

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-003**

**STATISTICAL REVIEW(S)**



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

# ADDENDUM TO STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 22-003/N000

**Drug Name:** Posaconazole Oral Suspension

**Indication(s):** Prophylaxis of Invasive Fungal Infections

**Applicant:** Schering-Plough Research Institute

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**Project Manager:** Kristen Miller, Pharm.D.

**Keywords:** DSI, Labeling

## 1. Introduction

This is an addendum to the statistical review of NDA 22-003 for Posaconazole oral suspension for the indication of prophylaxis of invasive fungal infections dated June 22, 2006. This addendum will report the results of the primary analysis for one of the two pivotal studies excluding one investigator whom the Division of Scientific Investigation (DSI) deems unreliable. The addendum will also include labeling recommendations for the clinical studies section of the label.

Two comparative Phase III studies were conducted using posaconazole as prophylaxis for the prevention of invasive fungal infections in high risk patients. C/I98-316 was a randomized double-blind active controlled trial of posaconazole versus fluconazole as control in HSCT recipients receiving high-dose immunosuppressive therapy for graft-versus-host disease (GVHD). Study P01899 was a randomized, open label, active controlled trial of posaconazole versus fluconazole or itraconazole as control (by center) in acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) patients with severe, prolonged neutropenia due to remission-induction chemotherapy.

Based on the inspection results, DSI considers that the data from \_\_\_\_\_ site \_\_\_\_\_ are not reliable. This investigator enrolled 23 subjects into study C/I98-316. Section 2 reports the results of the primary analysis excluding this site.

Section 3 reports suggestions for the drug label and section 4 contains a corrected table from the original statistical review dated June 22, 2006.

For details of the study design, analysis, and results, please see complete statistical review dated June 22, 2006. For details of the DSI inspection, please see DSI review.

## 2. Primary Analysis without Site \_\_\_\_\_

The Division of Special Pathogen and Transplant Products based on the results of an inspection by the Division of Scientific Investigation requested that the primary analysis of study C/I98-316, a pivotal study in NDA 22-003, exclude all subjects enrolled from \_\_\_\_\_

The rate of clinical success of site \_\_\_\_\_ along with the rate of clinical success of study C/I98-316 excluding this site are reported in the following table. Clinical failure was defined in the protocol as the occurrence of a proven or probable invasive fungal infection (IFI), receipt of more than 5 days of empiric treatment with a systemic antifungal drug other than the study drug during the Primary Time Period, or discontinuation from the Primary Time Period (i.e., subject not followed for the entire duration of the period). These results are for all randomized patients during the primary time period. The primary time period is from randomization to day 112 (i.e., 16 weeks).

**Table 1: Study C/I98-316 Primary Results Excluding Site —**

	Sponsor's Endpoint of Clinical Success (FDA primary)	
	Posaconazole	Fluconazole
Complete Study Results 95.01% Confidence Interval*	202/301 (67%) (-2.7, 12.2)	189/299 (63%)
Study results excluding site — 95.01% Confidence Interval*	8/12 (67%) 194/289 (67%) (-3.4, 11.8)	7/11 (64%) 182/288 (63%)

\* 95.01% confidence interval of the difference of posaconazole minus fluconazole using a normal approximation adjusted by baseline stratification factor GVHD (acute or chronic). See original review for details of statistical methods. Note that 3 subjects with missing stratification information were considered as ACUTE in these analyses.

Study results removing site — broken down by reason for failure are given here in Table 2. The results excluding site — are not qualitatively different than those results with site — included. The overall statistical conclusions remain unchanged from those in the original statistical review.

**Table 2: Analysis of Clinical Failure during the primary time period (All randomized Patients)**

	Clinical Response	
	Posaconazole (N=289)	Fluconazole (N=288)
	n (%)	n (%)
Clinical Success	194 (67%)	182 (63%)
Clinical Failure	95 (33%)	106 (37%)
Due to		
IFI	16	25
Death*	56	57
Use of Systemic Therapy	10	10
Not followed	23	30
95.01% CI for the difference in success rates	(-3.4, 11.8)	

\*: 10 posaconazole patients and 16 fluconazole patients were counted in both IFI and death. All other outcomes are ranked by order in the table.

#95.01% confidence interval of the difference of posaconazole minus fluconazole using a normal approximation adjusted by baseline stratification factor as described in the original statistical review. Note that 3 patients with missing stratification information were considered ACUTE for these analyses.

### 3. Labeling Recommendations

In this section is the suggested text for the clinical studies section of the posaconazole labeling. Note that these suggestions follow the 2006 Guidance titled “Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.”

Note that the definition of the primary endpoint for study 2 (P01899) reported in the table below is based on the clinical team’s analysis reported in the medical officer’s review. Currently only the primary time points for each study are included, through 16 weeks for

study 1 and on therapy plus 7 days for study 2. However, if the clinical team feels that it is most appropriate to have both an “on therapy” time point along with a fixed time point for both studies, we recommend that they be included without confidence intervals.

## CLINICAL STUDIES

### Prophylaxis of *Aspergillus* and *Candida* Infections

Two randomized, controlled studies were conducted using posaconazole as prophylaxis for the prevention of invasive fungal infections (IFIs) among patients at high risk due to severely compromised immune systems.

The first study (Study 1) was a randomized, double-blind trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic anti-fungal therapy. (Patients may have met more than one of these criteria.) Study 1 assessed all patients while on study therapy plus 7 days and at 16 weeks post-randomization. The mean duration of therapy was comparable between the two treatment groups (80 days, posaconazole; 77 days, fluconazole). **TABLE 5** contains the results from Study 1.

**TABLE 5. Results from Blinded Clinical Study 1 in Prophylaxis of IFI in All Randomized Patients with hematopoietic stem cell transplant (HSCT) and graft-vs-host disease (GVHD)**

	Posaconazole n = 289	Fluconazole n = 288
<i>Through 16 weeks</i>		
Clinical Failure <sup>a,d</sup>	95 (33%)	106 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	25 (9%)
( <i>Aspergillus</i> )	7 (2%)	19 (7%)
( <i>Candida</i> )	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths	56 (19%)	57 (20%)
Proven / probable fungal infection prior to death	10 (3%)	16 (5%)
SAF <sup>b,c</sup>	10 (9%)	10 (10%)
Event free lost to follow-up <sup>e</sup>	23 (8%)	30 (10%)
a: Patients may have met more than one criteria defining failure. b: SAF – systemic antifungal therapy c: Use of SAF criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days), subjects counted who did not have an IFI or death. d: 95% confidence interval (posaconazole-fluconazole) = (-11.8%, +3.4%) e: Patients who are lost to follow-up (not observed for 112 days), and who did not meet another clinical failure endpoint. These patients were considered failures.		

There were fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients receiving fluconazole. Overall mortality at 16 weeks was similar [POS 58/301 (19%) vs. FLU 59/299 (20%)].

The second study (Study 2) was a randomized, open-label study that compared posaconazole oral suspension (200 mg three times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes. As in Study 1, efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic anti-fungal therapy. (Patients might have met more than one of these criteria.) Study 2 assessed patients while on treatment plus 7 days and 100 days post-randomization. The mean duration of therapy was comparable between the two treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole). **TABLE 6** contains the results from Study 2.

**TABLE 6. Results from Open Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with hematologic malignancy and prolonged neutropenia**

	Posaconazole n = 304	Fluconazole/Itraconazole n = 298
<i>On therapy plus 7 days</i>		
Clinical Failure <sup>a,b</sup>	87 (29%)	137 (46%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
( <i>Aspergillus</i> )	2 (1%)	20 (7%)
( <i>Candida</i> )	3 (1%)	2 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	18 (6%)	26 (9%)
Proven / probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF <sup>c,d</sup>	63 (21%)	88 (30%)
a: 95% confidence interval (posaconazole-fluconazole/ itraconazole) = (-25.3%, -10.1%). b: Patients may have met more than one criteria defining failure. c: SAF – systemic antifungal therapy d: Use of SAF criterion is based on protocol definition (empiric/IFI usage >3 consecutive days), subjects counted who did not have an IFI or death..		

Aspergillosis was the most common breakthrough infection. There were fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients receiving fluconazole or itraconazole [2/304 (1%) vs. 20/298 (7%)]. A decrease in all cause mortality at day 100 was observed in favor of posaconazole [POS 44/304 (14%) vs. FLU/ITZ 64/298 (21%)].

Posaconazole is not indicated for the treatment of invasive fungal infections.

For information on a pharmacokinetic / pharmacodynamic analysis of patient data see **CLINICAL PHARMACOLOGY, Exposure Response Relationship**.

#### 4. Errata

During the re-analysis of study C/I98-316 a slight error in a table 11 of the original review was found. The breakdown for reason for failure was one patient off in two categories. The original review reported 24 patients “Not followed” in the posaconazole arm instead of 10 and 9 patients in the “Use of Systemic Therapy” row in the fluconazole arm instead of 30. The overall numbers of clinical success and failure were reported correctly in the original review so this change does alter any qualitative conclusions or any confidence intervals reported originally.

**Table 11: Analysis of Clinical Failure during the primary time period (All randomized Patients)**

	Clinical Response	
	Posaconazole (N=301)	Fluconazole (N=299)
	n (%)	n (%)
Clinical Success	202 (67%)	189 (63%)
Clinical Failure	99 (33%)	110 (37%)
Due to		
IFI	16	27
Death*	58	59
Use of Systemic Therapy	10	9
Not followed	10	30
95.01% CI for the difference in success rates	(-2.7, 12.2)	

\*16 posaconazole patients and 16 fluconazole patients were counted in both IFI and death. All other outcomes are ranked by order in the table.

#95.01% confidence interval of the difference of posaconazole minus fluconazole using a normal approximation adjusted by baseline stratification factor as described in the original statistical review. Note that 3 patients with missing stratification information were considered ACUTE for these analyses.

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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:** 22-003/N000

**Drug Name:** Posaconazole Oral Suspension

**Indication(s):** Prophylaxis of Invasive Fungal Infections

**Applicant:** Schering-Plough Research Institute

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**Keywords:** Non-inferiority studies, composite endpoints, missing data

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- 2> Analysis of prophylaxis for aspergillosis alone
- 3> Non-inferiority design with comparators not approved for the indication sought by the applicant (namely all invasive fungal infections)
- 4> Justification for the non-inferiority margin
- 5> Limitations of statistical methods to resolve issues of concentration-response relationship found by the clinical pharmacology reviewer

These issues are discussed in detail in Section 5.1.1. Furthermore, on June 20, 2006, the clinical team decided to redefine the clinical success endpoint that would be included in the drug label. Use of this redefined endpoint (not reported in this review) does not change the qualitative conclusions of the studies from the results that are reported here.

The following table provides a summary of clinical success rates for the two studies (C/I98-316 and P01899). For study C/I98-316, clinical failure was defined in the protocol as the occurrence of a proven or probable IFI, receipt of more than 5 days of empiric treatment with a systemic antifungal drug other than the study drug during the Primary Time Period, or discontinuation from the Primary Time Period (i.e., subject not followed for the entire duration of the period). For study P01899, clinical failure was defined by the review team as follows: occurrence of a proven or probable IFI, receipt of 4 or more days of empiric treatment with another antifungal for suspected IFI, use of IV alternative antifungal medication for >3 consecutive days or  $\geq 10$  cumulative days, discontinuation due to an AE regardless of determination of causality, discontinuation due to treatment failure, withdrawn from the study for any reason, lost to follow-up during the oral treatment phase (oral treatment plus 7 days) or death during the oral treatment phase. Note that the review team redefined the sponsor's defined clinical failure for study P01899 since in the sponsor's analysis some patients who died were not considered clinical failures and since the sponsor only included discontinuations due to *drug-related* adverse events in the definition of failure.

**Table 1: Summary of study results for C/198-316 and P01899 (All Randomized Subjects)**

	C/198-316*		P01899*	
	Posaconazole (N=301)	Fluconazole (N=299)	Posaconazole (N=304)	Flu/Itra (N=298)
	n (%)	n (%)	n (%)	n (%)
Clinical Success	202 (67%)	189 (63%)	166 (55%)	126 (42%)
Clinical Failure*	99 (33%)	110 (37%)	138 (45%)	172 (58%)
Due to				
IFI	16	27	7	25
Death**	58	59	18	26
Use of Systemic Therapy	10	9	63	88
Not followed/discontinued	24	30	51	35
CI for the difference***	(-2.7, 12.2)		(4.3, 20.1)	

\*: Primary time point is at 16 weeks for study C/198-316 and at end of oral therapy plus 7 days for study P01899.

\*\* : For study C/198-316, 10 posaconazole patients and 16 fluconazole patients were counted as both IFI and death. For study P01899, 1 posaconazole patient and 2 control patients were counted as both IFI and death. All other outcomes are ranked by order in the table.

\*\*\*: 95.01% CI for study C/198-316 and 95.13% CI for study P01899

## 2. INTRODUCTION

### 2.1 Overview

Posaconazole is a triazole antifungal that has been developed for the treatment and prophylaxis of fungal infections. This current submission, NDA 22-003, is for the following \_\_\_\_\_ :

NOXAFIL (posaconazole) is indicated for prophylaxis of invasive fungal infections, \_\_\_\_\_ in patients, 13 years of age and older, who are at high risk of developing these infections, such as hematopoietic stem cell transplant (HSCT) recipients or those with prolonged neutropenia.

On December 21, 2005 the sponsor submitted this current NDA (22-003) for the indication prophylaxis of fungal infections and NDA 22-027 for the indication of treatment of oropharyngeal candidiasis. At that time the sponsor requested priority review of posaconazole based on the "randomized clinical trials in the prophylaxis of

life-threatening invasive fungal infections (IFI) including both yeasts and moulds.” The medical division granted NDA 22-003 a priority review for the indication of prophylaxis of invasive fungal infections.

Two comparative Phase III studies were conducted using posaconazole as prophylaxis for the prevention of invasive fungal infections in high risk patients. C/I98-316 was a randomized double-blind active controlled trial of posaconazole versus fluconazole as control in HSCT recipients receiving high-dose immunosuppressive therapy for graft-versus-host disease (GVHD). Study P01899 was a randomized, open label, active controlled trial of posaconazole versus fluconazole or itraconazole as control (by center) in acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) patients with severe, prolonged neutropenia due to remission-induction chemotherapy. The sponsor’s primary outcome in these two studies was incidence of proven and probable IFIs during a 112 day period (for C/I98-316) or during the on-treatment period (for P01899). Note that the division considers patients who die or receive therapy for empiric treatment of an IFI as failures as well.

These studies will be discussed in detail in this review.

## 2.2 Data Sources

The sponsor submitted the results of two Phase III studies to support the use of posaconazole for prophylaxis of invasive fungal infections. Data sets for both studies were submitted electronically and were used in the review of these studies. The locations of these data sets are as follows:

\\Cdsub1\N22003\N\_000\2005-12-21\m5\53-clin-stud-rep\537-crf-ipl\study-report-c98316

and

\\Cdsub1\N22003\N\_000\2005-12-21\m5\53-clin-stud-rep\537-crf-ipl\study-report-p01899

*Note that for study C/I98-316, the notation “C” designates the US protocol and “I” designates the international protocol; however, they contain exactly the same content.*

All submitted data sets were found to be adequately documented.

### **3. STATISTICAL EVALUATION**

This submission contains two controlled studies (P01899 and C/98-316) submitted to support efficacy of posaconazole for the prophylaxis of invasive fungal infections.

#### **3.1 Evaluation of Efficacy**

##### **3.1.1. Study C/198-316**

###### **3.1.1.1 Study Design and Endpoints**

This was a phase 3, randomized, multi-center, double-blind (double-dummy), active control, parallel group, non-inferiority study of posaconazole (200 mg TID) versus fluconazole (400 mg QD) for the prophylaxis of invasive fungal infections (IFI) in high-risk subjects with graft-versus-host disease (GVHD) following allogeneic stem cell transplantation.

The primary objective of the study was to assess the efficacy of posaconazole versus fluconazole in preventing proven or probable IFI within the time period from randomization to 16 weeks after start of study drug.

Approximately 600 subjects were to be enrolled at approximately 85 study sites in North America, South America, Europe, South Africa, Singapore, Saudi Arabia, and Australia. Randomization was stratified by site and by type of GVHD (acute or chronic). The treatment duration was 16 weeks or until discontinuation. All subjects including those who discontinued the treatment were to be followed for the full 16-weeks treatment phase and the 2-month follow-up.

If, during treatment, subjects were unable to take oral study medication, study drug (suspension and capsules) may have been withheld until such time that oral medication (suspension and capsules) could be resumed. Non-azole systemic antifungal prophylaxis could be substituted during such an interruption of study drug (empiric therapy), but could not be administered for more than 5 days.

If at any time during the study a patient developed a fever or any other sign of invasive fungal infection a complete evaluation to determine the cause was to be performed. This included signs and symptoms, physical exam, blood count, culture, and/or histopathology of suspicious site of infection, urinalysis, and other clinical/laboratory evaluation. All subjects were then characterized as having either no IFI, possible IFI, probable IFI, or proven IFI. The investigator then determined how the patient should be managed clinically including whether patients required systemic antifungal therapy.

All subjects who were considered failures (determined by investigator or >5 days of systemic antifungal use) or were classified by the investigator as possible, probable, or proven IFI were to be referred to a panel of external, independent, experts in the area of opportunistic infections in transplant recipients in the USA, the Data Review Committee (DRC), for adjudication. The members of the DRC were blinded to the subject's treatment assignment. DRC adjudicated the subject's IFI status prior to database lock based on the evidence collected in case report forms.

A clinical failure was defined as either the DRC adjudicated presence of a proven or probable IFI or more than 5 days of empiric treatment with a systemic antifungal other than assigned study drug within 16 weeks of start of treatment with study drug. Subjects not followed for the entire 16-week treatment phase were also considered failures in the secondary efficacy analyses.

*It appears from this definition and the results of the study that treatment discontinuations would continue to be followed for outcome and not automatically considered as clinical failures.*

Key terms relating to times of observations or measurements were as follows:

**Baseline Date:** Date of first dose for treated subjects and date of randomization for subjects randomized but not treated.

**Start Date:** Date of first dose of study treatment.

**Stop Date:** Date of last dose of study treatment.

**Baseline:** Last measurement on or prior to Baseline Date.

**End of Treatment:** Last non-missing post-baseline measurement on or before Stop Date + 7.

**Primary Time Period:** Interval of time which begins on the Randomization Date and ends on the Baseline Date + 111 days.

**While on Treatment:** Interval of time which begins on the first day of treatment and ends on the last day of treatment + 7 days.

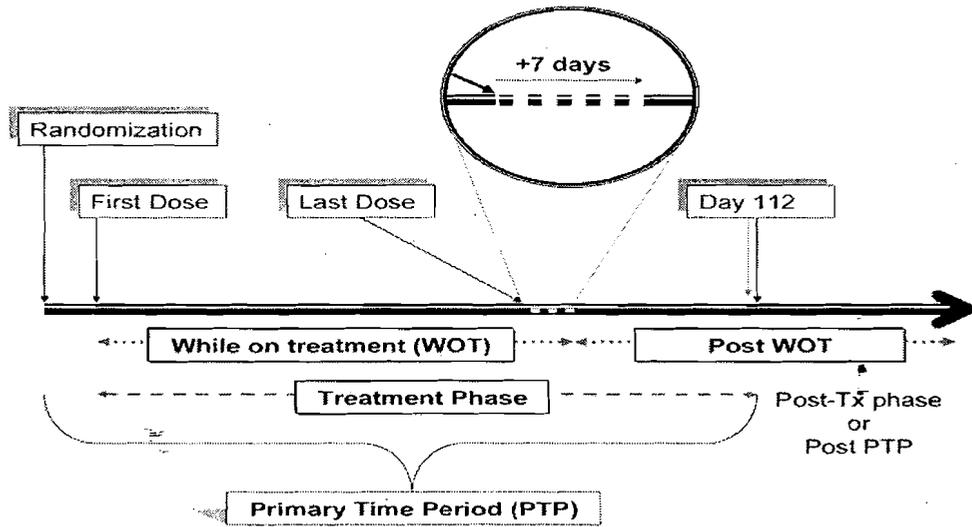
**Post While on Treatment:** Interval of time which begins on the last day of treatment + 8 days and ends on the last contact date.

**Treatment Phase:** Interval of time which begins on the Baseline Date and ends on the Baseline Date + 111 days.

**Follow-up to Primary Time Period:** Interval of time which begins on Baseline Date + 112 days and ends on the last contact date.

The following figure, Figure 1, depicting these terms is extracted from the applicant's study report (figure 2, page 47).

Figure 1: Study Period Diagram Study C/I98-316



The primary analysis population for the efficacy evaluation was the population of all randomized patients. The protocol-specified time period to be used for the primary efficacy analysis was the “Primary Time Period”. The protocol specified primary efficacy variable was defined as the DRC-adjudicated incidence of proven or probable invasive fungal infections.

*The review team had major concerns that the applicant’s primary efficacy variable did not include patients who died or were empirically treated with other systemic antifungal agents in addition to the study medication as failures. Due to this concern the reviewer’s analysis will focus on the endpoint clinical failure, which considers these patients as failures along with those with IFI. Please see section 5.1 for a discussion of this issue.*

The protocol specified primary efficacy analysis was based on a non-inferiority design based on the odds ratio adjusted for the stratification factor of acute versus chronic GVHD. If the upper limit of the 95.01% confidence interval (adjusted for two interim analyses) does not exceed a maximum value of 15% for a percent difference in incidence rates with respect to the incidence seen with fluconazole. See appendix for sponsor’s discussion of the computation of the maximum value.

The sponsor stated that an active control, non-inferiority study design versus fluconazole was chosen because a placebo control trial was not considered ethical and fluconazole was shown to be effective in preventing IFIs in subjects undergoing hematopoietic stem cell transplantation in the literature (Slavin<sup>1</sup> and Goodman<sup>2</sup>).

Fluconazole is approved in the US and Europe for prophylaxis of candidiasis in subjects undergoing bone marrow transplantation.

*At the protocol stage (IND 51662 N248) the medical division informed the applicant that since the comparator, fluconazole, is not approved for the broad indication proposed by the applicant (including aspergillus infections), a non-inferiority analysis would not be able to support the efficacy of posaconazole for the broad indication and that a superiority analysis would be needed to provide evidence that posaconazole is effective for invasive fungal infections (see Section 5.1).*

During the review of this NDA it was determined that the sponsor did not provide an adequate discussion of the non-inferiority margin used in this study. On 4/24/06 a fax was sent to the sponsor asking for this justification. The sponsor responded to this request on 5/23/06. The sponsor acknowledged the difficulty in determining an adequate non-inferiority margin for this indication and patient population. They referenced an article by Slavin<sup>1</sup> published in 1995.

*It is not clear if this reference study is similar enough to the current study to provide adequate justification for a 15% non-inferiority margin for a percent difference. This issue is discussed further in Section 5.1 Statistical Issues.*

The study design allowed for two interim analyses conducted in order to detect superiority of posaconazole at an early time point with significance levels adjusted in accordance with the O'Brien- Fleming procedure. The study was not stopped at either of these time points and the final analysis was carried out at a 0.0499 significance level.

Note that the sponsor defined additional populations for analysis including an efficacy evaluable and a modified intent to treat (defined after final protocol amendment). However, this reviewer considered only the all randomized population which was stated as primary in the protocol.

### **3.1.1.2 Study Populations**

As stated before, a total of 600 subjects were enrolled and randomized in a 1:1 ratio (301 to posaconazole and 299 to fluconazole) at 90 sites of whom 21 did not receive study medication (10 in posaconazole arm and 11 in fluconazole arm). The study began on March 1, 1999 and ended on February 27, 2003. The following table gives a summary of the patient disposition in the all randomized subject population.

**Table 2: Disposition of Patients (All Randomized Subjects)**

Disposition	Posaconazole (n=301)	Fluconazole (n=299)
Completed Treatment	165 (55%)	144 (48%)
Discontinued Treatment, but followed for the Primary Time period	42 (14%)	48 (13%)
Discontinued Treatment, AND not followed for the entire Primary Time Period	94 (31%)	105 (35%)

The following table gives a summary of reasons for treatment discontinuations.

**Table 3: Reason's for treatment discontinuations (all Randomized Patients)**

Reason for Treatment Discontinuation	Posaconazole (n=301)	Fluconazole (n=299)
Discontinued	136 (45%)	155 (52%)
Administrative	0	1
Adverse Event	100	98
Treatment Failure	8	24
In-Eligible	3	7
Non-Compliance	8	10
Did not wish to continue	17	15

The following table gives a summary of treatment duration and shows that the distribution of this factor was similar for the two treatment groups.

**Table 4: Distribution of Treatment Duration (all Randomized Patients)**

	Posaconazole (n=301)	Fluconazole (n=299)
Number treated	291	288
Treatment Duration (days):		
Mean (s.d.)	80 (42.88)	77 (42.71)
Median	111	108
Number of patients with treatment duration*:		
< 50 days (%)	90 (31.0%)	90 (31%)
50-100 days (%)	57 (19.5%)	69 (24%)
100 or more days (%)	144 (49.5%)	129 (45%)

\*: Percentage calculated out of number treated.

### 3.1.1.3 Demographic and Other Baseline Characteristics

All tables in this section have been derived from the sponsor's study report. The following table shows the distribution of subjects by demographic factors. The distribution of demographic characteristics is similar for the two treatment groups.

**Table 5: Demographic Characteristics of Subjects (All randomized Patients)**

Demographic Characteristic	Posaconazole (n=301)	Fluconazole (n=299)
Age (years)		
< 18 years	4 (1%)	8 (3%)
18-64 years	292 (97%)	286 (96%)
> 64 years	5 (2%)	5 (2%)
Mean (SD)	42.2 (11.4)	40.4 (12.2)
Median	43.0	41.0
Range	13-72	13-70
Sex		
Female	98 (33%)	112 (37%)
Male	203 (67%)	187 (63%)
Race		
Caucasian	259 (86%)	246 (82%)
Black	12 (4%)	18 (6%)
Asian	9 (3%)	10 (3%)
Hispanic	19 (6%)	24 (8%)
Other	2 (1%)	1 (< 1%)
Weight (kg)		
Missing	9	11
Mean (SD)	72.43 (16.63)	72.48 (16.38)
Median	70.95	70.4
Range	39.0-150.4	39.0-139.1
Height (cm)		
Missing	21	20
Mean (SD)	172.05 (10.18)	170.5 (10.13)
Median	172.85	170.7
Range	147.3-193.0	137.0-195.5
Region		
United States	117 (39%)	121 (40%)
Non-United States	184 (61%)	178 (60%)

The following table shows the distribution of subjects by disease characteristics. The distribution of disease characteristics is similar for the two treatment groups.

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**Table 6: Distribution of subjects by baseline disease characteristics (All randomized patients)**

Primary Underlying Diagnosis <sup>a</sup>	Posaconazole (N=301)	Fluconazole (N=299)
	n (%)	n (%)
Acute Myelogenous/Non-lymphocytic Leukemia	81 (27)	66 (22)
Acute Lymphoblastic Leukemia	25 (8)	36 (12)
Chronic Myelogenous Leukemia	98 (33)	104 (35)
Myelodysplastic Disorder	19 (6)	13 (4)
Non-Hodgkin's Lymphoma	40 (13)	35 (12)
Hodgkin's Lymphoma	2 (1)	7 (2)
Multiple Myeloma	10 (3)	12 (4)
Aplastic Anemia	8 (3)	7 (2)
Chronic Lymphoblastic Leukemia	10 (3)	11 (4)
Other Leukemia	3 (1)	0
Other	9 (3)	9 (3)
None	0	1 (<1)
<b>GVHD Class at Baseline</b>		
Acute Grade 1	3 (1)	1 (<1)
Acute Grade 2	135 (45)	136 (45)
Acute Grade 3	52 (17)	54 (18)
Acute Grade 4	12 (4)	6 (2)
Chronic Limited	2 (1)	1 (<1)
Chronic Extensive	96 (32)	99 (33)
Missing	1 (<1)	2 (1)

a: Subjects with multiple primary diagnoses are counted in each primary diagnosis category.  
Source: Sponsor's study report table 17.

The following table shows distribution of subjects by other subject characteristics.

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**Table 7: Distribution of Subjects by Other Characteristics (All randomized Patients)**

<b>Other Characteristics</b>	<b>Posaconazole (N=301)</b>	<b>Fluconazole (N=299)</b>
	<b>n (%)</b>	<b>n (%)</b>
<b>ECOG Performance Status</b>		
Grade 0, 1, or 2	269 (89)	258 (86)
Grade 3 or 4	24 (8)	28 (9)
Missing	8 (3)	13 (4)
<b>Neutropenia (Baseline ANC &lt;500/mm<sup>3</sup>)</b>		
Yes	6 (2)	1 (<1)
No	277 (92)	280 (94)
Missing	18 (6)	18 (6)
<b>Maximum Duration of Neutropenia Since Transplant (Total Days)</b>		
> 30 Days	9 (3)	14 (%)
15 to 30 Days	123 (41)	121 (40)
≤15 Days or None	169 (56)	164 (55)
<b>CMV Positive During Treatment</b>	<b>96 (32)</b>	<b>78 (26)</b>
<b>Baseline Corticosteroids (mg/kg/day)</b>		
≥2.0	41 (14)	32 (11)
<2.0 but ≥1.0	107 (36)	129 (43)
<1.0 but ≥0.4	108 (36)	100 (33)
<0.4 but ≥0	34 (11)	27 (9)
Dose Unknown	10 (3)	10 (3)
None	1 (<1)	1 (<1)
<b>No. of Immunosuppressive Agents at Baseline</b>		
1	64 (21)	48 (16)
2	151 (50)	168 (56)
3 or more	85 (28)	82 (27)
None	1 (<1)	1 (<1)

Source: Sponsor's study report table 17.

The following table shows some additional patient characteristics.

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**Table 8: Distribution of Subjects by Other Characteristics**

	Posaconazole (N=301) n (%)	Fluconazole (N=299) n (%)
<b>Prior History of Invasive Yeast or Mould</b>	<b>8 (3)</b>	<b>15 (5)</b>
<b>Oral Swish Positive for Yeast at Baseline</b>	<b>95 (32)</b>	<b>85 (28)</b>
<b>Oral Swish Positive for Yeast During Treatment</b>		
Persistently	27 (9)	29 (10)
Intermittently	84 (28)	77 (26)
Negative	190 (63)	193 (65)
<b>T-cell Depleted Stem Cells Transplanted at Latest Transplant Prior to Study Entry</b>	37 (12)	32 (11)
<b>Body Irradiation on or before Transplant Date</b>	135 (45)	146 (49)
<b>Aspergillus Antigen at Baseline</b>		
Positive ( $\geq 0.5$ at Baseline)	21 (7)	30 (10)
None	259 (86)	243 (81)
Missing	21 (7)	26 (9)
<b>Duration of Prior Antifungal Therapy on or Before First Dose</b>		
$\leq 7$ days	109 (36)	116 (39)
7 to 13 days	30 (10)	17 (6)
$\geq 14$ days	162 (54)	166 (56)
Mean (STD)	26.4 (38.76)	35.3 (82.23)
Median	16	19
Range	0 – 254	0 - 1002

Source: Sponsor's study report table 17.

Tables 7 and 8 show some imbalances (difference of 4% or more) between the two arms with respect to risk factors CMV infection and oral swish positive for yeast at baseline (against posaconazole) and no aspergillus antigen at baseline and use of more than 1 immunosuppressive agent at baseline (in favor of posaconazole). In addition, there was observed imbalance in favor of posaconazole in terms of number of patients who did not have immunosuppression prior to or within 2 weeks after randomization (85(28%) posaconazole and 59 (20%) fluconazole, as reported in sponsor's study report). The factor of baseline immunosuppression in this patient population clearly has potential to affect the underlying risk of invasive fungal infection. Therefore even small observed imbalances with respect to this factor can introduce bias in the setting of this prevention study and leads to caution when interpreting the study results. Regarding the other factors which have not been as well characterized in terms of their relevance to the risk of invasive fungal infection, the presence of even small imbalances (commonly occurring despite randomization) with respect to these factors can make the results of a prevention study difficult to interpret.

### 3.1.1.4 Efficacy Analysis Results

The primary efficacy variable, as specified in the protocol, is the DRC adjudicated incidence of proven or probable IFI for All Randomized Subjects during the Primary Time Period (from randomization to 111 days after the first dose of study drug for subjects who were treated, or 112 days post randomization for subjects who were

randomized but not treated). All proven and probable DRC-adjudicated IFIs during the Primary Time Period are summarized according to the infecting pathogen in the following table. Note that the differences seen in the number of pathogens is mainly driven by probable aspergillosis.

**Table 9: Distribution of Proven/Probable IFI by Pathogen Group during Primary Time Period (All randomized patients)**

	Number of Subjects	
	Posaconazole	Fluconazole
<b>Proven</b>	<b>11</b>	<b>13</b>
<i>Aspergillus</i>	2	7
<i>Candida</i>	4	4
Other	5	2
Pseudallescheria	1	0
Rhizomucor miehei	0	1
Trichosporon beigeli	1	0
Scedosporium prolificans	1	0
Mould	2	1
<b>Probable</b>	<b>5</b>	<b>14</b>
<i>Aspergillus</i>	5	14
<i>Candida</i>	0	0
Other	0	0

Source: Sponsor's study report, table 20

The following table shows the applicant's primary efficacy analysis that meets the non-inferiority criterion prospectively set by the applicant in the protocol. The non-inferiority margin of a 15% relative difference corresponds to a margin of 1.1625 (see Appendix and Section 5.1.1).

**Table 10: Sponsor's Primary Efficacy Analysis**

Subjects With Proven/ Probable IFI During the Primary Time Period <sup>a</sup>		Odds Ratio	P-value	95.01% CI	Max Value <sup>b</sup>
POS N=301 n (%)	FLU N=299 n (%)				
16 (5)	27 (9)	0.5614	0.0740	0.2959 – 1.0651	1.1625

a: Interval of time which begins on the Randomization Date and ends on the Baseline Date + 111 days. Per protocol, the primary efficacy analysis was performed on All Randomized Subjects during this time period.

b: Calculated value corresponding to 15% relative difference in incidence of proven/probable IFI with respect to the incidence of fluconazole and the total number of proven/probable IFI observed.

CI = Confidence Interval; IFI = invasive fungal infection.

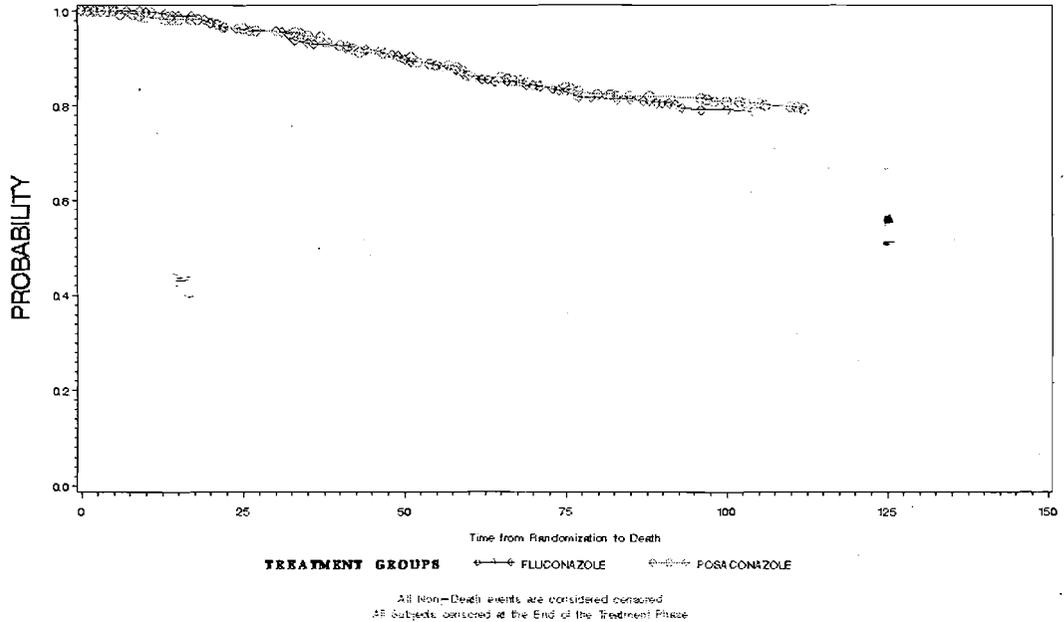
Source: Sponsor's study report, table 21

The sponsor conducted additional analyses of the primary endpoint using different analysis populations, including all treated, modified intent to treat and efficacy evaluable (per protocol). The all treated and modified intent to treat showed similar results to the all randomized population. However, the results for the efficacy evaluable population did not meet the sponsor's limit for non-inferiority.

The applicant also conducted an analysis of time to death during the treatment phase for all randomized subjects showing no statistically significant difference between the two

treatment groups (log-rank p-value= 0.8474). There did not appear to be any difference in the investigators-determined causes of death between the two arms. The following figure, Figure 2, is the sponsor's Kaplan-Meier graph from the study report (figure F-2.1, page 384).

**Figure 2: Kaplan-Meier Analysis of Time from Randomization to Death by Treatment Group for All Randomized Subjects, Study C/198-316**



The sponsor conducted an analysis of clinical failure as a secondary endpoint. Recall that clinical failure was defined in the protocol as the occurrence of a proven or probable IFI, receipt of more than 5 days of empiric treatment with a systemic antifungal drug other than the study drug during the Primary Time Period, or discontinuation from the Primary Time Period (i.e., subject not followed for the entire duration of the period). FDA's clinical review team defined clinical failure slightly differently as follows: occurrence of a proven or probable IFI or Death, receipt of more than 4 days of empiric treatment with a systemic antifungal drug other than the study drug, or discontinuation due to non-compliance, loss to follow-up, adverse event or for other reason. For both Sponsor's as well as FDA-defined clinical failure analysis adjusting for the interim analysis and for the stratification factor of classification (acute vs. chronic) of GVHD at baseline, showed no statistically significant difference between the two groups. This analysis is considered more valid than the analysis of IFI alone since many subjects received other antifungal medication for 4 or more consecutive days or more than 10 total days for empiric treatment. Note that there was no pre-specified non-inferiority margin for this endpoint. So the determination of non-inferiority is difficult in this setting. The following table reports these results.

**Table 11: Analysis of Clinical Failure during the primary time period (All randomized Patients)**

	Sponsor's definition		FDA definition	
	Posaconazole (N=301)	Fluconazole (N=299)	Posaconazole (N=301)	Fluconazole (N=299)
	n (%)	n (%)	n (%)	n (%)
Clinical Success	202 (67%)	189 (63%)	165 (55%)	150 (50%)
Clinical Failure	99 (33%)	110 (37%)	136 (45%)	149 (50%)
Due to				
IFI	16	27	16	27
Death*	58	59	58	59
Use of Systemic Therapy	10	9	11	10
Not followed/discontinued <sup>+</sup>	24	30	61	69
95.01% CI for the difference in success rates	(-2.7, 12.2)		(-3.0, 12.8)	

\*: 10 posaconazole patients and 16 fluconazole patients were counted in both IFI and death. All other outcomes are ranked by order in the table.

+ : "Not followed" applies to the sponsor's definition and "discontinued" applies to the FDA definition.

#95.01% confidence interval of the difference of posaconazole minus fluconazole using a normal approximation adjusted by baseline stratification factor as described by Fleiss<sup>6</sup>. Note that 3 patients with missing stratification information were considered ACUTE for these analyses.

*Note that from a statistical perspective these reviewers did not have concerns regarding the sponsor's defined clinical success endpoint. Since it was prospectively defined, we will use this endpoint as our "primary" endpoint. However, the FDA-defined endpoint was preferred by the clinical team and more closely matched the FDA-defined endpoint used in study P01899 as described in section 3.1.2. We consider this a sensitivity analysis and supportive of the sponsor's analysis of clinical success as the qualitative conclusions do not change.*

The following table (Source: Sponsor table 31 from study report) reports what medication patients received while on treatment. Notice that similar number of patients received antifungal therapy. Only patients who were on other antifungal medication for more than 4 or 5 days and who did not have a death or IFI were counted in the above table as failures.

**Table 12: Other Antifungal Medications patients received while on treatment (All Treated Patients)**

Medication	FOS N=291 N (%)	FLU N=268 N (%)
Any Antifungal	31 (11)	29 (10)
Amphotericin B	12 (4)	17 (6)
Ketoconazole	1 (<1)	0
Fluconazole	17 (6)	15 (5)
Itraconazole	3 (1)	3 (1)
Caspofungin Acetate	1 (<1)	4 (1)
Flucytosine	0	1 (<1)

While on Treatment = Interval of time which begins on the first day of treatment and ends on the last day of treatment + 7 days.

Note: A subject could have received more than one systemic antifungal medication.

*Note that the superiority of posaconazole was not achieved by the sponsor's primary analysis nor by the sponsor's analysis of clinical failure, considered more appropriate*

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by this reviewer. The sponsor does conduct an additional analysis of breakthrough invasive aspergillosis infections only and claims a superior result. Note that this is not considered a valid analysis as discussed in section 5.1.

The sponsor conducted many secondary analyses. These included analyses with the all randomized subject, all treated population, modified intent to treat population, efficacy evaluable population using time frames of the primary time period, treatment phase, while on treatment time period, post while on treatment time period and post treatment phase (for a total of 20 analyses). The sponsor found some results of these analyses with p-values < 0.05. In particular, the sponsor states that an analysis of all treated patients analyzed using a while on treatment time period (excluding the time prior to the start of therapy and time after end of therapy to 16 weeks) is a clinically meaningful timeframe. The sponsor found the results of this analysis to be significant. Note that the sponsor states in their study report regarding multiple comparisons and multiplicity that “(w)hile p-values and confidence intervals are provided for several other analyses, these are provided as supportive information and should be considered as such.”

### **3.1.2 Study P01899**

#### **3.1.2.1 Study Design and Endpoints**

This was a phase 3, randomized, multi-center, open-label, evaluator-blinded, active control, parallel group, non-inferiority study of posaconazole (200 mg TID) versus fluconazole (FLU 400 mg QD) or itraconazole (ITZ 200mg BID) for the prophylaxis of invasive fungal infections in high-risk subjects with prolonged neutropenia due to standard intensive induction chemotherapy given for a new diagnosis of acute myelogenous leukemia (AML), AML in first relapse, myelodysplastic syndromes (MDS), or other secondary myelogenous leukemias.

Prior to randomization of the first subject, each site was to designate the standard azole therapy (FLU or ITZ) that would be used for all subjects assigned to the reference arm at that site. Note that the choice of either FLU or ITZ as the comparator used at a site was guided by the incidence of mold infections at a particular hospital or clinic and the perceived risk of IFI. Subjects entering the study were to be stratified by site and primary diagnosis or condition: New diagnosis of AML/ AML in first relapse/ MDS or other diagnoses of secondary AML (therapy-related, antecedent hematological disorders).

Protocol-eligible subjects were then to be randomized in a 1:1 ratio to receive either 600 mg of POS (200 mg TID) or standard azole therapy (400 mg of FLU [400 mg QD] or 400 mg of ITZ [200 mg BID]). Treatment was to continue until recovery from neutropenia, complete remission, occurrence of an IFI, or other protocol-specified endpoints was reached, up to a maximal time period of 12 weeks or 84 calendar days from randomization, regardless of the number of days of dosing. Follow-up visits for all

subjects (including those who discontinued treatment early for any reason) were to occur 30 days after the last dose of study drug and 100 days after randomization. In the event of early discontinuation, all procedures and evaluations scheduled for the End-of-Treatment Visit were to be performed.

Subjects who developed a proven, probable, or possible IFI were to be discontinued from the study, and the outcome of the IFI was to be recorded at follow-up visits 100 days post randomization and 30 days post last dose. Subjects who received empiric antifungal therapy for fever of unclear origin may have received subsequent cycles of prophylaxis with study drug as long as there were no signs of active infection meeting the EORTC-MSG criteria for possible, probable, or proven IFI and all inclusion/exclusion criteria were satisfied.

Subjects who were temporarily unable to tolerate oral study drug may have received alternative intravenous (IV) antifungal therapy or an interruption in study drug administration for up to 3 days per cycle (or 10 days out of the total maximal treatment period of 84 days). Subjects who required more than 3 days of IV antifungal prophylaxis were to be considered non-evaluable per protocol, and were included in the "intent-to-treat" population for the primary efficacy analysis.

Acceptable IV alternatives were as follows:

- Subjects randomized to POS 200 mg oral suspension TID may have been treated with IV Amphotericin B (AMB deoxycholate, 0.3 to 0.5 mg/kg/day).
- Subjects randomized to standard azole therapy with FLU 400 mg oral suspension QD may have been switched to FLU 400 mg IV QD.
- Subjects randomized to standard azole therapy with ITZ 200 mg oral solution BID may have been switched to ITZ 200 mg IV BID.

Study drug was also to be temporarily discontinued in subjects undergoing a second course of anthracycline-based chemotherapy, until 24 hours after completion of the anthracycline component.

*The review team informed the applicant that alternative IV therapy should be the same between arms. Specifically, IV Amphotericin use should not be limited to the test arm only. However, the overall results of the study were not greatly affected by the use of different IV therapy.*

Subjects who required additional prophylaxis beyond the 12-week maximal treatment duration allowed per protocol may have been granted an extension for up to an additional 4 weeks if no drug-related AE or IFI was present.

Assessments of clinical response were to be based upon IFI incidence and clinical outcome of oral prophylaxis (treatment success or failure). The IFI status of each subject (no IFI; possible IFI; probable IFI; or proven IFI) was to be determined using

the criteria of the EORTC-MSG. For clinical management, the Investigator was to determine the subject's IFI status and characterize the subject's clinical course. For the purpose of statistical analyses, a panel of external evaluators (Data Review Committee [DRC]) was to determine the subject's IFI status. Members of the panel were physicians with expertise in the area of opportunistic infections in neutropenic subjects, and were blinded to the subject's treatment assignment. The panel was to review subject profiles consisting of clinical, microbiologic, laboratory, and radiologic data in the database to characterize the IFI status using EORTC-MSG standardized definitions.

A treatment failure was to be defined as the presence of a proven or probable IFI,  $\geq 4$  days of empiric parenteral (IV) antifungal treatment for a suspected IFI,  $>3$  consecutive days or  $\geq 10$  cumulative days of IV alternative study medication during the Treatment Phase, or discontinuation due to an AE considered possibly or probably related to study drug. Subjects who withdrew from the study for any reason and were subsequently lost to follow-up during the Treatment Phase were also to be considered treatment failures.

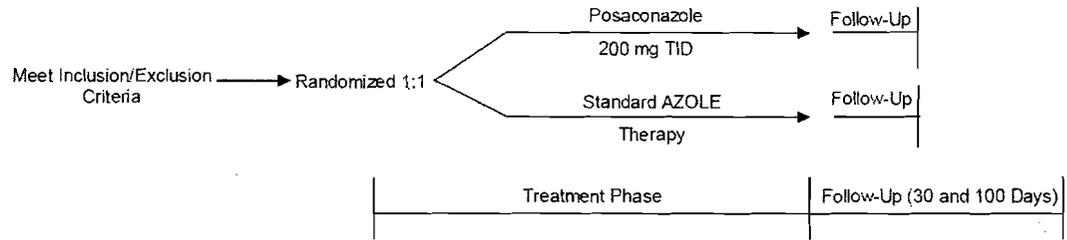
*There are concerns with the sponsor's definition of clinical failure. The sponsor has not considered all cause mortality in their definition. Furthermore, the sponsor limited treatment failure due to discontinuations to include only those due to an AE considered possibly or probably related to study drug. The determination of causality of AE is potentially biased and most often biased against the control arms since its adverse events profile is more widely known. See section 3.1.2.5 for reviewers' analysis of clinical failure.*

A total of 602 subjects were enrolled and randomized in 1:1 ratio (304 to posaconazole, 240 to fluconazole, 58 to itraconazole) at 89 sites of whom 13 did not receive study medication (7 in posaconazole arm and 6 in azole arm). Patients were enrolled in the study from North America, South America, Central America, Europe, South Africa, Dominican Republic, Puerto Rico, Singapore, and Australia from 8/8/02 to 4/5/05. Twenty-two (25%) sites were designated to use itraconazole as control. At these sites 65 patients were randomized to posaconazole and 58 to itraconazole. The remaining 67 (75%) sites used fluconazole as control and randomized 239 patients to posaconazole and 240 patients to fluconazole.

The following figure is extracted from the applicant's study report.

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**Figure 3: Study Period Diagram, Study P01899**



- Treatment is continued with each cycle of chemotherapy until clinical remission or other protocol-specified endpoints are reached, up to a maximum of 12 weeks or 84 calendar days from randomization.
- For each chemotherapy cycle, the first visit (Visit 2) is to be performed before the first dose of study drug.
- Follow-Up: 30 days after last dose date;  
100 days after randomization date.

The primary analysis population for the efficacy evaluation was the population of all randomized patients. The protocol-specified time period to be used for the primary efficacy analysis was the “Oral Treatment Phase” defined as the period from randomization to last dose of oral study medication plus 7 days or the discontinuation date for subjects randomized but never treated. The protocol specified primary efficacy variable was defined as the DRC-adjudicated incidence of proven or probable invasive fungal infections.

*During the review of the data analysis plan (IND 51662 N400) the review team informed the sponsor that patients who use systemic anti-fungal agents are not taken into consideration in the analysis of the primary endpoint and that they should be considered failures in the analysis of invasive fungal infections. Furthermore, comments stated that deaths due to all cause mortality should also be considered failures, as should patients who are lost to follow-up. The review also pointed out that it was not clear how missing data due to study drug discontinuation would be handled. The sponsor did not change the analysis of their primary endpoint based on these comments. Due to this concern the reviewer’s analysis will focus on the endpoint clinical failure defined as incidence of IFI, or use of other systemic antifungal agents in addition to the study medication, or discontinuations due to AE or deaths or loss to follow-up. Please see section 3.1.2.5 for this analysis and section 5.1 for a discussion of this issue.*

The protocol specified primary efficacy analysis was based on a non-inferiority design based on the difference between the treatment arms in terms of proven or probable IFI and a 4% non-inferiority margin on the difference in rates. The rationale stated by the applicant in the study report for the 4% margin in this study was based on one study in the literature.

*The review team informed the applicant that since the comparators, fluconazole and itraconazole, are not approved for the broad indication proposed by the applicant, a*

*non-inferiority analysis would not be able to support the efficacy of posaconazole and that a superiority analysis would be needed to provide evidence that posaconazole is effective. However, since as shown below, the results for this study support a superiority analysis the determination of a non-inferiority margin is not of great concern.*

The study design allowed for one interim analysis conducted when approximately 300 subjects completed the Treatment Phase in order to detect superiority of posaconazole at an early time point with significance levels adjusted in accordance with the O'Brien-Fleming procedure. The study was not stopped this time point and the final analysis was carried out at 0.0487 significance level and 95.13% confidence intervals were calculated.

*Note that the sponsor defined additional populations for analysis including an efficacy evaluable and a modified intent to treat (an all treated population). However, this reviewer considered only the all randomized population which was stated as primary in the protocol.*

### 3.1.2.2 Study Population

As stated before, a total of 602 subjects were enrolled and randomized in a 1:1 ratio (304 to posaconazole and 298 to fluconazole/itraconazole) at 110 sites of whom 13 did not receive study medication (7 in posaconazole arm and 6 in fluconazole/itraconazole arm). The following table gives a summary of the patient disposition in the all randomized subject population.

**Table 13: Disposition of Patients (All Randomized Subjects)**

Disposition	Posaconazole (n=304)	FLU/ITZ (n=298)
Completed Treatment Phase	159 (52%)	125 (42%)
Discontinued Treatment Phase	145 (48%)	173 (58%)
Entered Follow-Up	281 (92%)	275 (92%)
Completed Follow-Up	237 (77%)	220 (74%)

The following table gives a summary of reasons for treatment phase discontinuations.

**Table 14: Reason's for treatment phase discontinuations (all Randomized Patients)**

Reason for Treatment Discontinuation	Posaconazole (n=304)	FLU/ITZ (n=298)
Discontinued Treatment Phase	145 (48%)	173 (58%)
Administrative	1	0
Adverse Event	40	37
Treatment Failure	80	117
In-Eligible	3	3
Non-Compliance	6	4
Did not wish to continue	14	12
Lost to follow-up	1	0

As per the applicant's study report, three patients randomized to the posaconazole arm received treatment with fluconazole after their first cycle of chemotherapy and for one patient itraconazole was added to the posaconazole study treatment after the second cycle of chemotherapy. None of these patients developed IFI. These protocol deviations were not considered by the applicant to have had an impact on the study results.

The duration of therapy was similar between the two randomized arms. Thirteen subjects did not receive any randomized therapy (7 posaconazole subjects and 6 fluconazole/itraconazole subjects). Of those who received therapy the mean (SD) number of days of exposure of therapy was 28.9 (21.1) days for posaconazole and 24.9 (17.2) days for fluconazole/itraconazole. Eighty-eight percent of subjects in both arms received 7 or more days of treatment.

### **3.1.2.3 *Demographic and Other Subject Characteristics***

All tables in this section have been derived from the sponsor's study report. The following table shows the distribution of subjects by demographic factors. The distribution of demographic characteristics is similar for the two treatment groups.

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**Table 15: Demographic Characteristics of Subjects (All randomized Patients)**

Demographic Characteristic	POS (n=304)	FLU/ITZ (n=298)
Age (years)		
Mean (SD)	49 (16.5)	50 (16.1)
Median	53	53
Range	13 - 82	13 - 81
Age: Number (%) of Subjects		
<18 years	8 (3)	8 (3)
18 to <65 years	238 (78)	223 (75)
≥65 years	58 (19)	67 (22)
≤ Median age <sup>a</sup>	165 (54)	157 (53)
> Median age <sup>a</sup>	139 (46)	141 (47)
Race: Number (%) of Subjects		
Caucasian	220 (72)	231 (78)
Non-Caucasian	84 (28)	67 (22)
Black	16 (5)	9 (3)
Asian	13 (4)	9 (3)
Hispanic	51 (17)	47 (16)
Other <sup>b</sup>	4 (1)	2 (1)
Sex: Number (%) of Subjects		
Male	158 (52)	160 (54)
Female	146 (48)	138 (46)
Weight (kg)		
Mean (SD)	74 (18.6)	77 (17.9)
Median	72	75
Range	34 - 150	39 - 160
Missing	1 (<1)	7 (2)
Weight: Number (%) of Subjects		
<65 kg	95 (31)	83 (28)
≥65 to <85 kg	135 (44)	123 (41)
≥85 to <100 kg	50 (16)	62 (21)
≥100 kg	23 (8)	23 (8)
≤ Median weight <sup>a</sup>	167 (55)	136 (46)
> Median weight <sup>a</sup>	136 (45)	155 (52)
Region: Number (%) of Subjects		
US	81 (27)	78 (26)
Europe	125 (41)	127 (43)
Canada	14 (5)	14 (5)
Far East <sup>c</sup>	18 (6)	21 (7)
Latin America	66 (22)	58 (19)

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole; SD = standard deviation.

a: Pooled across all treatment groups.

b: Includes Indian, Native American, and mixed race.

c: Includes Australia and Singapore.

Source: Sponsor's study report table 13

The following table shows distribution of subjects by disease characteristics. The distribution of baseline disease characteristics is similar for the two treatment groups.

**Table 16: Distribution of subjects by baseline disease characteristics (All randomized patients)**

Baseline Characteristic	Number (%) of Subjects	
	POS (n=304)	FLU/ITZ (n=298)
Primary diagnosis at study entry		
AML (new diagnosis)	213 (70)	222 (74)
AML (first relapse)	42 (14)	38 (13)
MDS	49 (16)	38 (13)
Severity of neutropenia at Baseline		
Neutropenic	192 (63)	189 (63)
Severe neutropenia (ANC $\leq$ 100 cells/mm <sup>3</sup> )	73 (24)	71 (24)
Non-Severe neutropenia (ANC >100 cells/mm <sup>3</sup> to $\leq$ 500 cells/mm <sup>3</sup> )	119 (39)	118 (40)
Non-neutropenic (ANC $\geq$ 500 cells/mm <sup>3</sup> )	98 (32)	94 (32)
Missing or unknown	14 (5)	15 (5)
<i>Aspergillus</i> antigen status on or before first date of study drug <sup>a</sup>		
<0.5 GMI	230 (76)	231 (78)
0.5 - 1.5 GMI	8 (3)	7 (2)
>1.5 GMI	4 (1)	6 (2)
Missing or unknown	62 (20)	54 (18)
Colonization status at Baseline		
Negative	147 (48)	144 (48)
Positive	133 (44)	121 (41)
Missing or unknown	24 (8)	33 (11)
Use of systemic antifungals as prophylaxis prior to randomization		
No	262 (86)	256 (86)
Yes	42 (14)	42 (14)
1 to 3 days	32 (11)	31 (10)
4 to 7 days	5 (2)	7 (2)
>7 days	5 (2)	4 (1)
Mean (SD)	4 (7.4)	3 (5.4)
Median	1	1
Range	1 - 45	1 - 31
Mucositis score on or before first date of study drug <sup>a</sup>		
No mucositis	164 (54)	154 (52)
CTC Grade 1-2	93 (31)	97 (33)
CTC Grade 3-4	7 (2)	3 (1)
Missing or unknown	40 (13)	44 (15)

ANC = absolute neutrophil count; CTC = Common Toxicity Criteria; FLU = fluconazole; GMI = galactomannan index; ITZ = itraconazole; POS = posaconazole; SD = standard deviation.

a: For subjects who were randomized but not treated, result obtained on or before date of randomization is reported.

Source: Sponsor's study report table 14

The following three tables show distribution of subjects by important post-baseline subject characteristics and the use of systemic antifungal drugs during the study. These tables show that overall, important post-baseline characteristics were comparable between the treatment arms.

**Table 17: Distribution of Subjects by Post-baseline Characteristics (All randomized Patients)**

Post-Baseline Characteristic	Number (%) of Subjects	
	POS (n=304)	FLU/ITZ (n=298)
Total Chemotherapy Cycles Before or During the Treatment Phase		
1	174 (57)	182 (61)
2	96 (32)	89 (30)
3	34 (11)	25 (8)
4	0	2 (1)
Worst Neutropenia During the Treatment Phase		
Neutropenic	298 (98)	290 (97)
Severe Neutropenia (ANC $\leq 100$ cells/mm <sup>3</sup> )	264 (87)	261 (88)
Non-Severe Neutropenia (ANC $> 100$ cells/mm <sup>3</sup> to $\leq 500$ cells/mm <sup>3</sup> )	34 (11)	29 (10)
Non-Neutropenic (ANC $> 500$ cells/mm <sup>3</sup> )	1 (<1)	6 (2)
Missing or Unknown	5 (2)	2 (1)
Maximum Consecutive Days of Neutropenia During Treatment Phase		
0 to 7 days	25 (8)	26 (9)
>7 to 14 days	78 (26)	73 (24)
>14 to 21 days	98 (32)	115 (39)
>21 to 28 days	50 (16)	49 (16)
>28 days	53 (17)	35 (12)
N	304	298
Mean (SD)	20 (13.2)	18 (9.3)
Median	18	17
Minimum-Maximum	0 - 95	0 - 57

ANC = absolute neutrophil count; FLU = fluconazole; IFI = invasive fungal infection; ITZ = itraconazole;

Source: Sponsor's study report table 23

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**Table 18: Distribution of Subjects by use of SAF as empiric therapy for a suspected/proven IFI ( All Randomized Patients)**

SAF Used for the Treatment of a Suspected/Proven IFI	Number (%) of Subjects	
	POS (n=304)	FLU/ITZ (n=298)
No	223 (73)	186 (62)
Yes	81 (27)	112 (38)
1 to 3 days	12 (4)	9 (3)
4 to 7 days	32 (11)	60 (20)
>7 days	37 (12)	43 (14)
Mean (SD)	7 (3.0)	7 (2.1)
Median	7	7
Minimum-Maximum	1 - 24	1 - 17

FLU = fluconazole; IFI = invasive fungal infection; ITZ = itraconazole; POS = posaconazole; SAF = systemic antifungal therapy (other than study medication); SD = standard deviation.

Source: Sponsor's study report table 23

**Table 19: Distribution of Subjects by use of SAF for any reason (All Randomized Patients)**

Post-Baseline Characteristic	Number (%) of Subjects	
	POS (n=304)	FLU/ITZ (n=298)
SAF Used for Any Reason, Taken After First Day and Before Last Day of Study Drug		
No	278 (91)	276 (93)
Yes	26 (9)	22 (7)
1 to 3 days	12 (4)	14 (5)
4 to 7 days	8 (3)	4 (1)
>7 days	6 (2)	4 (1)
Mean (SD)	6 (7.1)	5 (8.5)
Median	4	2
Minimum-Maximum	1 - 28	1 - 39
Use of IV Study Medication		
No	287 (94)	268 (90)
Yes	17 (6)	30 (10)
1 to 3 days	11 (4)	18 (6)
4 to 7 days	4 (1)	8 (3)
>7 days	2 (1)	4 (1)
Mean (SD)	4 (3.8)	4 (4.3)
Median	3	3
Minimum-Maximum	1 - 13	1 - 22

FLU = fluconazole; IFI = invasive fungal infection; ITZ = itraconazole; POS = posaconazole; SAF = systemic antifungal therapy (other than study medication); SD = standard deviation.

Source: Sponsor's study report table 23

### 3.1.2.4 Applicant's Efficacy Analyses Results

The primary efficacy variable, as specified in the protocol and the data analysis plan, was the DRC-adjudicated incidence of proven or probable IFI for All Randomized Subjects from randomization to the end of the Oral Treatment Phase. The following table shows the applicant's primary efficacy analysis that meets the non-inferiority as well as statistical superiority criterion prospectively set by the applicant in the protocol.

**Table 20: Proven and Probable Fungal Infections during the oral treatment phase (All Randomized Patients)**

	Number (%) of Subjects		Difference	95.13% Confidence Interval for the Difference	P-Value
	POS (n=304)	FLU/ITZ (n=298)			
IFI	7 (2)	25 (8)	-6.09%	-9.68% to -2.50%	0.0009

FLU = fluconazole; IFI = invasive fungal infection; ITZ = itraconazole; POS = posaconazole.

Source: Table 15 of the sponsor's study report.

The sponsor conducted additional analyses using different analysis populations, including modified intent to treat and efficacy evaluable (per protocol). These showed similar results to the all randomized population. Results are also similar for the time frames 30 days post end of therapy and 100 days post randomization.

All proven and probable DRC-adjudicated IFIs during the primary time period are summarized according to the infecting pathogen in the following table. Once again as in Study C/198-316, the differences seen in the primary analysis is mainly driven by probable aspergillosis.

**Table 21: Distribution of Proven/Probable IFI by Pathogen during the Oral Treatment Phase**

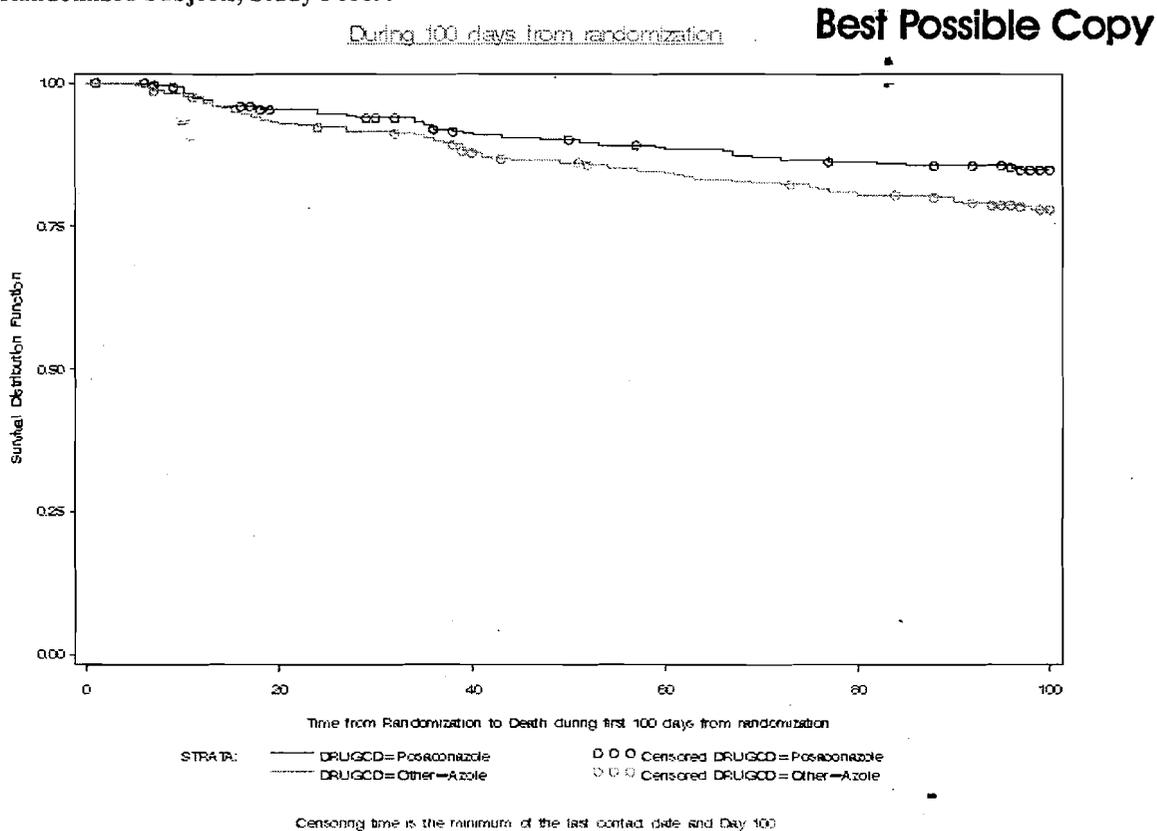
	Number of Subjects	
	Posaconazole	FLU/ITZ
<b>Proven</b>	<b>4</b>	<b>5</b>
<i>Aspergillus</i>	0	1
<i>Candida</i>	3	2
<i>Pseudallescheria</i>	0	1
<i>Zygomycetes</i>	0	1
Other	1	0
<b>Probable</b>	<b>3</b>	<b>20</b>
<i>Aspergillus</i>	2	19
<i>Candida</i>	0	0
Other	1	1

*The sponsor does conduct an additional analysis of breakthrough invasive aspergillosis infections only and they claim a superior result for this analysis as well. Note that this is not considered a valid analysis as discussed in section 5.1.*

The protocol stated that mortality will be recorded for the treatment phase and follow-up periods (30 days post-treatment and 100 days after randomization). The sponsor did

not report the analysis of time to death for the treatment phase, but reports that there was no statistically significant difference between treatment groups for the period 30 days post-treatment. The applicant's analysis of time to death during the period from randomization to 100 days post randomization for all randomized subjects showed a statistically significant difference between the two treatment groups (log-rank p-value= 0.0354). In this analysis, all subjects who were alive at 100 days post-randomization were censored at Day 100 or at the last follow-up observation in the case of premature discontinuation. The following figure, Figure 4, is the applicant's Kaplan-Meier graph from the study report (figure 5 in sponsor's study report, page 118).

**Figure 4: Kaplan-Meier Analysis of Time from Randomization to Death by Treatment Group for All Randomized Subjects, Study P01899**



The sponsor conducted an analysis of clinical failure as a secondary endpoint. Recall that clinical failure was defined in the protocol as the presence of a proven or probable IFI,  $\geq 4$  days of empiric parenteral (IV) antifungal treatment for a suspected IFI,  $>3$  consecutive days or  $\geq 10$  cumulative days of IV alternative study medication during the Treatment Phase, or discontinuation due to an AE considered possibly or probably related to study drug or withdrawal from the study for any reason with subsequent loss to follow-up during the oral treatment phase. The following table reports these results.

**Table 22: Distribution of clinical outcome (All Randomized Patients)**

Clinical Outcome	Number (%) of Subjects		Difference	95.13% Confidence Interval for the Difference	P-Value
	POS (n=304)	FLU/ITZ (n=298)			
Failure <sup>a</sup>	109 (36)	138 (46)	10.45%	2.59% to 18.32%	0.0091
Success	195 (64)	160 (54)			

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.

a: Thirteen subjects (7 POS, 6 FLU/ITZ) who were randomized but never treated were regarded as treatment failures for the statistical analysis of clinical outcome.

Source: Table 20 of sponsor's study report.

*Although the review team considered the above analysis more valid than the analysis of IFI alone it raised concerns regarding some deaths being considered as successes and the difficulties in establishing causality of death or adverse event. For reviewer's analysis of clinical failure, see section 3.1.2.5. For more detailed discussion of this point, the reader is referred to Section 5.1.*

### **3.1.2.5 Reviewers' Efficacy Analyses Results**

The review team considered clinical failure defined here as the most robust and appropriate endpoint in this prevention study: A patient is a clinical failure if a proven or probable IFI is present, received 4 or more days of empiric treatment with another antifungal for suspected IFI, use of IV alternative antifungal medication for >3 consecutive days or >= 10 cumulative days, discontinuation due to an AE regardless of determination of causality, discontinuation due to treatment failure, withdrawn from the study for any reason, lost to follow-up during the oral treatment phase (oral treatment plus 7 days) or death during the oral treatment phase. Subjects randomized but never treated were treated as failures as was done by the applicant. The following table reports the results of this analysis.

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**Table 23: Distribution of Clinical Failure as defined by the FDA Review Team (All Randomized Patients)**

Clinical Outcome of oral phase plus 7 days	Number (%) of subjects		Difference (POS-FLU/ITZ)**	95.13% confidence interval**	P-value**
	POS (N=304)	FLU/ITZ (N=298)			
	n (%)	n (%)			
Clinical Success	166 (55%)	126 (42%)	12.2%	(4.3, 20.1)	0.002
Clinical Failure	138 (45%)	172 (58%)			
Due to					
IFI	7	25			
Death*	18	26			
Use of Systemic Therapy	63	88			
Not followed/discontinued	51	35			

\*: For study P01899, 1 posaconazole patient and 2 control patients were counted as both IFI and death. All other outcomes are ranked by order in the table.

\*\* : Difference, p-value and 95.13% confidence interval of the difference (POS – FLU/ITZ) using a normal approximation adjusted by the control-site and baseline stratification factor as described by Fleiss<sup>6</sup>.

The reviewers conducted additional sensitivity analyses of clinical outcome defining all treatment discontinuations as failures and defining no treatment discontinuations as failures and similar results were obtained.

Given that this study used two different controls, based on site, it is of importance to check the consistency of results by control used in order to assess if pooling the information is valid. The following table reports the reviewers' analysis of clinical failure by each type of comparator used. Though the sites that used itraconazole had lower success rates, the treatment effect (difference between posaconazole and control) is similar. Test for homogeneity of odds ratio did not reject the null hypothesis of homogeneity.

**Table 24: Clinical failure by comparator used**

Clinical Outcome	Fluconazole Sites		Itraconazole sites	
	POS N=239	FLU N=240	POS N=65	ITZ N=58
Failure	99 (41)	132 (55)	39 (60)	40 (69)
Success	140 (59)	108 (45)	26 (40)	18 (31)
Difference in success rates, CI <sup>#</sup> and p-value	<b>13.6</b> (4.7, 22.4)	0.003	<b>9.0</b> (-7.9, 25.8)	0.3004

#95% confidence intervals (POS – Control) and p-value based on a normal approximation adjusted by the baseline stratification factor as described by Fleiss<sup>6</sup>.

### 3.2 Evaluation of Safety

The reader is referred to safety review by the medical officer Dr. Maureen Tierney. The following is a brief summary of that review.

Posaconazole is a relatively well tolerated azole with some of the same safety concerns as other members of the azole class and some possibly unique safety issues.

- Increase in hepatic adverse events including elevation in liver function tests and rare cases of severe liver injury in patients with severe underlying comorbidity.
- Drug interaction with cyclosporine (and tacrolimus) which can lead to severe, even fatal, cyclosporine toxicity.
- Inhibitor of CYP3A4
- Similar rates of increase of >60msec of QTc from baseline and QTC over 500 msec in POS prophylaxis patients as those who received fluconazole. No similar events recorded in healthy subjects. One case of torsades de Pointes in posaconazole prophylaxis pool of patients with severe electrolyte abnormalities.
- Mild increase in incidence of significant hypokalemia (13%) in comparison to fluconazole (10%.)
- Increase in number of patients with pulmonary embolus in the post stem cell transplant patients with GVHD who received posaconazole in comparison to fluconazole (6 versus 0).
- Mild increase in TTP ( and overall thrombocytopenia) and HUS in the post stem cell transplant patients with GVHD who received posaconazole in comparison to fluconazole.

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

##### **4.1 Gender, Race and Age**

##### **4.1.1 Study C/198-316**

The following table contains the results of the sponsor's clinical success endpoint and the sponsor's primary endpoint, proven or probable IFI breakthrough infections, for the subgroups of gender, race and age. For male subjects there appears to be little difference between the two treatments in either analysis. All the difference seen between the arms are with female subjects. A logistic model was run with gender and treatment and the interaction was not found to be significant. There was no strong trend seen in the breakdown by race, given that races other than Caucasian had fairly small sample sizes. There was also no strong trend with age when broken down by < 18, 18 – 65, and >= 65. Age or an interaction of treatment and age were also not significant when age was treated as a continuous variable in a logistic model.

**Table 25: Gender, Race and Age based subgroup analysis for Study C/I98-316 (All randomized Patients)**

	Sponsor's Endpoint of Clinical Success*		Sponsor's Primary Endpoint Proven or probable IFI**	
	Posaconazole	Fluconazole	Posaconazole	Fluconazole
<b>Gender</b>				
Males	133/203 (66)	124/187 (66)	11/203 (5)	11/187 (6)
Females	69/98 (70)	65/112 (58)	5/98 (5)	16/112 (14)
<b>Race</b>				
Caucasian	172/259 (66)	154/246 (63)	15/259 (6)	21/246 (9)
Hispanic	13/19 (68)	15/24 (63)	0/19 (0)	3/24 (13)
Black	10/12 (83)	11/18 (61)	0/12 (0)	2/18 (11)
Asian	5/9 (56)	8/10 (80)	1/9 (11)	1/10 (10)
American Indian	2/2 (100)	1/1 (100)	0/2 (0)	0/1 (0)
<b>Age</b>				
< 18	2/4 (50)	7/8 (88)	1/4 (25)	0/8 (0)
18 to < 65	198/292 (68)	180/286 (63)	14/292 (5)	25/286 (9)
>= 65	2/5 (40)	2/5 (40)	1/5 (20)	2/5 (40)

\* Sponsor's defined clinical success. Subject is considered a failure if a proven or probable IFI is present, received more than 5 days of empiric treatment with another antifungal during the primary time period, not followed for the entire 16 weeks of scheduled follow-up, or died.

\*\* Subject is considered a failure if proven or probable IFI is present. Results taken from table 17 in section 2.7.3 of sponsor's report.

#### 4.1.2 Study P01899

The following table contains the results of the reviewers' primary endpoint, clinical success, and the sponsor's primary endpoint, proven or probable IFI breakthrough infections, for the subgroups of gender, race and age. There was no strong trend seen in the breakdown by gender or age. All the difference seen between arms for the reviewer's clinical success is coming from Caucasians. However, note that all other races had fairly small sample sizes.

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**Table 26: Gender, Race and Age based subgroup analysis for Study P01899 (All randomized patients)**

	Reviewer's Clinical Success*		Sponsor's Primary Endpoint Proven or probable IFI**	
	POS	FLU/ITZ	POS	FLU/ITZ
<b>Gender</b>				
Males	91/158 (58)	66/160 (41)	3/158 (2)	12/160 (8)
Females	75/146 (51)	60/138 (43)	4/146 (3)	13/138 (9)
<b>Race</b>				
Caucasian	120/220 (55)	89/231 (39)	5/220 (2)	20/231 (9)
Hispanic	30/51 (59)	28/47 (60)	1/51 (2)	2/47 (4)
Black	9/16 (56)	5/9 (56)	0/16 (0)	1/9 (11)
Asian	2/13 (15)	2/9 (22)	1/13 (8)	2/9 (22)
Other ***	3/4 (75)	2/2 (100)	0/4 (0)	0/2 (0)
<b>Age</b>				
< 18	5/8 (63)	3/8 (38)	1/8 (13)	0/8 (0)
18 to < 65	132/238 (55)	95/223 (43)	4/238 (2)	18/223 (8)
>= 65	29/58 (50)	28/67 (42)	2/58 (3)	7/67 (10)

\* Reviewer's defined clinical success where patients is a failure if a proven or probable IFI is present, received 4 or more days of empiric treatment with another antifungal for suspected IFI, use of IV alternative antifungal medication for >3 consecutive days or >= 10 cumulative days, discontinuation due to an AE regardless of determination of causality, discontinuation due to treatment failure, withdrawn from the study for any reason, lost to follow-up during the treatment phase (treatment plus 7 days) or death during the treatment phase.

\*\* Subject is considered a failure if proven or probable IFI is present. Results taken from table 17 in section 2.7.3

\*\*\* Includes Native American, Indian and mixed race.

#### 4.2 Other Special/Subgroup Populations

The sponsor felt that it was important for the studies to be balanced across treatment by Acute or Chronic GVHD for study C/I98-316 and by Acute Leukemia (new or primary relapse) or Myelodysplastic syndrome for study P01899 and therefore, conducted their randomization stratified by these factors. The following table, Table 27, reports the clinical success by these stratification factors used at randomization. Though the clinical success rate does vary slightly across strata, the treatment effect (difference between posaconazole and control) remains fairly constant.

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**Table 27: Clinical success by stratification factors for Studies C/I98-316 and P01899 (All randomized patients)**

	Clinical Success*	
	Posaconazole	Control
Study C/I98-316**		
Acute GVHD	123/202 (60.9)	117/197 (59.3)
Chronic GVHD	78/98 (79.6)	72/100 (72.0)
Study P01899		
Acute Leukemia (new)	116/213 (55.5)	94/222 (42.3)
Acute Leukemia (primary relapse)	22/42 (52.3)	14/38 (36.8)
Myelodysplastic syndrome	28/49 (57.1)	18/38 (47.3)

\* Sponsor's defined clinical success for study C/I98-316. Reviewer's defined clinical success for study P01899 where patients is a failure if a proven or probable IFI is present, received 4 or more days of empiric treatment with another antifungal for suspected IFI, use of IV alternative antifungal medication for >3 consecutive days or >= 10 cumulative days, discontinuation due to an AE regardless of determination of causality, discontinuation due to treatment failure, withdrawn from the study for any reason, lost to follow-up during the treatment phase (treatment plus 7 days) or death during the treatment phase.

\*\* 3 subjects did not have GVHD status reported.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

#### 5.1.1 Statistical Issues

There were a number of statistical issues discovered in the review of the two prophylaxis studies (C/I98-316 and P01899). They include

- 1> Definition of the primary analysis
- 2> Analysis of prophylaxis for aspergillosis alone
- 3> Non-inferiority design with comparators not approved for the indication sought by the applicant (namely, all invasive fungal infections)
- 4> Justification for the non-inferiority margin
- 5> Limitations of statistical methods to resolve issues of concentration-response relationship found by the clinical pharmacology reviewer

These issues as well as a labeling comment will be discussed here.

#### 1. Definition of the primary analysis:

As mentioned in section 3.1, the review team had major concerns regarding the sponsor's primary efficacy endpoint. The applicant defined the primary efficacy endpoint as occurrence of IFI in all randomized patients during the pre-specified

(primary) time period. Though this endpoint is considered clinically meaningful, the concern arises regarding the details of the analysis and how subjects with essentially missing data are handled. For instance, subjects who die during the primary time period can no longer have a breakthrough IFI infection and this constitutes informative censoring. Considering these patients as “successes” may lead to biased estimates of the treatment effect. Therefore the review team decided it was more appropriate to perform the primary analysis on IFI by treating all-cause mortality and other events that lead to either informative censoring or missing data as failures. The review team’s position is supported by the literature on combined endpoints. This reviewer refers to the paper by Lubsen<sup>3</sup>. These authors discuss why analyzing specific non-fatal events in isolation may lead to spurious conclusions about efficacy unless the events considered are combined with all-cause mortality with examples of trials conducted in real time.

The review team discussed the inclusion of all-cause mortality versus IFI related (caused) mortality. It has been shown in the literature that it is quite difficult to determine if a death was possibly due to an invasive fungal infection. In Kirch<sup>4</sup> the authors discuss the frequency of misdiagnosis despite increased diagnostic technology with infections being one of the most common errors. Sharma<sup>5</sup> conducted a retrospective analysis of antimortem and postmortem pulmonary findings in patients receiving blood and bone marrow transplant recipients. They found that 5 of the 11 patients with pulmonary aspergillosis (45%) at autopsy were not receiving treatment for these conditions at the time of death. Also 10 of 16 patients (63%) being treated for suspected pulmonary aspergillosis at the time of death had no evidence of pulmonary aspergillosis at autopsy.

During a discussion of other events that can lead to informative censoring, it was made clear that as part of the clinical management, subjects who are thought to potentially have a fungal infection are often empirically treated with an anti-fungal drug in addition to the study medication. While many of these patients in the two studies (C/I98-316 and P01899) were determined to have not had a proven or probable fungal infection, the empiric treatment with the anti-fungal drugs other than study medication could have suppressed an early fungal infection, or these drugs could have contributed to the prevention of a fungal infection. Therefore, the review team felt that the events such as use of anti-fungal drugs other than the study medication during the study period along with loss to follow-up should also be considered as part of the composite primary endpoint.

## 2. Analysis of prophylaxis for Aspergillus alone

The sponsor conducted an analysis of the event of breakthrough aspergillosis infections and determined that a significant difference was found. This analysis in essence treated all deaths without an aspergillosis infection and all breakthrough fungal infections due to other pathogens as successes. This is a concern given that treatment of these other infections could have also treated an aspergillosis infection or could have helped to prevent one. We point again to the article by Lubsen<sup>3</sup> who discuss why analyzing specific non-fatal events in isolation may lead to spurious conclusions about efficacy.

### 3. Non-inferiority design with comparators not approved for the indication sought by the applicant (namely, \_\_\_\_\_ infections)

Regarding the use of fluconazole as the comparator in study C/198-316, the review team repeatedly had informed the applicant that since the comparator, fluconazole, is not approved for the broad indication proposed by the applicant, a non-inferiority analysis would not be able to support the efficacy of posaconazole for \_\_\_\_\_ infections and that a superiority analysis would be needed to provide evidence that posaconazole is effective for pathogens other than *Candida*. The results of this study show that there is not statistically sufficient evidence that posaconazole is superior to fluconazole in terms of clinical success. However the data do provide sufficient evidence of comparable performance of posaconazole to that of fluconazole in terms of clinical success established by means of non-inferiority with the sponsor's defined 15% margin (see the next discussion point). There is some indication that posaconazole may be effective in preventing aspergillosis due to the numerical difference in breakthrough fungal infections. However, we leave this determination to the clinical and microbiological reviewers.

Regarding the use of fluconazole and itraconazole as the comparators in study P01899, the sponsor was told that since these drugs were not approved for prophylaxis of fungal infections in this patient population, the sponsor would need to show a superior result. Given that the results do show statistically significant superiority of posaconazole, this issue is resolved in study P01899.

### 4. Justification for the non-inferiority margin

The sponsor proposed a 15% non-inferiority margin for the percent difference for study C/198-316. The review team requested justification of the proposed 15% non-inferiority margin from the sponsor on 4/24/06. In the sponsor's response on 5/23/06, the sponsor agreed that the exact rate of IFI is difficult to estimate particularly in this patient population, and published rates have ranged from 5% - 40%. The sponsor referred to the study by Slavin<sup>1</sup> which the sponsor states demonstrated the safety and efficacy of fluconazole for preventing opportunistic infections in subjects undergoing hematopoietic stem cell transplant. However, the population and the prophylaxis strategy in the Slavin article were not identical to study C/198-316. This article found the IFI rates were 17.6% for placebo and 6.6% for fluconazole (odds ratio of 3.3 for placebo versus fluconazole with 95% CI of [1.4, 6.5]). The sponsor then determined that a non-inferiority margin that would retain 50% of this effect would be 1.18. They argued that the selected margin based on 15% relative difference in IFI incidence with regard to fluconazole would correspond to a margin of 1.1625 for the odds ratio based on the observed number of 43 IFIs in the primary time period and this margin would retain more than 50% of the fluconazole effect.

The applicant's justification for the choice of non-inferiority margin is based on just one study that used different endpoints, different prophylaxis strategy and enrolled a different population of patients. The determination of an appropriate non-inferiority

margin is difficult in the setting of a treatment study. However, it is far more difficult in the setting of a prophylaxis indication. The literature shows superiority of fluconazole in a least one study referenced by the sponsor. The statistical team relied on the clinical team to determine if the subjects in this study are of similar risk for developing fungal infections as those in the reference study. Note that the review team has no evidence that the sponsor conducted a thorough search of all appropriate articles to determine the adequacy of their proposed non-inferiority margin. This is important because one should not ignore, and must take into account, literature (if it exists) that does not show superior efficacy of fluconazole over placebo as well.

5. Issues of concentration/response found by clinical pharmacology reviewer

The clinical pharmacology reviewer determined that there was a significant concentration response association between posaconazole levels obtained in study C/I98-316 and clinical response. The following table, reproduced from Seong Jang’s analysis, shows that subjects with the lowest quartile of posaconazole concentrations had a higher failure rate than those in the upper quartiles leading one to believe that patients who are not able to obtain high enough concentrations of posaconazole may obtain poorer outcomes because of it. The clinical pharmacology review commented on the high variability of concentrations seen with posaconazole and that absorption of posaconazole is highly affected by fat.

**Table 28: Incidence of Clinical Failure in the All Treated population during the Primary Time Period in 4 quartiles of POS C<sub>avg</sub> (Study C98-316).**

Quartiles	Q1	Q2	Q3	Q4
<b>C<sub>avg</sub> (ng/mL)</b>	<b>21.5-557</b>	<b>557-915</b>	<b>915-1563</b>	<b>1563-3650</b>
<b>Clinical Failure</b>	<b>44.4% (28/63)</b>	<b>20.6% (13/63)</b>	<b>17.5% (11/63)</b>	<b>17.5% (11/63)</b>

However, one problem with looking at the success rates of the lowest concentration group of posaconazole is that we do not know how fluconazole would have done in patients similar to those found in this lowest concentration group. There was some discussion that the posaconazole patients with the lowest exposure could have been a more ill group of patients.

We attempted to model posaconazole plasma concentrations versus baseline risk factors to see if a model that predicted much of the low concentration seen with posaconazole could be found. This model could then be used to predict for control patients hypothetical posaconazole concentrations. Control patients could then be grouped into similar quartiles for comparison. However, we were unable to come up with an adequate model (using either actual concentrations or binary endpoint based on the quartiles).

Absent convincing evidence that baseline risk factors alone can explain the low posaconazole levels, we continue to be concerned that the low posaconazole levels may be causing, at least in part, the low success rates in these subjects.

We would recommend the information on this exposure-response finding be included in the label and studied further in a phase IV commitment.

### Labeling

On June 20, 2006, the clinical team decided to redefine the clinical success endpoint that would be included in the drug label. Use of this redefined endpoint (not reported in this review) does not change the qualitative conclusions of the studies from the results that are reported here.

### **5.1.2 Collective Evidence**

Two comparative Phase III studies were conducted using posaconazole as prophylaxis for the prevention of invasive fungal infections in high risk patients. C/I98-316 was a randomized double-blind active controlled trial of posaconazole versus fluconazole as control in HSCT recipients receiving high-dose immunosuppressive therapy for graft-versus-host disease (GVHD). Study P01899 was a randomized, open label, active controlled trial of posaconazole versus fluconazole or itraconazole as control (by center) in acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) patients with severe, prolonged neutropenia due to remission-induction chemotherapy.

The following table provides a summary of clinical success rates for the two studies (C/I98-316 and P01899). For study C/I98-316, clinical failure was defined in the protocol as the occurrence of a proven or probable IFI, receipt of more than 5 days of empiric treatment with a systemic antifungal drug other than the study drug during the Primary Time Period, or discontinuation from the Primary Time Period (i.e., subject not followed for the entire duration of the period). For study P01899, clinical failure was defined by the review team as follows: occurrence of a proven or probable IFI, receipt of 4 or more days of empiric treatment with another antifungal for suspected IFI, use of IV alternative antifungal medication for >3 consecutive days or >= 10 cumulative days, discontinuation due to an AE regardless of determination of causality, discontinuation due to treatment failure, withdrawn from the study for any reason, lost to follow-up during the oral treatment phase (oral treatment plus 7 days) or death during the oral treatment phase. Note that the review team redefined the sponsor's defined clinical failure for study P01899 since in the sponsor's analysis some patients who died were not considered failures and since the sponsor only included discontinuations due to *drug-related* adverse events in the definition of failure.

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**Table 29: Summary of study results for C/I98-316 and P01899 (All Randomized Subjects)**

	C/I98-316*		P01899*	
	Posaconazole (N =301)	Fluconazole (N=299)	Posaconazole (N =304)	Flu/Itra (N=298)
	n (%)	n (%)	n (%)	n (%)
Clinical Success	202 (67%)	189 (63%)	166 (55%)	126 (42%)
Clinical Failure*	99 (33%)	110 (37%)	138 (45%)	172 (58%)
Due to				
IFI	16	27	7	25
Death**	58	59	18	26
Use of Systemic Therapy	10	9	63	88
Not followed/discontinued	24	30	51	35
CI for the difference***	(-2.7, 12.2)		(4.3, 20.1)	

\*: Primary time point is at 16 weeks for study C/I98-316 and at end of oral therapy plus 7 days for study P01899.

\*\* : For study C/I98-316, 10 posaconazole patients and 16 fluconazole patients were counted as both IFI and death. For study P01899, 1 posaconazole patient and 2 control patients were counted as both IFI and death. All other outcomes are ranked by order in the table.

\*\*\*: 95.01% CI for study C/I98-316 and 95.13% CI for study P01899

Note that some of the concerns of the interpretations of the results of these studies include difficulty in determining an appropriate non-inferiority margin for study C/I98-316 and the open-label nature of study P01899, along with the many issue inherent with the design and analysis of prophylaxis studies. However, we believe that collectively these two studies are supportive of the efficacy of posaconazole for prophylaxis of fungal infections in these patient populations.

## 5.2 Conclusions and Recommendations

The data from the two randomized, active-controlled clinical trials submitted in this application, collectively provide sufficient evidence of comparable performance of posaconazole to that of other azoles (namely fluconazole and itraconazole) in terms of clinical success (primarily defined as invasive fungal infection free survival) by means of non-inferiority design. There is some indication that posaconazole may be effective in preventing aspergillosis infection due to the numerical difference in probable breakthrough fungal infections. However, we leave this determination to the clinical and microbiological reviewers.

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## APPENDIX

The following is the sponsor's discussion of the computation of the maximum value to determine non-inferiority from the final protocol for study C/I98-316.

### Assessment of Noninferiority

Posaconazole will be considered to be at least noninferior to fluconazole, with respect to the primary efficacy endpoint based on all treated patients, if the upper limit of the **95.01%** confidence interval for the adjusted odds ratio, for the effect of treatment upon the incidence of proven or probable IFI, does not exceed a maximum value corresponding to a percentage difference in **incidence** (with respect to the **incidence** of fluconazole) of 15%. The maximum value will be computed as follows:

Let

$\tilde{\pi}_{POS}$  = Posaconazole **incidence** to be ruled out,

$\tilde{\pi}_{FLZ}$  = Fluconazole **incidence** to be ruled out,

$\hat{\pi}$  = Estimated overall **incidence** (Total number of events/Total number of patients),

$N_{POS}$  = Number of patients in the Posaconazole treatment group,

$N_{FLZ}$  = Number of patients in the fluconazole treatment group.

Then solve the following two equations for  $\tilde{\pi}_{POS}$  and  $\tilde{\pi}_{FLZ}$ :

$$\frac{N_{POS}\tilde{\pi}_{POS} + N_{FLZ}\tilde{\pi}_{FLZ}}{N_{POS} + N_{FLZ}} = \hat{\pi}$$

$$\frac{\tilde{\pi}_{POS} - \tilde{\pi}_{FLZ}}{\tilde{\pi}_{FLZ}} = 0.15$$

Then calculate the maximum value for the upper confidence limit of the odds ratio as:

$$\text{Maximum Value} = \frac{\tilde{\pi}_{POS}(1 - \tilde{\pi}_{FLZ})}{\tilde{\pi}_{FLZ}(1 - \tilde{\pi}_{POS})}$$

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