the end of therapy. No probable or proven infections occurred during the study.

Study FG463-21-03 is an open label, sequential, dose escalation Phase I/II study to determine the safety profile, the maximum tolerated dose and pharmacokinetics of FK 463 for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. The dose level of FK 463 was from 3.0 to 8.0 mg/kg per day.

A total of 36 patients were enrolled into this study. There were 30.6% (11/36) patients had a suspected fungal infection. No probable or proven infections occurred during the study.

The results of these three dose-response studies do not strengthen the evidence obtained in Study 50 for the following reasons. Only one study contained a comparator, however, it was too small to reach any meaningful conclusion. The dose and duration of the studies varied from the primary study, the patient populations were different and the rate of suspected fungal infections for FK463 were higher than that seen in study 050.

## 2.7 CONCLUSIONS AND RECOMMENDATIONS

The one study submitted for this indication failed to provide convincing evidence of the efficacy of FK463 as a prophylactic agent of \_\_\_\_\_ in patients undergoing hematopoietic stem cell transplantation. The analyses on the primary efficacy endpoint, the sponsor's analysis, yielded a p-value of 0.023. However, this was a problematic due to issues in the definition of primary efficacy endpoint, assessment of proven and probable infections, and duration of prophylaxis therapy. A sensitivity analysis conducted by the reviewer yielded a p-value of 0.087. No difference was observed in breakthrough of fungal infections (probable and proven) between FK463 and fluconazole. No difference was observed in failure analysis which consisted of investigator identified probable, proven, and suspected fungal infections between the two treatment groups. The difference in the suspected fungal infections between the two treatment groups was only marginally significant at 0.05 level for two-sided p-values ( $p=0.046$ ) by the reviewer's analysis. Furthermore, efficacy was not shown in the treatment of patients with \_\_\_\_\_ candidiasis (see medical reviews of \_\_\_\_\_). This information could have helped to support a prophylactic indication.

Subgroup analyses suggested that FK463 might be more efficacious compared to fluconazole in some special subgroups for the indication studied in this NDA. It was recommended that the sponsor should further explore the potential subgroups to which the prophylaxis treatment can benefit the most. It is possible to design a relatively small study focusing a special patient population to strengthen the evidence observed in Study 50.

**APPEARS THIS WAY  
ON ORIGINAL**

)

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Qian Li  
1/29/03 12:53:28 PM  
BIOMETRICS

Karen Higgins  
1/29/03 01:20:32 PM  
BIOMETRICS

Aloka Chakravarty  
1/31/03 02:17:51 PM  
BIOMETRICS

)