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RESEARCH**

APPLICATION NUMBER:
22-003

MEDICAL REVIEW

Medical Team Leader, Division Director, and Acting Office Director Review

Application Type	NDA 22-003
Submission Date	December 21, 2005
PDUFA Goal Date	June 22, 2006
Team Leader	Leonard Sacks, MD
Director	Renata Albrecht, MD
Acting Office Director	Ed Cox, MD, MPH
Review Completion Date	September 15, 2006
Established Name	Posaconazole
Trade Name	Noxafil®
Therapeutic Class	Antifungal Agent
Applicant	Schering-Plough Research Institute
Priority Designation	P
Formulation	Oral Suspension (40 mg/mL) in 4 oz bottle
Dosing Regimen	200 mg PO TID
Proposed Indication	Schering's ; 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.*
Intended Population	Patients 13 years of age and older

*FDA wording for indication is under the recommendations below

Recommendations:

This application should be approved for the indication, "NOXAFIL (posaconazole) is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft versus host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy."

The treatment regimen is 200 mg PO TID for the duration of time that the patient is at risk. In clinical trials, the average duration was 80 days in patients with HSCT and GVHD, and the average duration was 29 days in patients with hematologic malignancies and prolonged neutropenia from chemotherapy.

Absorption is enhanced by food, particularly fatty meals; therefore the **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** sections provide the following information:

"To enhance the oral absorption of posaconazole and optimize plasma concentrations:

- Each dose of NOXAFIL Oral Suspension should be administered with a full meal or liquid nutritional supplement. For patients who cannot eat a full meal or tolerate an oral nutritional supplement, alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.
- Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.
- Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are

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necessary, patients should be monitored closely for breakthrough fungal infections. (See **CLINICAL PHARMACOLOGY, Drug Interactions**)”

Similar text is included in the **PRECAUTIONS: Information to Patients** subsection.

Postmarketing Commitments:

1. A post approval study will be conducted among patients receiving antifungal prophylaxis. The study will enroll patients who are at risk for low absorption. Different dosing strategies including the use of therapeutic drug monitoring to increase plasma concentrations will be explored.

Protocol Submission:	by January 2007
Study Start:	by January 2008
Final Report Submission:	by March 2011

2. Detailed reports of thrombotic or microangiopathic events, such as hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), pulmonary embolus, etc. will be submitted quarterly for three years.
3. Utilization data and indications, when known, will be submitted every six months for three years.
4. Pediatric studies in patients 0-12 years of age who are at high risk for developing these infections are deferred under PREA until June 22, 2011.

Background – invasive fungal infections (IFI) in immunocompromised patients

Therapeutic advances in the fields of oncology and transplantation have led to new treatment options for patients, but many of the involved treatments (such as chemotherapy in oncologic diseases or immunosuppressive agents to prevent transplant rejection) result in compromised immunity. As a result of impaired immune function, these patients are at risk for opportunistic infections. Invasive fungal infections are particularly problematic in immunocompromised patients. The two major fungal species responsible for these infections are *Candida* spp. and *Aspergillus* spp. Infections with these agents in the immunocompromised host are associated with significant morbidity and mortality and *Aspergillus* infections are particularly ominous with high mortality rates.

Diflucan (fluconazole) is approved for the indication of prophylaxis of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy. Mycamine (micafungin) an echinocandin antifungal agent, is approved for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. Neither fluconazole nor micafungin is approved for preventing *Aspergillus* infections. The other approved systemic antifungal agents are not approved for prophylaxis of fungal infections in immunocompromised patients.

Synopsis of Efficacy and Safety:

Efficacy

NDA 22-003 contains data from the following types of studies in support of the efficacy of posaconazole:

- Data from two adequate and well-controlled clinical studies in the prophylaxis of invasive fungal infections in immunocompromised patients

remains highly fatal despite treatment. Thus the efficacy of posaconazole in reducing breakthrough infections with *Aspergillus* is of substantial medical importance in the management of patients who are highly immunosuppressed.

- Neither of the two studies identified more than a few isolates of other fungi (yeasts or molds other than *Candida* spp. or *Aspergillus* spp.), providing insufficient evidence to support the use of posaconazole for prevention of other fungal pathogens (pathogens other than *Candida* and *Aspergillus*).

Additional data supporting the efficacy of posaconazole include in vitro and animal study data demonstrating the activity of posaconazole against invasive fungal organisms, including *Aspergillus* and *Candida*, clinical data showing activity of posaconazole in the treatment of invasive fungal infections including *Aspergillus* infections refractory to other therapy and the efficacy of posaconazole in the treatment of patients with oropharyngeal candidiasis, demonstrated in several comparative clinical trials.

Analyses of exposure-response showed an apparent association between plasma levels (presumably a reflection of absorption of the 200 mg TID dose) and clinical response. Exposure was quite variable among patients, Cav ranged from 22 to 3650 ng/mL. In the analysis of C198-316 data, low exposure (Cav) was associated with higher clinical failure, suggesting that TDM for posaconazole should be further evaluated. However, as presented in more detail in the Clinical Pharmacology section below, at present, the fixed dose regimen will be approved as this was the dosing regimen studied and the labeling will reflect the importance of taking posaconazole with food or an oral nutritional supplement, potential drug interactions, and interference with absorption (e.g. diarrhea, vomiting).

Safety

An extensive safety database including the two prophylaxis studies (Studies C198-316 & PO1899), the comparative oropharyngeal studies (see Background, below), healthy volunteer studies and non-comparative treatment studies previously submitted were reviewed and summarized in the proposed product labeling. The safety of posaconazole therapy has been assessed in 1,844 patients. Posaconazole was generally well tolerated, and many adverse events were associated with underlying medical conditions and concomitant drugs. Several events were considered significant and warranted inclusion in the **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS** sections of the labeling (see more detailed safety summary below).

Hepatotoxicity

In previously reviewed healthy volunteer studies, mild reversible abnormalities in liver function were seen in healthy volunteers. In non-comparative studies of posaconazole in severely immunocompromised patients with invasive fungal infections, cases of liver failure and death were reported though drug attribution could not be determined. In comparative studies, elevation of transaminases was seen in all the azoles arms, and was somewhat more common in posaconazole-treated patients (9/605) than fluconazole-treated (2/539) or itraconazole-treated (0/58) patients.

Cyclosporine drug interaction

A drug interaction between posaconazole and cyclosporine resulting in elevated cyclosporine levels was reported by the investigators as possibly or probably related to 3 deaths. All azoles have a precaution regarding their effect on cyclosporine levels; posaconazole is the first to have a **WARNING** because of drug interaction resulting in fatality identified in the clinical studies. The Office of Surveillance and Epidemiology, Division of Drug Risk Evaluation (OSE/DDRE, formerly ODS/DDRE) is conducting review of AERS cases on azoles and certain immunosuppressants (specifically cyclosporine, tacrolimus, sirolimus), and labeling of these products will be updated as appropriate.

Cardiac repolarization

QTc prolongation was reported in similar percentages of posaconazole-treated patients (8/605) as fluconazole-treated (4/539) and itraconazole-treated (2/58) patients. A contraindication for use of

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transplant recipients with graft versus host disease or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

Background – posaconazole development program

Meanwhile, the company completed the 2 prophylaxis studies that are the subject of this NDA 22-003 and also requested treatment of oropharyngeal candidiasis, including refractory OPC, under administrative NDA 22-027. The NDAs were submitted after various discussions between Schering and FDA, and the pre-NDA meeting on October 25, 2005. NDA 22-003 was given a priority review (per CDER MaPP 6020.3) because of the company's findings of better prevention of *Aspergillus* infection compared to fluconazole and because there is currently no approved antifungal for such use. The PDUFA due date was June 22, 2006. NDA 22-027 was given a standard review with a due date of October 22, 2006.

Pediatric patients 13 years and older were included in the studies, studies in younger patients are deferred under PREA.

Posaconazole is a new second generation triazole that blocks the synthesis of ergosterol by inhibiting lanosterol 14 alpha-demethylase. Like voriconazole it demonstrates broad spectrum *in-vitro* antifungal activity. It is administered as an oral solution and shows variable absorption with a significant food effect. An intravenous formulation is not presently available.

The elimination half life is 35 hours. At a dose of 200 mg PO TID, absorption in immunocompromised patients varies widely. Based on Phase 1 studies, exposure is increased 3-4 fold when posaconazole is taken with a meal, especially a fatty meal.

Compared to voriconazole, there is somewhat more limited metabolism of posaconazole by CYP3A resulting in potentially less drug interactions. Nevertheless, clinically significant drug interactions have been noted, specifically at least three patients may have had a fatal posaconazole/cyclosporine drug interaction.

Preclinical toxicology studies demonstrated neurophospholipidosis in dogs, but this finding was not reproduced in monkeys. Human experience with the drug in approximately 3000 patients has not demonstrated neurotoxicity. Ocular adverse events commonly seen with voriconazole have not been observed with posaconazole, although blurred vision was reported by approximately 5% of subjects.

Chemistry: (see review by Dr Mark Seggel)

CMC and inspections were adequate, approval recommended.

Pharmacology/Toxicology: (see review by Dr Owen McMaster)

The pharmacology/toxicology review of the preclinical animal studies (submitted by cross reference from) recommended approval of the application. The finding of phospholipidosis was a subject of extensive investigation and discussion. In the end, it was determined that the effect was minimal at the expected human exposure, that there was no recognized functional consequence of phospholipidosis, that neurophospholipidosis was not expected in humans given negative monkey studies, that the effect was

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reversible over time, and that other marketed azoles and other products have been associated with phospholipidosis. The following summary is excerpted from Dr. McMaster's Review:

"Posaconazole has been studied in rats (up to two years), mice (up to two years), dog (up to one year), monkeys (up to one year) and rabbits. Phospholipidosis has been detected in all species exposed to posaconazole and is generally characterized by appearance of vacuolated cells of the monocyte/macrophage family. The cytoplasm of these cells contains masses that resemble plasma membrane. Posaconazole is thought to inhibit lysosomal phospholipases, thereby inhibiting the recycling of plasma membranes. The drug may also act like a number of other cationic amphiphilic compounds by inserting itself into the plasma membrane and disturbing turnover.

"Phospholipidosis is most often detected in the lung, spleen, thymus, lymph nodes, liver, bone marrow, adrenal gland, pituitary, ovaries and skin. The thalamus, medulla, spinal cord and intestinal ganglia are also affected in posaconazole treated dogs.

"Neuronal phospholipidosis was first observed in dogs in a twelve-month study. This consisted of vacuolation of neurons in thalamus, enlargement of axons of medulla, vacuolation of ganglia in small intestines and enlargement of axons of the spinal cord. Dogs treated for six months showed similar findings, though less frequently. Posaconazole was studied in dogs and monkeys in an attempt to determine the onset, functional effects and reversibility of the neuronal phospholipidosis. Animals were subjected to a number of neurological examinations. These included behavior, posture, gait, facial symmetry, muscle tone, patellar reflex, brainstem auditory evoked potentials, visual evoked potentials, somatosensory evoked potentials and peripheral nerve responses. No neuronal phospholipidosis was observed in the monkey. No functional consequences were observed in either species using the testing described above.

"Phospholipidosis is generally thought to be without functional consequences even when observed in many tissues. In fact, rats experiencing amiodarone-induced lung phospholipidosis, seem to be protected from the toxic effects of intratracheal silica (Environ. Health Perspec 102:327-378). Phospholipidosis was generally ameliorated after a drug-free period, but in some cases the changes were not completely reversed at the end of a three month drug-free study period. Phospholipidosis is not unique to posaconazole and is seen with other azoles such as itraconazole. It is also a well known feature of cationic amphiphilic compounds such as amiodarone, fluoxetine, imipramine and gentamicin."

Microbiology, Animal Models and Clinical Results from Prophylaxis Studies: (see also reviews by Dr. Suvarna and Dr. Bala)

In vitro microbiological activity was evaluated against various species of *Aspergillus*, *Fusarium*, *Coccidioides*, *Zygomycetes*, *Candida* species and *Cryptococcus*. However breakpoints for antifungal agents have not been established. Animal studies of prophylaxis in mice and rabbits supported efficacy for *Aspergillus fumigatus*, *Aspergillus flavus* and *Candida albicans*.

In Study C/198-316, there were 7 and 22 breakthrough fungal infections during the treatment phase in the posaconazole and fluconazole arms, respectively. The table below shows that during the treatment period, there are fewer *Aspergillus* infections in the posaconazole arm compared to the fluconazole arm (3 vs 17) and similar numbers of *Candida* infections (1 vs 3). There are too few other fungal isolates to make any conclusions about other fungi. By the 16 week follow up visit, there were a total of 16 vs 27 breakthrough infections.

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Pathogen group associated with proven (proven + probable) invasive fungal infections while on treatment in the all treated population in a randomized double-blind study C/198-316

Species	Posaconazole	Fluconazole
<i>Aspergillus fumigatus</i>	0 (0)	3 (6)
<i>Aspergillus flavus</i>	0 (0)	2 (2)
<i>Aspergillus terreus</i>	0 (0)	0 (1)
<i>Aspergillus niger</i>	0 (0)	0 (0)
<i>Aspergillus species</i>	0 (3)	2 (8)
<i>Aspergillus species</i> Total	0 (3)	7 (17)
<i>Candida albicans</i>	1 (1)	1 (1)
<i>Candida glabrata</i>	0 (0)	1 (1)
<i>Candida krusei</i>	0 (0)	1 (1)
<i>Candida parapsilosis</i>	0 (0)	0 (0)
<i>Candida species</i>	0 (0)	0 (0)
<i>Candida species</i> Total	1 (1)	3 (3)
<i>Rhizomucor miehei</i>	0 (0)	1 (1)
<i>Pseudoallescheria boydii</i>	1 (1)	0 (0)
<i>Scedosporium prolificans</i>	0 (0)	0 (0)
<i>Trichosporon biegelii</i>	1 (1)	0 (0)
Other mold	1 (1)	1 (1)
Other fungal species Total	3 (3)	2 (2)
Total	4 (7)	12 (22)

(Table from Dr. Bala's Review)

In Study PO1899, there were 7 and 25 breakthrough infections during the treatment phase in the posaconazole and fluconazole/itraconazole arms, respectively. There are fewer *Aspergillus* infections in the posaconazole arm compared to the control arm (2 vs 20) and similar numbers of *Candida* infections (3 vs 2). By the 100 day follow up visit, there were a total of 14 posaconazole and 33 control breakthrough IFIs.

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Pathogen group associated with proven (proven + probable) invasive fungal infections while on treatment in all treated populations in a randomized open label evaluator blinded study P01899

Species	Posaconazole	Fluconazole	Itraconazole
<i>Aspergillus fumigatus</i>	0 (0)	0 (1)	0 (1)
<i>Aspergillus flavus</i>	0 (0)	0 (2)	0 (0)
<i>Aspergillus</i> species	0 (2)	1 (12)	0 (4)
<i>Aspergillus</i> species Total	0 (2)	1 (15)	0 (5)
<i>Candida glabrata</i>	2 (2)	1 (1)	0 (0)
<i>Candida krusei</i> + <i>Candida parapsilosis</i>	0 (0)	1 (1)	0 (0)
<i>Candida tropicalis</i> + mold	1 (1)	0 (0)	0 (0)
<i>Candida</i> species + Mold	0 (1)	0 (0)	0 (0)
<i>Candida</i> species Total	3 (4)	2 (2)	0 (0)
<i>Rhizomucor arrhizus</i>	0 (0)	1 (1)	0 (0)
<i>Pseudoallescheria boydii</i>	0 (0)	1 (1)	0 (0)
<i>Pneumocystis carinii</i>	1 (1)	0 (0)	0 (1)
Other fungal species Total	1 (1)	2 (2)	0 (1)
Total	4 (7)	5 (19)	0 (6)

(Table from Dr. Bala's Review)

Clinical Pharmacology: (see review by Dr Seong Jang; Team Leader Dr Philip Colangelo)

Absorption is dependent on food intake. The labeling reflects the levels achieved following 200 mg of posaconazole when given in the fasted and fed state, including absorption following a high-fat meal. Absorption (C_{max} and AUC) is increased by 3-fold after a meal and 4-fold after a high fat meal. The labeling reads:

“The AUC and C_{max} of posaconazole are approximately 3 times higher when administered with a nonfat meal or nutritional supplement (14 gm fat) and approximately 4 times higher when administered with a high-fat meal (~50 gm fat) relative to the fasted state. In order to assure attainment of adequate plasma concentrations, it is recommended to administer posaconazole with food or a nutritional supplement. (See **DOSAGE AND ADMINISTRATION**.)”

Table 1: The mean (%CV) pharmacokinetic parameters of posaconazole determined after a 200 mg single dose fasted, with a non-fat, and a high fat meal in healthy volunteers (Study I96-099)

Dose (mg)	C _{max} (ng/mL)	T _{max} ^a (hr)	AUC(l) (ng-hr/mL)	Cl/F (L/hr)	T _{1/2} (hr)
200 mg fasted	132 (50)	3.50 (1.5-36 ^b)	4,179 (31)	858 (25)	23.5 (25)
200 mg nonfat	378 (43)	4 (3-5)	10,753 (35)	350 (39)	22.2 (18)
200 mg high fat	512 (34)	5 (4-5)	15,059 (26)	234 (24)	23.0 (19)

a: Median (range)
 b: The subject with T_{max} of 36 hrs had relatively constant plasma levels over 36 hrs (1.7 ng/ml difference between 4 hrs and 36 hrs)

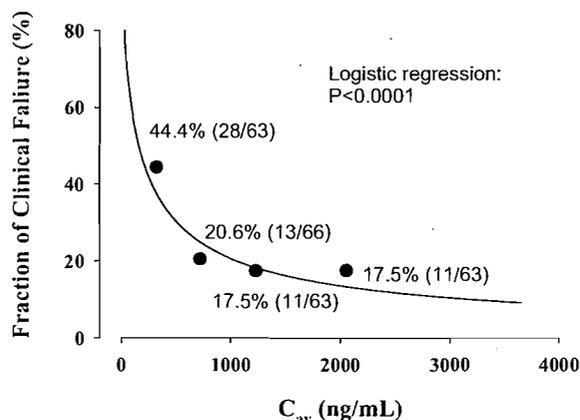
Therefore, the **CLINICAL PHARMACOLOGY** section, the **PRECAUTIONS/Information to Patients** section, and the **DOSAGE AND ADMINISTRATION** section will include information on the importance of (a) taking posaconazole with a meal or nutritional supplement, (b) caution about diarrhea as possibly interfering with good absorption, and (c) caution about drug interactions that may reduce posaconazole levels and suggest that patients should be carefully followed for development of IFI or receive alternative antifungal therapy.

Posaconazole is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. It is also an inhibitor primarily of CYP3A4, therefore information on various drug interactions is summarized in the labeling.

An analysis of exposure-response was conducted that showed an association between lower posaconazole levels and lower clinical efficacy in study 316. The recommendation was that the following information be included in labeling, and that TDM be implemented. The recommendation was made that patients whose posaconazole level after the first day is < 700 ng/mL should have their dose increased from 200 mg TID to 400 mg TID to achieve higher levels.

The following recommendation is from Dr Jang's review.

“In Study 316, the exposure-response analyses revealed a high inter-patient variability of steady-state posaconazole average concentrations (C_{av}) (range 22 to 3650 ng/mL) and a significant relationship between a higher incidence of clinical failure and lower C_{av} following oral suspension administration of 200 mg TID (Figure 1).”



“**Figure 1.** POS exposure-response relationship for patients in the All Treated population during the Primary Time Period (N=252) (Study C98-316). Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{av})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of C_{av} (closed circles) are plotted to assess the goodness-of-fit.

“The incidence of clinical failure with posaconazole was significantly higher in the lower quartile of C_{av} (i.e., Q1) compared with the other three higher C_{av} quartiles (i.e., Q2-Q4) (Table 4)., This suggested that following administration of posaconazole 200 mg TID, the C_{av} was not sufficiently high in 25% of patient population.”

Table 4. Incidence of Clinical Failure in the All Treated population during the Primary Time Period for 4 quartiles of POS C_{av} (Study C98-316). (from Dr Jang’s review)

Quartiles	Q1	Q2	Q3	Q4
C _{av} (ng/mL) ^a	322 [21.5-557]	718 [557-915]	1231 [915-1563]	2055 [1563-3650]
Clinical Failure	44.4% (28/63)	20.6% (13/63)	17.5% (11/63)	17.5% (11/63)
Proven/probable IFIs	4.76% (3/63)	4.76 % (3/63)	1.59% (1/63)	3.17% (2/63)
Empirical use of Sys. Antifungal ^b	17.5% (11/63)	3.17% (2/63)	6.35% (4/63)	4.76% (3/63)
Death	34.9% (22/63)	20.6% (13/63)	17.5% (11/63)	11.1% (7/63)
Discontinuation ^c	23.8% (15/63)	14.3% (9/63)	9.52% (6/63)	9.52% (6/63)

There is some overlap in the rows.

^a: Median [Range]

^b: Use of systemic antifungal agents in addition to study drug more than 5 days, from all causes

^c: Discontinuation due to any reason

After extensive discussion, it was determined that the detailed information described above and a recommendation for TDM should not be included in labeling at this time, but that further study of dose response and/or TDM should be performed. The company was, however, asked to evaluate the exposure-response in a subsequent study, and agreed to a post-marketing study (See PMC in approval letter). The concerns regarding this finding were that (a) the study was not prospectively designed to evaluate this relationship, and results were not consistent between the two studies CI98-316 and PO1899 (b) not all patients had PK data collected (c) the levels were drawn at different time points during the dosing interval (d) data were not collected about meal and relationship of dosing to meals (e) the association could not be interpreted as causal but might also be related to underlying host factors instead – several components of the composite endpoint such as deaths and empiric antifungal use reflected progression of the underlying disease or drug intolerance and did not indicate breakthrough fungal infections with a high degree of fidelity (f) there were no prospective data demonstrating that the patients with the low levels would respond to higher doses by gaining greater systemic exposure and corresponding clinical success. Hence, the finding of an apparent exposure-response relationship should be viewed as hypothesis generating and should be further studied. Also, the rate of adverse GI adverse events was correlated with higher posaconazole levels, and there was no safety data for the proposed 400 mg TID dosing regimen. The company was also reluctant to accept the specific quantitative information proposed, but did agree to address this issue in a post-marketing study.

Clinical and Statistical Summary of Studies C/198-316 (Study 1) and PO1899 (Study 2)
 (please see reviews by Dr Maureen Tierney, Dr Jyoti Zalkikar; Statistical TL Karen Higgins)

Efficacy data from two adequate and well controlled studies in prophylaxis were submitted and reviewed. Both studies enrolled patients at high risk for invasive fungal infections because they were severely immunocompromised due to their underlying medical conditions. The review of this priority application and the composite clinical endpoint was challenging. There were various requests for additional analyses from the company and various sensitivity analyses conducted by the reviewers to understand not just the breakthrough fungal infections in these studies, but also the rather complex composite clinical end point. Based on all these analyses, it was determined that posaconazole was safe and effective in preventing infections due to *Aspergillus* and *Candida*; and the studies are briefly summarized below; much of this information is also presented in the CLINICAL STUDIES section of the posaconazole package insert regarding “**Prophylaxis of Invasive Fungal Infections (IFIs)**”

Synopsis of studies C98-316 and P01899 supporting the requested indication:

Study C98-316 (Study 1)

Study C98-316 was a randomized, double-blinded, active control prophylaxis study in subjects with graft versus host disease receiving high dose immunosuppressive therapy following allogeneic marrow

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transplantation. Patients were randomized in equal numbers to receive posaconazole 200mg three times daily as an oral suspension or fluconazole 400mg as oral capsules. Treatment was to be given for 16 weeks.

Study visits were performed every 2 weeks from initiation of therapy until the completion of 16 weeks of therapy. Two additional follow up visits were performed on week 20 and 24.

In this study population with significant underlying morbidity as result of graft versus host disease, progressive malignancy and/or immunosuppression, many patients did not complete the 16 week course of therapy. Among the 291 patients who received posaconazole and 288 who received fluconazole the mean respective durations of therapy were 80 and 77 days.

In the Agency's analysis, Clinical failure was defined as a composite endpoint comprising:

- *proven or probable invasive fungal infection*
- *death*
- *empiric antifungal use*
- *loss-to-follow-up (not applicable to the "on therapy" analyses)*

The clinical diagnosis of invasive fungal infection or the decision to use empiric antifungal therapy was made by the investigator. Each such case was adjudicated by an independent data review committee blinded to treatment. The adjudicated outcomes incorporated information acquired later such as autopsy or galactomannan results, and using EORTC/MSG criteria, IFI's were classified as probable or proven.

Outcome was assessed in each patient seven days after the end of therapy (where loss-to-follow-up and other events occurring after premature cessation of prophylaxis were censored) and at the end of 16 weeks (where events occurring after cessation of prophylaxis were included).

Outcome in CI98-316 (Study 1)

	Posaconazole n =301	Fluconazole n = 299
<i>On therapy plus 7 days</i>		
Clinical Failure	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(<i>Aspergillus</i>)	3 (1%) (0 proven, 3 probable)	17 (6%) (7 proven, 10 probable)
(<i>Candida</i>)	1 (<1%) (proven)	3 (1%) (proven)
(Other)	3 (1%)	2 (1%)
All Deaths	22 (7%)	24 (8%)
Proven / probable fungal infection prior to death	2 (<1%)	6 (2%)
SAF ^{a,b}	27 (9%)	25 (8%)
<i>Through 16 weeks</i>		
Clinical Failure ^c	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(<i>Aspergillus</i>)	7 (2%)	21 (7%)
(<i>Candida</i>)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths	58 (19%)	59 (20%)
Proven / probable fungal infection prior to death	10 (3%)	16 (5%)
SAF ^{a,b}	26 (9%)	30 (10%)
Lost to follow-up ^d	24 (8%)	30 (10%)

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a: SAF – systemic antifungal therapy
 b: Use of SAF criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days).
 c: 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%)
 d: Lost to follow-up means the subject was not observed for 112 days from Baseline

To eliminate overlap in these components, the single reason for failure in each patient was determined hierarchically in the order shown in the table.

CI98-316 (Study 1)	Posaconazole n = 301	Fluconazole n = 299
On therapy plus 7 days		
Clinical failure	50/301 (17%)	55/299 (18%)
IFI*	7 (4 proven, 3 probable)	22 (12 proven, 10 probable)
Deaths	20	18
Empiric antifungal therapy	23	15
Through 16 weeks		
Clinical Failure ^c	99/301 (33%)	110/299 (37%)
IFI*	16	27
Deaths	48	43
Empiric antifungal therapy	11	10
LTF	24	30

In these composite endpoints, the most notable difference between the arms was the incidence of invasive fungal infection.

A marked reduction in the incidence of proven or probable *Aspergillus* infection was observed in the posaconazole arm.

Among the 51 patients who entered the study with a positive test for *Aspergillus* antigen, development of IFI due to *Aspergillus* occurred in 1/21 posaconazole-treated and 6/30 fluconazole-treated patients.

Similar studies reported in the medical literature demonstrate the effect size of fluconazole over placebo in the prophylaxis of invasive fungal infections (IFI) in immune compromised patients. In a study by Goodman (1992), et al, in the *New England Journal of Medicine*, fluconazole was compared to placebo for the prevention of IFI in patients post bone marrow transplantation. In this study, 15.8% of the patients in the placebo-arm experienced systemic fungal infection compared to 2.8% in the fluconazole-arm. A similar study was reported by Slavin (*Journal of Infectious Diseases*, 1995) where 18% of placebo-treated patients had a systemic fungal infection versus 7% in fluconazole-treated patients. Similar studies were also performed in patients with hematologic malignancies with neutropenia from cancer chemotherapy. Rotstein (*Clinical Infectious Diseases*, 1999) reported that the rate of proven and probable IFI in the placebo arm was 24% (32/133) and 6.5% (9/141) in the fluconazole arm. Winston (*Annals of Internal Medicine*, 1993) reported only proven IFIs with rates of 8% in placebo patients and 4% in fluconazole patients. In all these reported studies, the effect of fluconazole exceeded the effect of placebo.

The Applicant's primary endpoint for studies C98-316 and P01899 differed from the composite endpoint that the Agency used to evaluate these studies. The endpoint the Applicant used was similar to that described in the studies above. In these analyses the effect of posaconazole differentiates itself from its active comparators.

Applicant's Results from Clinical Studies in Prophylaxis of Invasive Fungal Infections C198-316 and PO1899

Study	Posaconazole	Comparator ^a	P-Value
Proportion (%) of Patients With Proven/Probable IFIs			
On-Treatment Period ^b			
1899 ^d	7/304 (2)	25/298 (8)	0.0009
316 ^e	7/291 (2)	22/288 (8)	0.0038
Fixed-Time Period ^c			
1899 ^d	14/304 (5)	33/298 (11)	0.0031
316 ^d	16/301 (5)	27/299 (9)	0.0740
Proportion (%) of Patients With Proven/Probable Aspergillosis			
On-Treatment Period ^b			
1899 ^d	2/304 (1)	20/298 (7)	0.0001
316 ^e	3/291 (1)	17/288 (6)	0.0013
Fixed-Time Period ^c			
1899 ^d	4 /304 (1)	26 /298 (9)	< 0.0001
316 ^d	7/301 (2)	21/299 (7)	0.0059

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

- a: FLU/ITZ (1899); FLU (316).
- b: In 1899 this was the period from randomization to last dose of study medication plus 7 days; in 316 it was the period from first dose to last dose of study medication plus 7 days.
- c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the Baseline day to 111 days post-baseline.
- d: All Randomized
- e: All Treated

Given the results of these studies across the timepoints evaluated and that the comparator drugs are active comparators, the difference between posaconazole and placebo, although not measured directly, is substantial.

Deaths: There were 22 (7%) deaths in the posaconazole arm and 24 (8%) in the fluconazole arm at the “on therapy plus 7 days” evaluation. At a late follow up visit after completion of the study (through 16 weeks) there were 58 (19%) deaths in the posaconazole arm and 59 (20%) in the fluconazole arm.

In this study, an analysis of population pharmacokinetic data indicated a correlation between patients with the lowest serum concentrations of posaconazole and the highest rates of clinical and mycological failure (see page 10 of this document). It was unclear whether low serum concentrations were a covariate with, or a cause of an unfavorable outcome. Pending further study, physicians should be advised that patients unable to take this oral medication together with a high fat meal may achieve subtherapeutic drug levels.

Study P01899 (Study 2)

Study P01899 was a randomized, evaluator- blinded study conducted in a population >12 years of age with prolonged neutropenia following intensive induction chemotherapy for new diagnosis of acute leukemia or myelodysplasia. One hundred and ten sites in the US and overseas participated. Study arms were balanced in the percentage of patients with AML (~70% of the study population), relapse of AML and myelodysplastic syndromes, and in the severity of neutropenia (nadir WBC <=100 cells/ul in ~87% of the population).

The mean duration of therapy was 29 days for posaconazole and 25 days for fluconazole or itraconazole.

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Patients were randomized to posaconazole 200 tid or one of two control drugs, depending on the center -- fluconazole 400qd or itraconazole 200 bid. All drugs were given as oral solutions. Selection of the comparator azole was left to the discretion of each study site.

For periods when oral drugs could not be administered, patients in the posaconazole arm were treated with intravenous amphotericin B while those on the fluconazole or itraconazole arms were treated with the corresponding intravenous formulations of these drugs, for a maximum of 3 days. Episodes of intravenous antifungal use were infrequent, occurring in 6% of posaconazole treated subjects, and 10% of comparator treated subjects.

Dosing was continued until resolution of neutropenia, complete remission, or to a maximum of 84 days. Study visits occurred at the end of treatment (plus 7 days), 30 days after the end of treatment and at day 100 after initiation of study drug.

In the Agency's analysis, Clinical failure was defined as for study CI98-316.

Similar to study CI98-316, outcome was assessed in each patient seven days after the end of therapy (where loss-to-follow-up and other events occurring after premature cessation of prophylaxis were censored) and at the end of 100 days (where events occurring after cessation of prophylaxis were included).

Outcome in PO1899 (Study 2)		
	Posaconazole n =304	Fluconazole/Itraconazole n = 298
<i>On therapy plus 7 days</i>		
Clinical Failure ^a	82 (27%)	126 (42%)
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	17 (6%)	25 (8%)
Proven / probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF ^{b,c}	67 (22%)	98 (33%)
<i>Through 100 days post-randomization</i>		
Clinical Failure	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(<i>Aspergillus</i>)	2 (1%)	26 (9%)
(<i>Candida</i>)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven / probable fungal infection prior to death	2 (1%)	16 (5%)
SAF ^{b,c}	98 (32%)	125 (42%)
Lost to follow-up ^d	34 (11%)	24 (8%)
a: 95% confidence interval (posaconazole-fluconazole) = (-22.8%, -7.8%). b: SAF – systemic antifungal therapy c: Use of SAF criterion is based on protocol definition (empiric/IFI usage >4 consecutive days). d: Lost to follow-up means the subject was not observed for 100 days from randomization		

The results demonstrated statistical superiority of posaconazole compared to pooled comparators.

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To eliminate overlap in these components, the single reason for failure in each patient was determined hierarchically in the order shown below.

PO1899 (Study 2)	Posaconazole n = 304	Fluconazole/Itraconazole n = 298
On therapy plus 7 days		
Clinical Failure ^a	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7	25
All Deaths	17	25
SAF ^{b,c}	58	76
Through 100 days post-randomization		
Clinical Failure	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14	33
All Deaths	42	48
SAF ^{b,c}	68	86
Lost to follow-up ^d	34	24

Table: Pathogens responsible for breakthrough IFI (probable or proven) among all randomized patients during the period from initiation of prophylaxis until 7 days after completion of prophylaxis in each patient.

	Posaconazole	Fluconazole	Itraconazole
<i>Aspergillus</i>	2 (both probable)	15 (1 proven, 14 probable)	5 (all probable)
<i>Candida</i>	3 (all proven)	2 (both proven)	0
Other	2 (1 probable, 1 proven)	2 (both proven)	1 (probable)

Deaths:

There were 17 (6%) posaconazole- treated patients and 25 (8%) comparator-treated patients who died. By 100 days after initiation of therapy, death rates were 44 (14%) for posaconazole-treated patients and 64 (21%) for comparator-treated patients (p=0.035 (log rank statistics)). These results suggest that posaconazole may offer a mortality advantage in this population.

Timing of the Action

The review of this priority application and the composite clinical endpoint was challenging. There were various requests for additional analyses from the company and various sensitivity analyses conducted by the reviewers to understand the findings. At the time of the PDUFA goal date the review of NDA 22-003 had not been completed. Therefore we missed the PDUFA goal date. After missing the goal date, we became aware of the Division of Scientific Investigations (DSI) inspection of an investigator involved with several clinical studies including Schering's study C198-316. After learning about the issues with this site in study C198-316, we consulted DSI for their recommendations on further inspections (see DSI Inspections below). Inspections of five clinical sites from the prophylaxis studies in NDA [redacted] were performed.

DSI inspections

(Please see the DSI reviews by Dr. Young, and Ms. Storms, and the memorandum for Ms. Miller) In response to a complaint, DSI performed an inspection of [redacted]

The DSI inspection of [redacted] examined several clinical trials in which [redacted] participated. A form 483 was issued citing a number of areas of noncompliance across the studies inspected with a recommendation of OAI. The initial recommendation from DSI was to exclude the data

from [redacted] site. On August 29, 2006, the applicant asked that the data from [redacted] site be maintained based upon Schering's careful monitoring and independent verification of the data from [redacted] site and supplied documentation in support of their request. The request and supporting documentation was reviewed by DSI. Following review of the material provided, DSI conclusion is, in part, as follows: "[redacted] data may be included in the final analysis of C/I 98-316 for reasons outlined below. It should be made clear to everyone that inclusion of [redacted] data does not constitute endorsement of the way in which he conducted his clinical trials." The documents states that, "data submitted from [redacted] site can be relied upon because what data was reported in the CRFs was verified by the study monitors against source documents following SOPs created for all Schering-Plough clinical trials and C/I98-316 specifically and created at a time before any question was raised about [redacted] performance as an investigator. That [redacted] study was monitored per SOP is supported by the monitoring reports in terms of number of visits and kinds and quantity of deficiencies identified and brought to the site's attention." (For additional details of Dr. Young's findings, please see Dr. Young's review.) Based upon the recommendation from DSI, [redacted] data are included in the analyses for Study C/I 98-316.

DSI performed inspections of five sites from the prophylaxis studies. The sites were selected for inspection due to high enrollment. Of the five sites inspected, three received a field classification of NAI, and two received a field classification of VAI. The recommendations across the sites inspected with regard to assessment of data integrity are that the data from the sites appear acceptable. (For additional details, please see Ms. Storms DSI review.)

Summary:

NDA 22-003 for Noxafil (posaconazole) oral suspension should be approved for the indication, "NOXAFIL (posaconazole) is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft versus host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy."

The treatment regimen is 200 mg PO TID for the duration of time that the patient is at risk. In clinical trials, the average duration of posaconazole treatment was 80 days in patients with HSCT and GVHD, and 29 days in patients with hematologic malignancies and prolonged neutropenia.

Posaconazole is the first antifungal approved for prevention of fungal infections due to *Aspergillus*, and the third drug approved for prevention of *Candida* infections. Currently fluconazole and micafungin are approved for *Candida* prophylaxis; fluconazole is available as oral and IV therapy, micafungin is IV only.

Absorption of posaconazole is strongly influenced by food and therefore the drug needs to be given with a full meal or a nutritional supplement. An exposure response assessment showed an association between low posaconazole levels and clinical failure; the outstanding issue is whether the low levels are due to the patients' underlying medical condition and inability to ingest a full meal or whether the posaconazole levels and success rates are low because these are significantly compromised patients. This issue will be addressed by the company in postmarketing.

Posaconazole is a CYP3A4 inhibitor and therefore drug interactions can occur. In the clinical trial database, clinically significant interactions included three fatalities that may be due to a posaconazole/cyclosporine drug interaction (one in the clinical prophylaxis studies and two in other treatment studies). Hence, the Warning paragraph has been included in the Noxafil (posaconazole) product labeling regarding the interaction between cyclosporine and posaconazole.

Many of the treatment-emergent adverse reactions were consistent with the underlying medical conditions. Most common events included fever, nausea, diarrhea and hypokalemia and occurred at similar frequency in posaconazole-treated and comparator-treated patients. Noteworthy adverse events included hepatic

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toxicity and the cyclosporine drug interaction. There were cases of thrombocytopenia, TTP/HUS, and pulmonary embolism that were included in labeling and will be evaluated in postmarketing.

As one of the postmarketing commitments for NDA 22-003, the applicant will conduct a study in patients receiving antifungal prophylaxis who are at risk for low absorption. Different dosing strategies including the use of therapeutic drug monitoring (TDM) to increase plasma concentrations will be explored to evaluate exposure-response and TDM.

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CLINICAL REVIEW

Application Type NDA 22-003
Submission Number N-000-S4
Submission Code P

Letter Date December 20, 2005
Stamp Date December 22, 2005
PDUFA Goal Date June 22, 2006

Reviewer Name Maureen R. Tierney, MD, MSc.
Review Completion Date July 30, 2006

Established Name Posaconazole
(Proposed) Trade Name Noxafil
Therapeutic Class Azole-Anti-fungal
Applicant Schering Corporation

Priority Designation P

Formulation Oral Suspension
Dosing Regimen 200 mg po TID
Indication Prevention of IFI
Intended Population Patients post Bone Marrow
Transplantation with GVHD or with Hematologic
Malignancy at High Risk for Neutropenia

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1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Two studies were presented for the evaluation of the safety and efficacy of posaconazole in the prevention of IFI in severely immunocompromised hosts. Please see below.

Table 1: Clinical Studies of Prophylaxis of IFI

Study Number	Type of Study	Population	Study Drug	Control
CI98-316	Randomized, DB	Acute leukemia or Myelodysplastic Syndrome Post HSCT +GVHD	Posaconazole 200mg po TID N=301	Fluconazole 400 mg po qD N=299
P01899	Randomized, OL	Hematologic Malignancy at High Risk for Neutropenia post Chemotherapy	Posaconazole 200mg po TID N=304	Fluconazole 400 mg po qD(N=240) or Itraconazole 200mg po BID (N=58)

Please See Section 4.2 Tables of Clinical Studies Section p.20 for further detail on study sites.

1.3.2 Efficacy

In the first double-blind clinical study described above, in patients post hematopoietic stem cell transplant with GVHD, posaconazole was shown to be noninferior to fluconazole in clinical outcome defined as the occurrence of proven or probable invasive fungal infection, death, or use of systemic anti-fungal therapy for greater than 4 days during both the While on Treatment period (oral therapy plus 7 days) or the prespecified primary time period of 16 weeks (where lost to followup was also included as clinical failure.). Mortality was similar between the groups. The majority of deaths were secondary to the underlying disease, its complications or its primary therapy. The incidence of IFI, especially Aspergillus infection, was lower in the posaconazole arm. Please see the table below. Placebo rates of the incidence of proven/probable IFI in this population range from 15 to 18%. (6, 16.)

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Division and the Medical Officer recommend that posaconazole in a dose of 200mg given by oral suspension three times daily be used in the prevention of invasive fungal infection (IFI) due to *Aspergillus* and *Candida* in patients with severe immunocompromise such as post stem cell transplant patients with graft versus host disease (GVHD) or patients with hematologic malignancies with prolonged neutropenia be approved. The duration of therapy will depend upon the length of time the patient remains at risk for IFI. However, the safety of posaconazole for the prophylaxis of these infections has only been assessed up to 4 months.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Division has requested quarterly detailed reports of all patients with thrombotic or microangiopathic events such as TTP (thrombotic thrombocytopenic purpura), HUS (hemolytic uremic syndrome), or PE (pulmonary embolus), etc. for 3 years.

1.2.2 Required Phase 4 Commitments

The Division requests that a study be performed to look at low levels of posaconazole absorption and clinical outcome using different dosing strategies and evaluating the potential benefit of TDM (therapeutic drug monitoring.)

The Division has requested quarterly detailed reports of all patients with thrombotic or microangiopathic events such as TTP, HUS, or PE, etc. for 3 years.

1.2.3 Other Phase 4 Requests

The Division has requested that the Sponsor provide utilization data with indication when known biannually for 3 years.

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Table 2: 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 = 301	Fluconazole n = 299
On therapy plus 7 days		
Clinical Failure ^a	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(<i>Aspergillus</i>)	3 (1%)	17 (6%)
(<i>Candida</i>)	1 (<1%)	3 (1%)
(Other)	3 (1%)	2 (1%)
All Deaths	22 (7%)	24 (8%)
Proven / probable fungal infection prior to death	2 (<1%)	6 (2%)
SAF ^{b,c}	27 (9%)	25 (8%)
Through 16 weeks		
Clinical Failure ^{a,d}	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(<i>Aspergillus</i>)	7 (2%)	21 (7%)
(<i>Candida</i>)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths	58 (19%)	59 (20%)
Proven / probable fungal infection prior to death	10 (3%)	16 (5%)
SAF ^{b,c}	26 (9%)	30 (10%)
Event free lost to follow-up ^e	24 (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). d: 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%) 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.		

In the second open label study in patients with hematologic malignancy with prolonged neutropenia from cancer chemotherapy posaconazole was superior to the combined standard azole arm (either fluconazole or itraconazole depending on the site but 4/5 of the control patients received fluconazole) in clinical outcome (defined as defined as the occurrence of proven or probable invasive fungal infection, death, or use of systemic anti-fungal therapy for greater than 3 days during both the Treatment Phase (oral therapy plus 7 days) or 100 days post randomization. Posaconazole performed better against fluconazole than itraconazole (superior to fluconazole in clinical outcome and IFI incidence and noninferior for these same parameters against itraconazole but the number of patients enrolled at these sites was much smaller.) Mortality was similar between the groups at the end of treatment but was lower in the posaconazole arm at 100 days post randomization. The incidence of IFI especially *Aspergillus* infection was lower in the posaconazole arm. Most of the difference between the posaconazole arm and fluconazole/itraconazole arm in this

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study was in probable *Aspergillus* infection. Rates for proven *Aspergillus* infection were low and similar among the groups. Placebo rates for this population range from 8% in one study which included only proven IFIs to 33% when proven and probable IFIs are included. (19, 13) Please see the table below.

Table 3: 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
On therapy plus 7 days		
Clinical Failure ^{a,b}	82 (27%)	126 (42%)
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	17 (6%)	25 (8%)
Proven / probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF ^{c,d}	67 (22%)	98 (33%)
Through 100 days post-randomization		
Clinical Failure ^b	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(<i>Aspergillus</i>)	2 (1%)	26 (9%)
(<i>Candida</i>)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven / probable fungal infection prior to death	2 (1%)	16 (5%)
SAF ^{c,d}	98 (32%)	125 (42%)
Event free lost to follow-up ^e	34 (11%)	24 (8%)
<p>a: 95% confidence interval (posaconazole-fluconazole/ itraconazole) = (-22.9%, -7.8%).</p> <p>b: Patients may have met more than one criteria defining failure.</p> <p>c: SAF – systemic antifungal therapy</p> <p>d: Use of SAF criterion is based on protocol definition (empiric/IFI usage >3 consecutive days).</p> <p>e: Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.</p>		

An exposure-response relationship analysis was performed by Dr. Jang. In this analysis it was shown that for the first study (C98-316) at lower serum levels of posaconazole (<700 ug/ml) there was a higher incidence of IFI than at levels above 700 ug/ml. This association was not as apparent for the second study (P01899.) Please see tables below.

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Table 4. Incidence of Proven/Probable IFIs between those patients whose POS C_{avg} was ≤ 700 ng/mL and those patients whose POS C_{avg} was >700 ng/mL (Study C98316).

C_{avg} (ng/mL)	≤ 700 ng/mL (N=92)	>700 ng/mL (N=160)
Incidence of Prove/Probable IFIs	6.52% (6/92)	1.88% (3/160)
Incidence of Aspergillosis	4.35% (4/92)	0.63% (1/160)

Table 5: Incidence of Proven/Probable IFIs between those patients whose C_{avg} was ≤ 700 ng/mL and those patients whose C_{avg} was >700 ng/mL (Study P01899).

C_{avg} (ng/mL)	≤ 700 ng/mL (N=155)	>700 ng/mL (N=60)
Incidence of Prove/Probable IFIs	3.87% (6/155)	0% (0/60)

Even though a mortality advantage was shown only in the second study, the demonstration of a consistent pattern of at least non-inferiority in clinical outcome and IFI in the 2 studies and the demonstration of an exposure response relationship in at least one of the studies supports the efficacy of posaconazole in the prophylaxis of IFI due to *Candida* and *Aspergillus*. Since the mortality rate in these populations is very high due to the underlying diseases and the complications of their treatment it is difficult to demonstrate a mortality advantage. However, since IFI due especially to *Aspergillus* and other molds has a high mortality rate, one can conclude that reducing the incidence of such infections would translate into a mortality benefit in clinical practice. A decreased incidence of IFI may also allow patients to receive more therapy for their underlying disease. The presence of an active fungal infection may reduce the ability for the patient to receive further immunosuppressing therapy that might be necessary in combating the underlying malignancy or transplant rejection.

1.3.3 Safety

In summary, posaconazole is a relatively well tolerated azole with some of the same safety concerns as other members of the azole class and some unique safety issues. Overall the potential benefits of this agent in the reduction of invasive fungal infections in severely immunocompromised patients outweigh its potential risks.

There were 3 deaths considered by the investigators to be possibly or probably related to posaconazole therapy. One of the deaths was felt to be probably related to a posaconazole drug interaction producing severe neurologic cyclosporine toxicity and death. The other 2 were possibly related—one secondary to multi-organ failure and the other partly due to persistent hyperbilirubinemia and liver failure with micronodular cirrhosis found at autopsy. There were more serious adverse events that were considered to be treatment related in the posaconazole arms than the comparator arms (10 versus 6%) but fewer adverse events leading to death or discontinuation in the posaconazole arm than in comparators.

Some of the possible adverse events of concern were:

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- 1-Increase in hepatic adverse events including elevation in liver function tests and rare cases of severe liver injury in patients with severe underlying comorbidity;
- 2-Drug interaction with cyclosporine which can lead to severe, even fatal, cyclosporine toxicity. Similar interactions might also be possible with tacrolimus or sirolimus;
- 3-Inhibition of CYP3A4-such interactions could result in effects on QTc and in reduced levels of posaconazole which may result in subtherapeutic effect;
- 4-Similar rates of increase of >60 msec of QTc from baseline and QTc over 500 msec in prophylaxis patients as those who received fluconazole. No similar events recorded in healthy subjects. One case of Torsades de Pointes in prophylaxis pool of patients with severe electrolyte abnormalities;
- 5-Mild increase in incidence of hypokalemia (13%) in comparison to fluconazole (10%) which may influence changes in QTc;
- 6-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 to 0.);
- 7-Mild increase in TTP and HUS in the post stem cell transplant patients with GVHD who received Posaconazole in comparison to Fluconazole. These events may be related to toxicity with cyclosporine, tacrolimus, and sirolimus;
- 8-Most common adverse events that were likely to be drug related were gastrointestinal-nausea, vomiting, diarrhea, and hepatic.

Recommendations:

1. Include in labeling:

- Warning about cyclosporine interaction (and potential interactions with tacrolimus and sirolimus) and potentially fatal toxicity. Recommend initial cyclosporine, tacrolimus, or sirolimus dose reduction when posaconazole therapy is begun and monitor levels more frequently.
- Precaution about QT effects and interaction with CYP3A4 drugs with QT prolonging potential.
- Warning about hepatic adverse events and recommendation for hepatic enzyme monitoring
- Precaution about Pulmonary embolus, TTP, HUS, and thrombocytopenia in post stem cell transplant patients with GVHD
- Recommendation to measure K⁺, platelets frequently.

2. Phase 4 safety reports:

- Quarterly detailed reports of the occurrence of thrombotic or microangiopathic events including TTP, HUS or PE should be filed with the Division.

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1.3.4 Dosing Regimen and Administration

Posaconazole is to be administered as an oral suspension of 200 mg (5 mL) three times a day. Each dose of Posaconazole will need to be given with a full meal or with a liquid nutritional supplement in patients who cannot eat a full meal in order to enhance the oral absorption of posaconazole and optimize plasma concentrations. The duration of therapy is based on recovery from neutropenia or immunosuppression. However, the safety of posaconazole for the prophylaxis of these infections has only been assessed up to 4 months.

In the prior submission of NDA 195 patients had received posaconazole 800 mg po daily for the treatment of various refractory invasive fungal infections for between 91 and 365 days and 57 received this dose for longer than 365 days. The longest any patient received posaconazole was 1061 days.

1.3.5 Drug-Drug Interactions

Posaconazole is an inhibitor primarily of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole. The concomitant administration of the following drugs may reduce the serum levels of posaconazole and result in elevated levels of the listed drug: cyclosporine, tacrolimus, sirolimus, midazolam, and rifabutin. Dose reduction of cyclosporine and tacrolimus and more frequent monitoring of cyclosporine levels should be performed when posaconazole therapy is initiated. Cases of cyclosporine toxicity including fatalities have been reported with concomitant cyclosporine and posaconazole therapy. Additional clinical studies demonstrated that no clinically significant effects on phenytoin, zidovudine, lamivudine, ritonavir, indinavir, or caffeine were observed when administered with posaconazole; therefore, no dose adjustments are required for these co-administered drugs. Phenytoin levels should be monitored.

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions and should not be administered with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4.

Posaconazole administration with glipizide does not require a dose adjustment in either drug; however, glucose concentrations decreased in some healthy volunteers administered the combination. Therefore, glucose concentrations should be monitored in accordance with the current standard of care for patients with diabetes when posaconazole is co-administered with glipizide.

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1.3.6 Special Populations

There were no important differences in safety or efficacy of posaconazole noted in those patients who were between 13 and 18 or those over 65. The drug was not studied in pregnant or nursing women. Of the 605 patients randomized to posaconazole in the prophylaxis clinical trials, 63 (10%) were ≥ 65 years of age. In addition, 48 patients treated with ≥ 800 mg/day posaconazole in another indication were ≥ 65 years of age. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

The populations who will be prescribed this drug are severely immunocompromised with significant co-morbidity. There was a slight increase in thrombotic/microangiopathic events in patients post stem cell transplant with GVHD who received posaconazole. These events have been reported as complications of these underlying conditions. A Phase 4 program of expedited reports of these events will help determine if some interaction of posaconazole with the underlying disease state or its immunosuppressive therapy is present.

There were 28 pediatric subjects (ranging in age from 13 to 17 years) in the 2 prophylaxis studies. Similar proportions of pediatric subjects experienced serious adverse events or other clinically significant adverse events compared with the overall subjects in the prophylaxis studies. The prophylaxis pool contained 12 pediatric subjects treated with posaconazole and 16 pediatric subjects treated with fluconazole. Of the 12 pediatric subjects in the posaconazole group, 9 completed the treatment phase. Two pediatric subjects in the posaconazole treatment group died for reasons unlikely related to study drug treatment, as determined by investigators. One died as a result of the AE of intracranial hemorrhage 14 days following the end of treatment with posaconazole. Another died as a result of the progression of the underlying disease, AML, 8 days following the end of treatment with posaconazole.) Of the 16 pediatric subjects treated with fluconazole, 5 completed the treatment phase. Three pediatric subjects in the fluconazole treatment group died for reasons unlikely related to fluconazole treatment.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Posaconazole is a triazole antifungal agent available as a suspension for oral administration. Like other triazole drugs, such as voriconazole; posaconazole blocks the synthesis of fungal cell membrane ergosterol, by inhibiting fungal cytochrome P-450 enzyme lanosterol 14 α -demethylase.

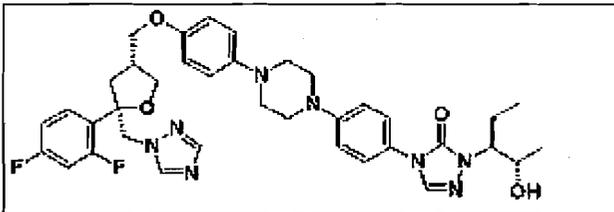
The proposed dosing regimen for posaconazole (Oral Suspension) is 200mg po TID with food or nutritional supplement. Posaconazole is supplied in a 4-ounce (123 mL) bottle containing 105 mL of suspension. Each mL provides 40 mg of posaconazole. Posaconazole was studied in patients \leq 13 years.

PROPRIETARY Name: Noxafil

NONPROPRIETARY Name: Posaconazole, SCH 56592.

CHEMICAL Name: 2,5-Anhydro-1,3,4 -trideoxy-2-C- (2,4-difluorophenyl) - 4 -[[4 -[4 -[4 -[1[(1S, 2S)-1-ethyl-2-hydroxypropyl] -1,5-dihydro-5-oxo-4H-1,2,4-triazole-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)-D-threo-pentitol

STRUCTURAL FORMULA:



Molecular weight: 700.78

Empirical Formula: C₃₇H₄₂F₂N₈O₄

2.2 Currently Available Treatment for Indications

FLUCONAZOLE: Prophylaxis. DIFLUCAN is also indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.

MICAFUNGIN: Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

2.3 Availability of Proposed Active Ingredient in the United States

Posaconazole is a new molecular entity; it is not currently marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products:

The adverse events primarily associated with the azoles are hepatic, cardiac and dermatologic. There is also a significant potential for drug-drug interactions. Specific toxicities associated with the use of individual agents are listed in the approved labels and briefly described below.

Ketoconazole: Ketoconazole inhibits cytochrome P450 3A4 enzyme system. In addition, to the potential for hepatic toxicity; QT prolongation and torsades de pointes are described in a **black box** warning in the approved label.

Cardiac toxicity, in the form of QT prolongation is related to potential drug interactions. Co administration of ketoconazole with drugs such as terfenadine or astemizole is contraindicated. Ketoconazole will also affect the levels of cyclosporine, tacrolimus, and sirolimus.

Itraconazole: A potent P-450 CYP3A4 inhibitor. In addition to the potential for congestive heart failure; QT prolongation and torsades de pointes are described in a black box warning in the approved label. Cardiac toxicity, manifested by a negative inotropic effect was observed in humans and in dogs. The QT effect is related to potential drug interactions. Co-administration of itraconazole with drugs such as cisapride, quinidine, and dofetilide is contraindicated. Itraconazole will also affect the levels of cyclosporine, tacrolimus, sirolimus.

Fluconazole: A highly selective inhibitor of P-450 sterol C-14 α -demethylase. Similar to other azoles, fluconazole is associated with drug interactions. For example, coadministration

of fluconazole with terfenadine is contraindicated. Other potential adverse events associated with the use of fluconazole include hepatic toxicity and exfoliative dermatitis.

Drug Interactions-Cyclosporine: DIFLUCAN may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving DIFLUCAN and cyclosporine.

Voriconazole: Extensive hepatic metabolism by cytochrome P-450 enzymes (CYP2C19, CYP2C9, and CYP3A4), leading to an extensive list of drug-drug interactions. Visual disturbances are common after voriconazole administration (~30%); vision usually returns to baseline after voriconazole is discontinued. Similar to the other azoles, voriconazole has the potential to cause hepatic, cardiac, and dermatologic toxicity

Drug Interactions-Cyclosporine (CYP3A4 substrate): In stable renal transplant recipients receiving chronic cyclosporine therapy, concomitant administration of oral voriconazole (200 mg Q12h for 8 days) increased cyclosporine C_{max} and AUC_T an average of 1.1 times (90% CI: 0.9, 1.41) and 1.7 times (90% CI: 1.5, 2.0), respectively, as compared to when cyclosporine was administered without voriconazole. When initiating therapy with voriconazole in patients already receiving cyclosporine, it is recommended that the cyclosporine dose be reduced to one-half of the original dose and followed with frequent monitoring of the cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine levels should be frequently monitored and the dose increased as necessary.

Sirolimus is contraindicated in patients taking voriconazole.

2.5 Presubmission Regulatory Activity

Schering Plough Research Institute (SPRI) submitted IND 51,662 for SCH56592 (posaconazole) oral suspension on October 4, 1996. A further development meeting was held on December 13, 2000. On October 6, 2003, a pre-NDA meeting was held to discuss the preclinical and clinical data for posaconazole.

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3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please see CMC review

3.2 Animal Pharmacology/Toxicology-

Please see Dr. McMaster review

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

NDA — was an electronic submission of 2 studies evaluating the efficacy and safety of posaconazole in the prevention of IFI.

4.2 Tables of Clinical Studies

Table 6: Clinical Studies of Prophylaxis of IFI

Study Number	Type of Study	Population	Study Drug	Control
CI98-316	Randomized, DB	Acute leukemia or Myelodysplastic Syndrome Post HSCT +GVHD	Posaconazole 200mg po TID N=301	Fluconazole 400 mg po qD N=299
P01899	Randomized, OL	Hematologic Malignancy at High Risk for Neutropenia post Chemotherapy	Posaconazole 200mg po TID N=304	Fluconazole 400 mg po qD or Itraconazole 200mg po BID Total N=298

Study Sites

1. C98-316:

90 Sites; 40% of sites US; 60% foreign (mostly Europe and Australia)
Most sites enrolling less than 10 patients.

The following is a list of the largest (>20 subjects) sites in study C98-316.

I43 N=49 – Durrant, Australia
I20 N=36 – Ullmann, Germany (also large enroller in P01899)
I12 N=29 – Lipton, Toronto
C15 N=23 – Chandrasekar, Detroit
C12 N=23 – Vesole, Milwaukee
C35 N=22 – Langston, Atlanta
C25 N=21 – Tarantolo, Omaha

2. P01899

110 sites:
US: 26.5%
Europe 42%
Latin America 20.5%
Far East 6.5%
Canada 5%
Most sites enrolling less than 10 patients

The following is a list of the largest (>20 subjects) sites in study P01899.

2 N=30 – Cornely, Germany
15 N=28 – Maertens Belgium
139 N=26 – Winston, Los Angeles, CA
41 N=24 – Perfect, Durham, NC
153 N=23 – Helfgott, New York, NY
3 N=21 – Ullmann Germany (also large enroller in study 316)

4.3 Review Strategy

- 1-Read submission thoroughly
- 2-Evaluated study designs
- 3-Randomly reviewed 10% of CRFs to see if concurred with DRC conclusions
- 4-Reviewed all proven/probable cases of IFI, deaths and the drug attributable serious AEs
- 5-Evaluated efficacy results and re-analyzed data using different outcomes based on consultation with statistical colleagues
- 6-Evaluated safety results and referred to original safety review of prior submission.

4.4 Data Quality and Integrity

All clinical outcome data from both studies was reviewed by a blinded Data Review Committee consisting of experts in the field of infections in immunocompromised hosts. The Medical Officer's review of cases was consistent with that of the data review committees. The members of the DRCs are listed in Appendix 3. A referral to the DSI (FDA-Division of Scientific Investigation) was made and the appropriate investigation of clinical research sites were undertaken. At the time of this writing these routine investigations were on-going.

4.5 Compliance with Good Clinical Practices

The sponsor's statement was submitted and reviewed and appeared in compliance with good clinical practices.

4.6 Financial Disclosures

OMB Form 0910-0396 was submitted and reviewed.

5 CLINICAL PHARMACOLOGY

5.1 5.1 and 5.2 Pharmacodynamics and Pharmacokinetics

Please see Clinical Pharmacology review by Dr. Seong Jang.

Please also note that in many of the tables below authored by Dr. Jang there is a reference to tablets or capsules. The dosage form approved will be an oral suspension. The pk parameters are similar.

The oral posaconazole formulation is absorbed with a T_{max} of approximately 5 hours and kinetics are linear with single and multiple doses until 800 mg after which no further increases in exposure are observed. Multiple daily doses result in an over 180% increase in exposure over the once daily dose. Posaconazole is widely distributed and is highly protein bound. Adequate oral absorption requires the intake of a fatty meal simultaneously. See tables below by Dr. Jang.

Table 7: Pharmacokinetic parameters (Mean±SD [range]) of POS tablets on Day 14 after oral (Q12 hr) administration of POS tablets for 14 days (n=9/Dose)

(Study I96-089)

	200 mg BID	400 mg BID	Fold Difference
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C_{max} (ng/mL)	1753±466 [1020-2230]	4150±816 [2920-5710]	2.37
AUC_{0-12} (ng·hr/mL)	16801±4319 [8929-21960]	39206±8020 [24475-47985]	2.33

Table 8: Pharmacokinetic parameters (Mean±SD [range]) of POS following single oral administration of POS tablets to healthy male volunteers (n=6 for each dose). (Study I95-098)

	200 mg	400 mg	Fold Difference
C_{max} (ng/mL)	332±70.8 [273-470]	611±190 [424-964]	1.84
AUC_{inf} (ng·hr/mL)	10896±3411 [5650-14634]	20264±6781 [12716-29387]	1.86

Table 9: Pharmacokinetic parameters (Mean±SD [range]) of POS (n=20) after a single oral administration of 400 mg oral suspension after a 10-hr fast or a high-fat breakfast (Study I96099)

	Suspension (fasted)	Suspension (high-fat meal)	Fold Difference
C_{max} (ng/mL)	132±65.8 [45.7-267]	512±176 [241-1016]	3.88
AUC_{inf} (ng·hr/mL)	4179±1285 [2705-7269]	13885±5655 [7854-34824]	3.3

Table 10: Pharmacokinetic parameters (Mean (CV%)) of POS (n=20) after a single oral administration of 200 mg oral capsule after a 10-hr fast or a high-fat breakfast (Study I95099)

	Capsules (fasted)	Capsules (high-fat meal)	Fold Difference
C_{max} (ng/mL)	102.3 (39%)	531.4 (32%)	5.2
AUC_{inf} (ng·hr/mL)	3588 (37%)	14293 (38%)	3.98

5.2 There are no major circulating metabolites and inhibitors of CYP450 are likely not to alter posaconazole concentrations. Elimination of posaconazole is slow with a mean half life of 35 hours (range 20-66 hours). Recovery of posaconazole is mostly in feces (77% of radiolabeled dose) of which most is the parent drug (66%). Renal clearance contributes approximately 14% to elimination.

5.3 5.3 Exposure-Response Relationships

From collaborative work of Drs. Jang, Colangelo, Higgins, and Tierney, authored by Dr. Jang:

The exposure-response analyses revealed a strong relationship between a higher incidence of Clinical Failure (Clinical failure is defined as proven/probable IFI, death, use of >4 days of

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antifungal therapy, discontinuations due to adverse events, and lost to follow-up) with lower plasma exposure to POS, suggesting that ensuring high plasma exposure to POS appears to be needed especially for patients whose steady state average concentration (C_{avg}) is low (see Figure 1). Further analyses showed:

- (a) The exposure-response relationship for POS effectiveness for the prophylaxis against IFIs was not significantly confounded with any patient demographic covariates
- (b) POS concentration of 350 ng/mL determined at 3 to 5 hours post dose on Day 2 after the beginning of POS treatment would result in a steady-state C_{avg} of 700 ng/mL and subsequently result in the incidence of Clinical Failure of <25%. Plasma concentration monitoring of POS may be used as a tool to identify those patients who will have lower than desired plasma exposure.
- (c) The increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.
- (d) There would be no additional safety findings with 400 mg TID for those patients whose C_{avg} was ≤ 700 ng/mL (i.e., with 200 mg TID). Based on the dose-proportional PK of POS, following 400 mg TID administration to patients whose C_{avg} was ≤ 700 ng/mL (i.e., with 200 mg TID), C_{avg} would not be expected to be greater than 3650 ng/mL, which is the highest C_{avg} observed in patients treated with 200 mg TID in Study C98316.

MO Comment: The above are all preliminary findings and further studies to test these hypotheses will be performed as part of a Phase 4 program.

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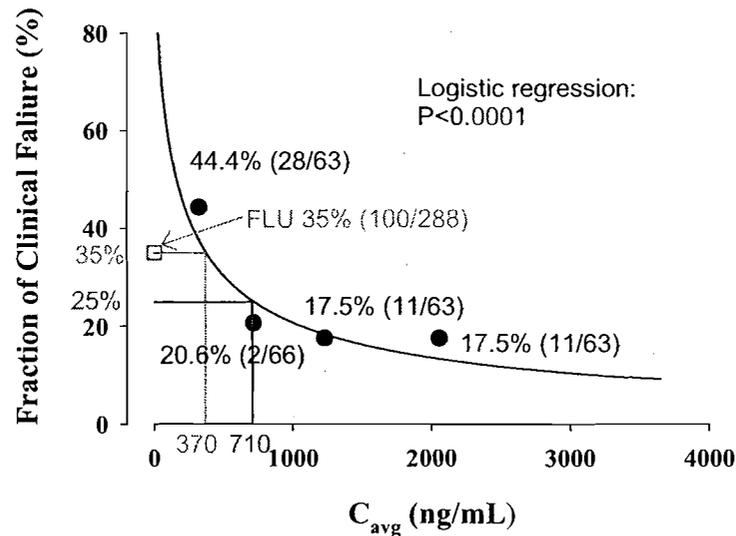


Figure 1: POS exposure-response relationship for patients in the All Treated population during the Primary Time Period (N=252) (Study C98-316)

Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of C_{avg} (closed circles) are plotted to assess the goodness-of-fit. The response rate for patients treated with fluconazole (FLU, open square) is plotted as a reference. The blue lines showed that 710 ng/mL of C_{avg} is required to achieve 25% Clinical Failure rate. The red lines showed that 370 ng/mL of C_{avg} is required to achieve 35% Clinical Failure rate.

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The threshold concentration of 700 ng/mL as C_{avg} also appears appropriate in terms of the incidence of Proven/Probable IFIs, because the incidence of Proven/Probable IFIs also tended to be greater for patients whose C_{avg} was ≤ 700 ng/mL compared with patients whose C_{avg} was >700 ng/mL. Tables S2 and S3 shows the incidence of Prove/Probable IFIs between group of patients whose C_{avg} was ≤ 700 ng/mL and group of patients whose C_{avg} was >700 ng/mL in Study C98316 and P01899, respectively.

Table 11: Incidence of Proven/Probable IFIs between those patients whose POS C_{avg} was ≤ 700 ng/mL and those patients whose POS C_{avg} was >700 ng/mL (Study C98316).

C_{avg} (ng/mL)	≤ 700 ng/mL (N=92)	>700 ng/mL (N=160)
Incidence of Prove/Probable IFIs	6.52% (6/92)	1.88% (3/160)
Incidence of Aspergillosis	4.35% (4/92)	0.63% (1/160)

Table 12: Incidence of Proven/Probable IFIs between those patients whose C_{avg} was ≤ 700 ng/mL and those patients whose C_{avg} was >700 ng/mL (Study P01899).

C_{avg} (ng/mL)	≤ 700 ng/mL (N=155)	>700 ng/mL (N=60)
Incidence of Prove/Probable IFIs	3.87% (6/155)	0% (0/60)

When dose is adjusted from 200 mg TID to 400 mg TID, based on the threshold C_{avg} of 700 ng/mL, the percent of patients whose C_{avg} is ≤ 700 ng/mL would be decreased from 37% (92/252) to 14% (35/252). The Clinical Failure rate for patients whose C_{avg} was ≤ 700 ng/mL (i.e., with 200 mg TID) would be reduced from 37% (34/92) to 25% (23/92) (Table S4).

Table 13: Percent of patients whose C_{avg} is ≤ 700 ng/mL and Clinical Failure rate as a function of POS dosing regimen

$C_{avg} \leq 700$ ng/mL	200 mg TID	400 mg TID (projection)
% of patients whose C_{avg} is ≤ 700 ng/mL	37% (92/252)	14% (35/252)
Clinical Failure rate in patients whose C_{avg} was ≤ 700 ng/mL	37% (34/92)	25% (23/92)

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Table 14: Incidence of Clinical Failure and Proven/Probable IFIs in the All Treated population during the Oral Treatment Phase in 4 concentration quartiles of POS (Study P01899).

C_{avg} (ng/mL)	Clinical Failure	Proven/probable IFI
89.65-322	54.7% (29/53)	3.77% (2/53)
322-490	37.0% (20/54)	1.85 % (1/54)
490-733.5	46.3% (25/54)	5.56% (3/54)
733.5-2200	27.8% (15/54)	0% (0/54)

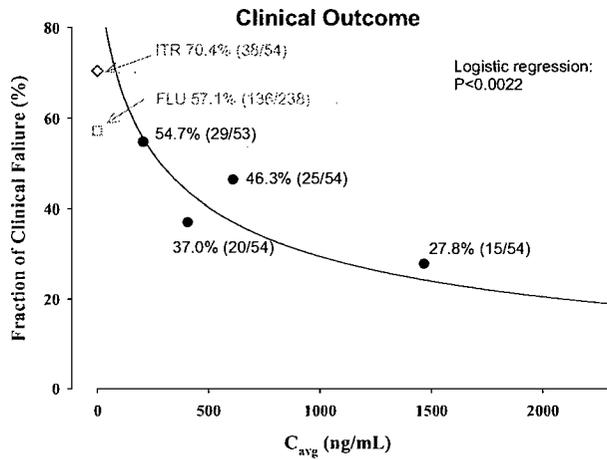


Figure 2: POS exposure-response relationship for patients in All Treated population during the Oral Treatment Phase (n=215) (Study P01899).

Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 concentration quartiles (closed circles) are plotted to assess the goodness-of-fit. The response rates in patients treated with fluconazole (FLU, open square) and itraconazole (ITZ, open diamond) are plotted as references.

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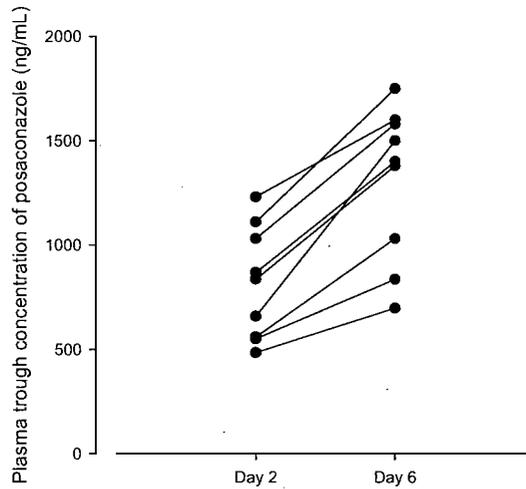


Figure 3: Plasma trough concentrations of POS following oral administration of 200 mg BID on Day 2 (i.e., after 4th dose) and Day 6 (i.e., after 12th dose) in healthy subjects (N=9/dose) (Study I96089).

Table 15: Calculated plasma concentrations of POS before C_{avg} reaches 700 ng/mL at Day 7 (presumed at steady state) following oral administration of POS 200 mg TID.

Day	No. of Dose	Plasma concentration of POS (ng/mL)
1	1	67
	2	186
	3	238
2	4	286
	5	331
	6	371
3	7	408
	8	442
	9	474
4	10	503
	11	529
	12	553
5	13	576
	14	596
	15	615
6	16	632
	17	648
	18	663
7	19	676
	20	689
	21	700

For the calculation, 7.6 ± 2.8 of accumulation ratio (R_{0-12h}) obtained following oral administration of POS 200 mg BID for 14 days (Study I96089) were used.

Table 16: POS C_{avg} in patients who has Proven/Probable IFIs (Study C98316)

Subject ID	C_{avg} (ng/mL)	Quartile	Pathogen
I004000048	99	Q1	Aspergillosis
I004000049	158	Q1	Aspergillosis
I004000050	319	Q1	Candidiasis
I004000051	565	Q2	Aspergillosis
I004000052	681	Q2	Aspergillosis
I004000053	691	Q2	Other Fungi
I004000054	1562	Q3	Aspergillosis
I004000055	2080	Q4	Candidiasis
I004000056	2190	Q4	Other fungi

Table 17: Incidence of Proven/Probable IFIs in Q1-Q2 vs. Q3-Q4 (Study C98316).

	Q1-Q2 (N=126)	Q3-Q4 (N=126)
C_{avg} (ng/mL)	21.5-915	915-3650
Incidence of Prove/Probable IFIs	4.76% (6/126)	2.38% (3/126)
Incidence of Aspergillosis	3.17% (4/126)	0.79% (1/126)

Table 18: POS C_{avg} in patients who had Proven/Probable IFIs (Study P01899)

Subject ID	C_{avg} (ng/mL)	Quartile	Pathogen
0054001468	254	Q1	Aspergillosis
0010001371	294	Q1	Other Fungi
0015001239	417	Q2	Aspergillosis
0015001415	491	Q3	Candidiasis
0057001492	606	Q3	Candidiasis
0002001271	629	Q3	Other Fungi

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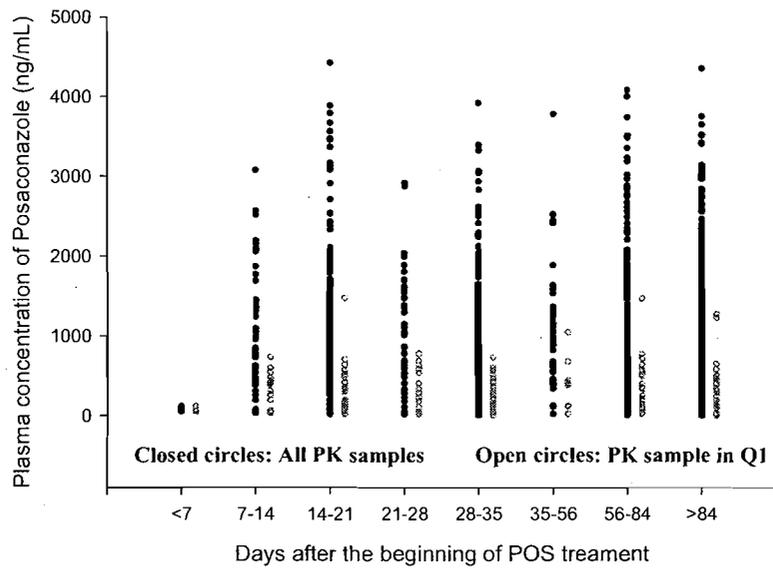


Figure 4: Plasma concentrations of POS (PK sample number=870) in all patients (n=252) as a function of time (days) after the beginning of POS treatment. (Study C98316)

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Table 19: Incidence of treatment-emergent and drug-related (Possible and Probable) AEs (%) in the All Treated population in 4 quartiles of average plasma concentration POS (C_{avg}) (N=450; Studies C98-316 and P01988). Datasets from Study C98-316 and P01899 were pooled for these analyses.

	1 st Q (n=119)	2 nd Q (N=121)	3 rd Q (N=120)	4 th Q (N=120)	P value ^b
C_{avg} (ng/mL) ^a	205±105 [2.51-355]	498±77.1 [355-626]	835±138 [626-1118]	1751±538 [1118-3650]	
Diarrhea	3.36%	4.96%	8.33%	6.67%	0.4378
Nausea	7.56%	6.61%	10%	12.5%	0.3746
Vomiting	3.36%	4.96%	7.5%	6.67%	0.4639
Discontinuation	8.4%	7.44%	14.2%	17.5%	0.0595
Bilirubinemia	1.68%	3.31%	4.17%	3.33%	0.4787
SGOT increased	1.68%	2.48%	4.17%	3.33%	0.4016
SGPT increased	1.68%	3.31%	5%	3.33%	0.4911
Hepatic enz. increased	1.68%	3.31%	4.17%	3.33%	0.4787
Hypokalemia	0.84%	1.65%	4.17%	2.5%	0.4818
Rash	0.84%	1.65%	4.17%	3.33%	0.1739

^a: Mean±SD [range]

^b: Logistic regression for the relationship between the incidence of treatment-related adverse events and C_{avg}

MO COMMENT: The above pk data and analyses suggest there is an exposure response relationship. It also suggests there may be an association between low serum levels and poorer outcome, especially in the post stem cell transplant population. These preliminary results need to be further studied in Phase 4. The possible benefit of therapeutic drug monitoring in the administration of this drug also needs further evaluation but should not preclude approval.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

There were 2 studies submitted to evaluate the safety and efficacy of posaconazole in the prevention of IFI in severely immunocompromised hosts.

Table 20: Clinical Studies of Prophylaxis of IFI

Study Number	Type of Study	Population	Study Drug	Control
CI98-316	Randomized, DB	Acute leukemia or Myelodysplastic Syndrome Post HSCT +GVHD	Posaconazole 200mg po TID N=301	Fluconazole 400 mg po qD N=299
P01899	Randomized, OL	Hematologic Malignancy at High Risk for Neutropenia post Chemotherapy	Posaconazole 200mg po TID N=304	Fluconazole 400 mg po qD(N=240) or Itraconazole 200mg po BID (N=58)

Since the populations in each of the studies were quite different the results of each study will be examined individually for the efficacy analysis. In each section below Study C98-316 will be presented first followed by Study P01899.

6.1.2 General Discussion of Endpoints

C98-316

Efficacy Endpoints

Primary Efficacy Variable

Sponsor: “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).”

Division: Clinical failure-defined as proven/probable IFI, death, receipt of more than 4 days of systemic antifungal therapy, or lost to followup in the All Treated Population and the Per Protocol (Efficacy Evaluable) population during the Primary Time Period and the While on Treatment Period.

Secondary Efficacy Variables

Sponsor: Clinical outcome is a secondary endpoint designed to evaluate a potential treatment effect regarding clinical failure. Clinical failure was defined in the protocol as the occurrence of a proven or probable IFI, receipt of more than 4 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 (ie, subject not followed for the entire duration of the period.)

Division: Incidence of Proven plus Probable IFI in the All Randomized population and the Per Protocol population during the While on Treatment and Primary Time Period.

Sponsor and Division:

The time from randomization to death for All Treated Subjects was analyzed using the Kaplan-Meier method during the Treatment Phase; all subjects who did not die, were censored at the end of the Treatment Phase or at the last follow-up observation in the case of premature discontinuation.

Incidence of Aspergillus infection in both the All Randomized Patients Population and in the Per Protocol Population.

Study P01899

Efficacy Endpoints

Sponsor Primary Efficacy Variable

The Sponsor's primary efficacy variable was the incidence of proven or probable IFI from randomization to the end of the Oral Treatment Phase, defined as the period from randomization to last dose of oral study medication plus 7 days. The subject's IFI status was determined by the DRC according to the EORTC-MSG criteria.

Division Primary Efficacy Variable

The Division determined that the primary efficacy analysis should be the comparison of Clinical Failure in the All Treated population (ITT) and All Randomized populations in the 3 treatment groups during the oral treatment phase. **Clinical failure**-defined as proven/probable IFI, death, receipt of more than 3 days of systemic antifungal therapy, or lost to followup.

Secondary Variables

Clinical Failure at 100 days

Incidence of IFI in All Treated and Efficacy Evaluable populations (Division)

IFI due to Aspergillus

Time to Death and Incidence of Death

Time to IFI

Time Periods

The Efficacy variables were assessed at these time intervals:

Study C98-316

While on Treatment- Time from first day of drug until last day of drug + 7 days.

Primary Time Period- Randomization plus 111 days (16 weeks.)

Study P01899

Oral Treatment Phase –from randomization to the last dose of oral study drug + 7 days (or the discontinuation date for subjects randomized but never treated).

30 day-30 days after the last dose of study drug

100 day -100 days after randomization

6.1.3 Study Design

Study C98-316 Prevention of IFI in Patients Post Stem Cell Transplant with GVHD

This was a Phase 3, randomized, multicenter, double-blind, active control, comparative study of Posaconazole (200 mg TID) versus Fluconazole (400 mg QD) in the prophylaxis of invasive fungal infections in high-risk subjects with GVHD following allogeneic hematopoietic progenitor cell (stem cell) transplantation.

Approximately 600 subjects were to be enrolled at approximately 85 sites. Subjects entering the study were stratified by site and according to the type of GVHD (acute or chronic). Protocol-eligible subjects were randomized to receive either 600 mg POS (200 mg three times a day), or 400 mg FLU once daily. Treatment was to continue for 16 weeks or until an IFI occurred. All subjects were

eligibility and evaluability criteria. Specifically, in order to be considered evaluable, subjects were to have met all of the following criteria:

- Take at least 80% of the assigned treatment (over the entire treatment phase) or up to the development of proven or probable IFI.
- Meet key inclusion/exclusion criteria. Subjects who met the MITT definition of acute or chronic GVHD and iatrogenic immunosuppression as defined in the protocol, who did not receive any prohibited medications concurrently with study treatment that could compromise FLU or POS pharmacokinetics, and who complied with study visit schedules (data available to 16 weeks or date of discontinuation).
- Did not drop out of the treatment phase before 16 weeks since the start of study drug, other than for proven or probable IFI.
- In the absence of a proven or probable IFI (as determined by the DRC), did not receive more than 5 consecutive days of empiric therapy with a systemic antifungal during the treatment phase.
- Did not receive more than 5 days of a systemic antifungal during a study drug interruption.
- For subjects who developed a proven or probable IFI, the IFI must have occurred more than 5 days from start of study drug.

Study P01899-Prevention of IFI in Patients with Acute Hematologic Malignancy at High Risk for Prolonged Neutropenia:

This was a Phase 3, randomized, evaluator-blind, active control, parallel group, multicenter study of :

**POS (200 mg three times daily [TID]) versus
FLU (400 mg once daily [QD]) or ITZ (200 mg twice daily [BID])**

for prophylaxis against IFIs.

The study population consisted of high-risk subjects with prolonged neutropenia due to standard intensive induction chemotherapy given for a new diagnosis of AML, AML in first relapse, MDS, or other secondary myelogenous leukemias.

A blinded panel of external expert evaluators (Data Review Committee [DRC]) was to determine if subjects in either treatment arm developed proven, probable, or possible IFI on the basis of European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC-MSG) criteria.

Approximately 600 subjects were to be randomized at 110 sites. Prior to randomization of the first subject, each site was to designate the standard azole

to be followed one and two months after the 16-week treatment phase, including those subjects who developed an IFI during treatment. Subjects who discontinued treatment early for reasons other than the development of an IFI were also to be followed for the full 16-week treatment and the 2-month follow-up.

All subjects were to have periodic evaluations for the presence of fungal infection. These evaluations were to include signs and symptoms of infection, a physical examination, fungal blood cultures, chest x-ray and chest CT scan if clinically indicated. Serial *Aspergillus* antigen testing and fungal PCR were also to be performed at a central laboratory. These results were not to be made available for clinical decision-making, but rather to be analyzed at the end of the study for the purpose of correlating the results of the tests with the clinical outcome.

At any time during the study, if a subject developed a fever, or any other sign or symptom of infection, a complete infection episode evaluation was to be performed. This examination for bacterial, fungal, viral, and parasitic etiologies as clinically indicated included signs and symptoms evaluation, physical exam, complete blood count, cultures and/or histopathology of any clinically-suspicious site of infection, urinalysis, urine culture, chest x-ray and additional radiographic imaging, or other clinical/laboratory evaluation. During the evaluation of episodes of suspected infection, fungal blood cultures, *Aspergillus* antigen testing and fungal PCR were to be performed twice per week; the drawing of the second sample was to be separated from the first by at least 24 hours. *Aspergillus* antigen testing (serum and other sterile fluids if clinically indicated and available) and fungal PCR were performed at a central laboratory. If results were needed for clinical management, duplicate samples were sent to the local laboratory. More frequent fungal blood cultures or *Aspergillus* antigen testing may have been performed as clinically indicated. Each infection diagnostic work-up and its outcome was to be separately recorded on the Case Report Form (CRF) by the investigator. Based on review of the infection episode evaluations recorded by the investigator for each subject, all subjects were to be characterized as having either no IFI (including all bacterial, viral, superficial fungal or non-fungal infectious syndromes), possible IFI, probable IFI, or proven IFI. All subjects who were considered treatment failures (according to the investigator or the usage of >5 days of systemic antifungal use) or who were classified by the investigator as having possible, probable, or proven IFI were to be referred to the Data Review Committee for adjudication. For clinical management, the investigator determined the subject's IFI status and clinical course, and determined if the subject was a treatment failure and required systemic antifungal therapy. In all cases of death during the study period, the investigator was to assess the immediate cause of death and attribute it to AEs, progression of GVHD, complications of IFI, or other causes. When autopsies were performed, the investigator was to summarize the pertinent clinical findings and indicate if the death was directly or indirectly due to IFI or due to other causes.

For statistical analysis purposes, a panel of external, independent, blinded experts in the USA, the Data Review Committee (DRC), adjudicated the subject's IFI status based on the evidence collected in the Case

	Baseline	Treatment Phase										Post-Treatment Phase	
		Day 1	Wk 2	Wk 4 (Mo 1)	Wk 8	Wk 8 (Mo 2)	Wk 10	Wk 12 (Mo 3)	Wk 14	Wk 16 (Mo 4)	Wk 20 (Mo 5)	Wk 24	
Details Informed Consent	X												
Review Inclusion/Exclusion Criteria	X												
Randomization	X												
Treatment Box Number Assigned	X			X									
Medical History	X												
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Weight	X		X			X		X		X		X	X
Vital Signs (Temperature, Blood Pressure, Pulse, Respiratory Rate)	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam ¹	X	X	X	X	X	X	X	X	X	X	X	X	X
Detailed Neurological Exam	X									X			X
ECOG Performance Evaluation	X					X				X			X
Safety Labs ²	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (Serum) ³	X					X				X			
Fungal Blood Culture ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X
Aspergillus Antigen ^{5,6,7}	X	X	X	X	X	X	X	X	X	X	X	X	X
Fungal PCR ⁸	X	X	X	X	X	X	X	X	X	X	X	X	X
Fungal Cultures (Other Study Sites)		As clinically indicated during infection episode evaluation											
Crab-Comb Fungal Culture ⁹	X	X	X			X		X		X		X	X
Fungal Inocula to Designated Lab for Susceptibility Test ¹⁰		Any isolate cultured any time during study											
Electrocardiogram	X		X							X			
Plasma for PKC Levels ¹¹		X	X			X		X		X			
Chest X-ray	X ¹	Infection episode evaluation											
Other X-ray/CT Scan/Diagnostic Imaging		As clinically indicated during infection episode evaluation											
Check CT Scan	X ¹	As clinically indicated during infection episode evaluation											
Sign and Symptom of Infection (Screening Question)	X	X	X	X	X	X	X	X	X	X	X	X	X

Discontinuation of Therapy

Subjects could have withdrawn from the study at any time at their own discretion. In addition, subjects were to be removed from this study under the following circumstances:

- Subjects who, in the opinion of the investigator, should have been discontinued for their well being.
- Subjects without a proven or probable IFI who received more than 4 consecutive days of empiric therapy with a systemic antifungal.
- Subjects who received more than 4 days of systemic antifungal prophylaxis with an antifungal other than study drug during study drug interruptions resulting from an inability to ingest oral medication.
- Subjects who developed a Grade 4 (life threatening) AE considered probably related to study drug.
- Subjects who became pregnant during the treatment phase.
- Subjects who required medications known to interact with azoles and which may lead to life-threatening side effects: terfenadine, astemizole, cisapride, ebastine.
- Subjects who required dialysis, or whose estimated creatinine clearance is <20 mL/min.
- Subjects who require medications known to lower the serum concentration/efficacy of azole antifungals: rifampin, carbamazepine,

phenytoin, rifabutin, barbiturates, isoniazid.

- Subjects with a prolonged QTc interval on a manual measurement of their post-baseline EKG: change from Baseline of >60 msec or any QTc >450 msec for males or QTc >470 for females. Study drug may be interrupted while evaluation and treatment of other etiologies is ongoing, and restarted within five days if QTc is within normal limits (≤ 450 msec for males, ≤ 470 msec for females).
- Subjects who developed a proven or probable IFI

Analysis Plan

The sponsor identified all suspected IFI cases by selecting all subjects from the All Randomized Subjects subset (n=600) who had data recorded that were suspicious for invasive fungal infections, having met any one of the following criteria:

- IEE (Infection Episode Evaluation) which the investigators have classified as proven, probable, or possible IFI according to the protocol-specified criteria.
 - Systemic antifungal drug use (SAF) for >4 consecutive days or >10 total days from first dose of study drug to Day 112.
 - Treatment failure selected by the investigator as the final status for either the treatment phase or the follow-up phase.
 - Two or more consecutive positive *Aspergillus* galactomannan antigen results (central or local lab galactomannan index [GMI] ≥ 0.5).
 - Any subject with a positive culture suggestive of an IFI.
 - Any subject with histopathology results suggestive of an IFI.
 - Any subject with recorded AEs suggestive of an IFI.

The following definitions were used for the data sets that were analyzed:

All Randomized Subjects: Subjects who were randomized and signed informed consent. This subset is the focus of the primary efficacy analysis and of the safety analysis.

All Treated Subjects: Subjects who were randomized and received at least one dose of study drug.

Modified Intent-to Treat Subset: This subset is defined as subjects who were randomized and received at least one dose of study drug (capsules or suspension) who meet protocol specified criteria for acute or chronic GVHD at baseline or who have sufficient levels of iatrogenic immunosuppression to consider them high risk for IFI.

Efficacy-Evaluable Subjects or Per Protocol: All randomized subjects who met key

on or before Stop Date + 7.

Primary Time Period: Interval of time which begins on the Randomization Date and ends on the Randomization 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

A key consideration of the study design is the definition of the primary efficacy analysis period that was based on the 16-week Treatment Phase, the Primary Time Period. This time period is fixed at 16-weeks post Baseline, regardless of when study treatment ends. A significant proportion of subjects discontinued study treatment prematurely for a variety of reasons, resulting in wide variability among subjects for total treatment exposure. In addition some patients continued therapy for longer than the 16 week period. Thus, in the analysis of this study it would be useful to look at clinical outcome and the incidence of IFI in the While on Treatment period as well as the fixed primary time point.

Table 21: Schedule of Study Evaluations-from Study Report 98-316, NDA 22-003

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Dosage form: 40 mg/mL oral suspension.

Timing in relation to meals: study medication to be taken with food.

• Fluconazole: 400 mg once daily (taken at approximately the same time each day preferably in the morning).

Dosage form: 100 mg encapsulated fluconazole tablets or capsules.

• Placebos to Match:

Posaconazole: oral suspension.

Fluconazole: capsule.

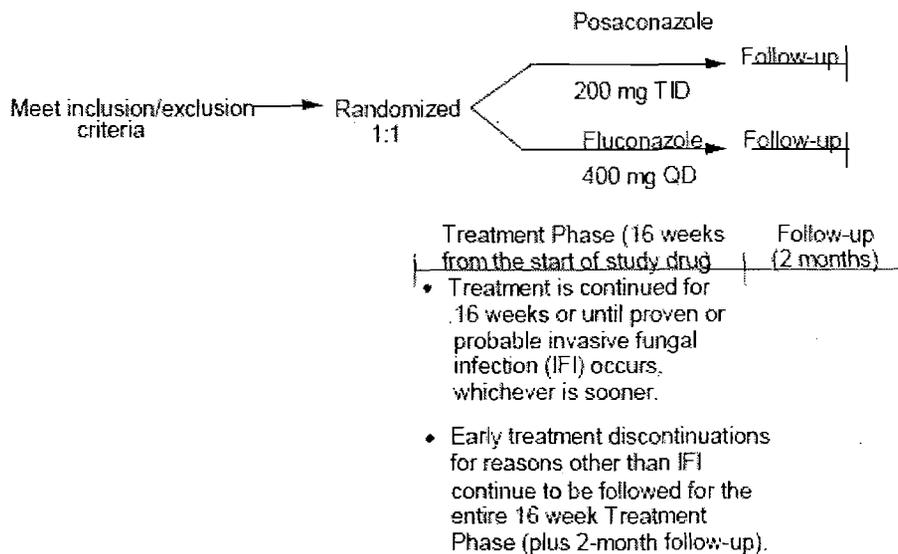


Figure 5: Study Design C98-316, from Study Report C98-316, NDA 22-003

TIMEPOINTS:

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.

End of Treatment: Last non-missing post-baseline measurement

Report Forms. The members of the panel, physicians with expertise in the area of opportunistic infections in transplant recipients, were blinded to the subject's treatment assignment. The panel reviewed patient profiles (consisting of clinical, microbiologic, laboratory and radiological data in the database) and narrative summaries (summarizing the chronology of the events, risk factors for IFI, diagnostic tests, and treatments) in order to characterize the IFI status using the EORTC - MSG standardized definitions.

Inclusion Criteria

• Basic Demographics

Male or female subjects were to be 13 years or greater, weighing >34 kg, any race.

• Disease Definition

Hematopoietic progenitor cell transplant subjects with the following risk factors for invasive fungal infections;

may have fulfilled either (1), OR (2) [a or b] below:

(1) Grade 2-4 acute GVHD being treated with high dose immunosuppressive therapy requiring the addition or substitution of one of the following to the subject's prior immunosuppressive regimen:

- a) at least 1 mg per kg per day of methylprednisolone or equivalent,
 - b) antithymocyte globulin (ATG) for the therapy of acute GVHD,
 - c) tacrolimus, mycophenolate mofetil, or other steroid-sparing immunosuppressive regimen:
- OR

(2) Chronic GVHD being treated with high dose immunosuppressive therapy requiring the addition or substitution of at least one of the following to the subject's prior immunosuppressive regimen:

- (a) at least 1 mg per kg of prednisone (0.8 mg per kg methylprednisolone or equivalent), every second day,
- (b) the addition of one or more immunosuppressive therapies to the subject's prior maintenance regimen so that the subject is on at least two therapies for the treatment of chronic extensive GVHD (such therapies may include tacrolimus, mycophenolate mofetil, PUVA therapy, radiation therapy, or photophoresis)

(3) Subjects must meet the clinical criteria of Grade 2-4 acute GVHD or chronic GVHD at the time of randomization, or be likely to continue on high dose immunosuppressive therapy as outlined in items 1 or 2 above for management of GVHD for more than 2 weeks.

- Classification of subjects into acute or chronic GVHD should be made on the basis of the clinico-pathologic characteristics of the GVHD, rather than on the interval of time between the transplant and onset or exacerbation of the GVHD. If a subject has features of both acute and chronic GVHD, that subject's GVHD classification should be made based on the dominant clinico-pathologic characteristics.
- Subjects can be randomized while on antifungal prophylaxis as long as that prophylaxis is discontinued prior to the start of study drug.

• **General**

Subject (parent or legal guardian for minor) must be willing to give written informed consent.

Subjects must be able to adhere to dosing, mandatory procedures and visit schedules.

Subjects must be able to take study medication (suspension and capsules) orally.

Females of childbearing potential must use a reliable barrier-type method of contraception. For subjects taking oral contraceptives, an additional reliable barrier-type method must have been used during this study.

Females of childbearing potential must have a negative serum pregnancy test at Baseline or within 72 hours prior to start of study drug.

Exclusion Criteria

History of proven or probable mould infection requiring secondary prophylaxis.

• Subjects who are suspected of having an invasive fungal infection, excluding *Pneumocystis carinii* infection.

• Use of medications that are known to interact with azoles and that may lead to life-threatening side effects: terfenadine, cisapride, ebastine at entry or within 24 hours prior to entry; or astemizole at entry or within 10 days prior to entry.

• Use of medications that are known to lower the serum concentration/efficacy of azole antifungals: rifampin, carbamazepine, phenytoin, rifabutin, barbiturates, isoniazid at entry or within 1 week prior to entry.

• Subjects receiving vinca alkaloids or anthracyclines at entry.

• Subjects with an ECG with a prolonged QTc interval by manual reading: QTc >450 msec for males and QTc >470 msec for females.

• Any condition requiring the use of prohibited drugs.

• Neurologic disorder or impairment expected to be progressive.

• Subjects whose laboratory results indicated one of the following:

Hepatic function studies: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >10 times upper limit of normal.

Estimated creatinine clearance <20 mL/minute subjects requiring dialysis.

• General

Prior enrollment in this study.

Women who are pregnant or nursing.

History of hypersensitivity or idiosyncratic reactions to azole drugs.

Investigational (new chemical entity) drug use in the 30 days prior to enrollment.

Subjects with a high probability of death within 7 days of enrollment.

Subjects who in the opinion of the investigator had clinical conditions which may have made evaluation of the safety and efficacy of this drug difficult.

Study Procedures

Treatments Administered

• Posaconazole: 600 mg daily, administered three times a day (200 mg TID) for 16 weeks.

therapy (FLU or ITZ) that would be used for all subjects assigned to the reference arm at that site. Subjects entering the study were to be stratified by primary diagnosis or condition (see below):

- New diagnosis of AML
- AML in first relapse
- MDS or other diagnoses of secondary AML
-

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 were 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.

All subjects were to have baseline and periodic evaluations for the presence of fungal infection. These evaluations were to include signs and symptoms of infection, a physical examination, fungal cultures, and a baseline chest X-ray and chest CT scan if the baseline chest X-ray was abnormal. Serial *Aspergillus* antigen testing and fungal PCR were also to be performed. The results were to be analyzed at the end of the study and correlated with clinical outcome.

A fungal infection episode evaluation (IEE) was to be performed when initiation of empiric or definitive antifungal therapy was clinically indicated. Microbiologically documented infections of a non-fungal etiology were to be recorded as adverse events (AEs). The IEE was to include an assessment of signs and symptoms of infection on physical examination, fungal cultures, and radiographic scans. Fungal blood cultures, *Aspergillus* antigen, and fungal PCR were to be done at least twice, approximately 7 days apart, starting within 48 hours of the onset of symptoms. *Aspergillus* antigen testing (serum and other sterile fluids if clinically indicated and available) and fungal PCR were to be performed at a central laboratory. If results were needed for clinical management, duplicate samples were sent to the local laboratory. More frequent fungal blood cultures or *Aspergillus* antigen testing may have been done as clinically indicated.

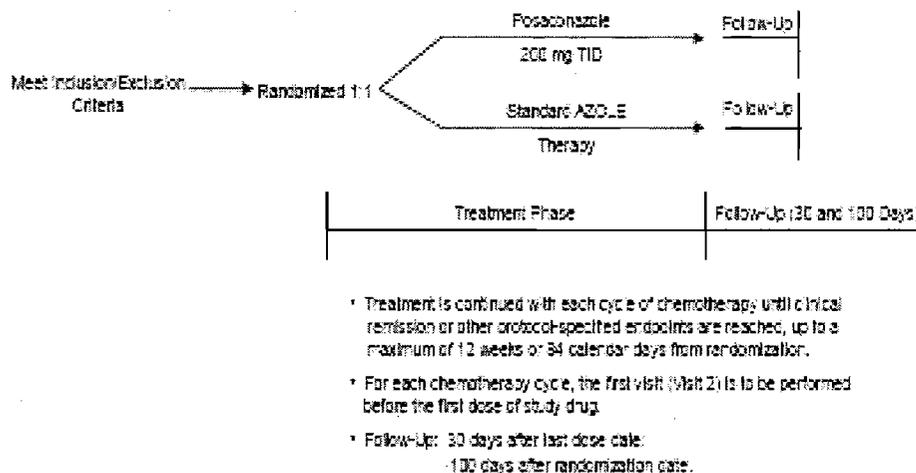
Assessments of clinical response were to be based upon IFI incidence and clinical outcome of oral prophylaxis (treatment success or failure). The IFI status of each subject (no IFI; possible IFI; probable IFI; or proven IFI) was to be determined using the criteria of the EORTC-MSG. For clinical management,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

In the original protocol, a treatment failure was to be defined as the presence of a proven or probable IFI, ≥ 4 days of empiric parenteral (IV) antifungal treatment for a suspected IFI, >3 consecutive days or ≥ 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 including death during the Treatment Phase were also to be considered treatment failures. In the analysis agreed upon in the review of the results clinical failure was defined as proven or probable IFI, death, use of systemic antifungal therapy for longer than 3 days, or lost to follow-up.

Safety and efficacy data, including clinical database listings and tabulations, SAE reports and capsule summaries, and information on IFI episodes, were to be reviewed periodically by a Data Monitoring Committee (DMC) consisting of external experts who were not directly involved with the conduct of the study.

An assessment of safety and tolerance was to be based on an evaluation of adverse events (AEs), deaths, study discontinuations, and laboratory results.



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Figure 6: Study Design from Study report P01899, NDA 22-003

Inclusion Criteria

1. Basic demographics: Male or female subjects of any race, ≥ 13 years of age, weighing >34 kg.
2. Disease definition:
Anticipated or documented prolonged neutropenia (ANC $<500/\text{mm}^3$ [$0.5 \times 10^9/\text{L}$]) at Baseline or likely to have developed within 3 to 5 days and last at least 7 days due to:
 - Standard intensive induction chemotherapy, anthracycline-based or other accepted regimen (excluding any investigational agent), for a new diagnosis of AML
 - Reinduction chemotherapy for AML in first relapse
 - Myelosuppressive induction therapy for MDS in transformation to AML or other diagnoses of secondary AML (therapy related, antecedent hematological disorders) other than chronic myelogenous leukemia in blast crisis
3. Subjects' clinical laboratory safety tests (blood chemistries) must have been within normal limits or clinically acceptable to the Investigator/Sponsor (ie, no Grade 4/life-threatening abnormalities).
4. Subjects must have been free of any clinically significant disease (other than the primary hematologic disease) that would interfere with the study evaluations.
5. Subjects (and/or parent/guardian for subjects under 18 years of age) must have been willing to give written informed consent and able to adhere to dosing, study visit schedule, and mandatory procedures (as long as local regulations were met).
6. Females of childbearing age must have been using a medically accepted method of birth control before beginning study-drug treatment and agreed to continue its use during the study or been surgically sterilized (eg, hysterectomy or tubal ligation). Female subjects of childbearing potential should have been counseled in the appropriate use of birth control while in this study. Female subjects who were not currently sexually active must have agreed and consented to use one of the above-mentioned methods if they were to become sexually active while participating in the study.
7. Female subjects of childbearing potential must have had a negative serum pregnancy test (beta-hCG) at Baseline or within 72 hours before the start of study drug.

Exclusion Criteria

1. Female subjects who were pregnant, intended to become pregnant, or were nursing.
2. Excluded prior treatments:
Subjects previously treated with Amphotericin B (AMB), FLU, or ITZ for proven or probable IFI within 30 days of enrollment.
3. Excluded treatments prior to specific study phases:
Subjects who had taken the following drugs: those known to interact with azoles and may have led to life threatening side effects (terfenadine, cisapride, and ebastine at entry or within 24 hours before entry, or astemizole at entry or within 10 days before entry); those known to lower the serum concentration/efficacy of azole antifungal agents: cimetidine, rifampin, carbamazepine, phenytoin, rifabutin, barbiturates, and isoniazid at entry or within 24 hours before entry; and those receiving vinca alkaloids or anthracyclines with evidence of cardiotoxicity.

4. Subjects who were in a situation or had any condition that, in the opinion of the Investigator, may have interfered with optimal participation in the study, ie, any condition requiring the use of prohibited drugs or unstable medical conditions other than the hematological disorder such as cardiac or neurologic disorder or impairment expected to be unstable or progressive during the course of this study (eg, seizures or demyelinating syndromes, acute myocardial infarction within 3 months of study entry, myocardial ischemia, unstable congestive heart failure, unstable arrhythmias, atrial fibrillation with ventricular rate <60/min, history of torsades de pointes, symptomatic ventricular or sustained arrhythmias, or unstable electrolyte abnormalities [eg, \geq Grade 2 hypokalemia or hypomagnesemia]).
5. Subjects who had used any investigational drugs or biologic agents other than their chemotherapy regimens within 30 days of study entry.
6. Subjects who had participated in any other clinical study within 30 days of study entry.
7. Subjects who were part of the staff personnel directly involved with this study.
8. Subjects who were a family member of the investigational study staff.
9. Prior enrollment in this study, or other POS studies.
10. Subjects with a history of hypersensitivity or idiosyncratic reactions to azole agents or amphotericin B.
11. Subjects with Eastern Cooperative Oncology Group (ECOG) performance status >2 prior to induction chemotherapy for their underlying disease.
12. Subjects with known or suspected invasive or systemic fungal infection at Baseline (randomization).
13. Subjects with renal insufficiency (estimated creatinine clearance less than 20 mL/minute at Baseline or likely to require dialysis during the study).
14. Subjects having an ECG with a prolonged QTc interval by manual reading: QTc greater than 450 msec for men and greater than 470 msec for women.
15. Subjects with moderate or severe liver dysfunction at Baseline, defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase levels greater than 5 times the upper limit of normal (ULN), or a total bilirubin level greater than 3 times the ULN.
16. Subjects with a history of acute lymphoblastic leukemia or chronic myelogenous leukemia.
17. Subjects with a history of allogeneic hematopoietic stem cell or bone marrow transplantation for any diagnosis or autologous stem cell transplantation for the underlying diagnosis.

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Table 22: Treatment Study P01899, adapted from Study Report P01899, NDA 22-003

Treatments Administered

	Posaconazole	Fluconazole	Itraconazole
Dose	200 mg (5 mL) PO TID	400 mg (10 mL) PO QDa	200 mg (20 mL) PO BID
Dosage form	40 mg/mL oral suspension	40 mg/mL dry powder for oral suspension	10 mg/mL oral solution
Timing in relation to meals	Should be taken with food or oral nutritional supplement containing fat caloriesb	May be taken with or without food	Should be taken without food, or at least without grapefruit or grapefruit juice
Alternative IV formulation	AMB 0.3 to 0.5 mg/kg/day administered via IV infusion over 4 to 6 hours	FLU 400 mg QD administered via 2-hour IV infusion (200 mg/hour)	ITZ 200 mg BID administered via 1-hour IV infusion
AMB = amphotericin B deoxycholate; FLU = fluconazole; ITZ = itraconazole; a: Or 200 mg (5 mL) QD if estimated creatinine clearance is 20-50 mL/min.			

MO COMMENT:

The use of amphotericin in the POS arm and IV Fluconazole or Itraconazole in the Fluconazole or Itraconazole arms, respectively, as the IV Study Drug used for short (<4 Day) durations when patients were unable to take oral study medication introduces an important bias into these results especially as the long half life of amphotericin may have impacted the development or detection of IFI. The following comments had been sent to the Sponsor during protocol review:

“The use of temporary amphotericin B in patients unable to take oral medications may affect the interpretation of results when used in the POS arm and excluded from the standard azole arm. Use of the current proposed design by the sponsor constitutes a reviewable issue and may significantly weaken the study results. The Agency encourages the use of temporary amphotericin B in both arms of the study to minimize the potential bias that may be introduced”

RANDOMIZATION and BLINDING

Prior to randomization of the first subject, each study center was to designate the standard azole therapy (FLU or ITZ) that would be used for all subjects assigned to the reference arm at that study center. Subjects were to be stratified based on

their primary diagnosis or condition (new diagnosis of AML; AML in first relapse; or MDS or other diagnoses of secondary AML [therapy related, antecedent hematological disorders]):

At the time of randomization, each subject was to be assigned a unique subject number by an independent central randomization organization. Subject numbers were to be assigned sequentially within each region (Canada, Europe [EU1, EU2, EU3], Far East, Latin America [LA1, LA2, LA3], and US) and stratum combination and by type of center (those using FLU or those using ITZ as standard azole therapy). Subjects were to be randomized in a 1:1 ratio to either POS or standard azole therapy, according to a computer-generated code. Subjects who discontinued were not to be replaced.

All investigators and patients were blinded to drug assignment.

Subject Discontinuation Criteria

Subjects may have withdrawn from the study at any time of their own volition. In addition, subjects were to be removed from the study under the following circumstances:

- Subjects who developed a Grade 4 (life-threatening) adverse event considered probably related to study drug. (Study drug may have been continued at the discretion of the Investigator [in consultation with the Project Physician or designee] in the case of Grade 4 AEs that were considered possibly related, or Grade 3 AEs that were considered possibly or probably related to study drug.)
- Failure to comply with at least 80% of the scheduled dosing, evaluations, or other requirements of the study.
- Pregnancy.
- Initiation of empiric systemic antifungal (SAF) therapy (eg, AMB) for suspected fungal infection according to the Infectious Diseases Society of America guidelines for the empiric treatment of febrile neutropenia. Subsequent cycles of prophylaxis may only have been started if the subject did not meet any criteria for possible, probable, or proven IFI.
- Documentation of a fungal infection (proven, probable, or possible IFI) according to EORTC-MSG criteria. Additional cycles of study drug prophylaxis were not permitted for these subjects.
- Subjects who, following randomization, required drugs that were known to interact with azoles and may have led to life-threatening side effects: terfenadine, astemizole, cisapride, and ebastine.
- Subjects who, following randomization, required drugs known to lower the serum concentration/efficacy of azole antifungals: rifampin, carbamazepine, phenytoin, rifabutin, barbiturates, isoniazid, and cimetidine.
- Subjects with a prolonged QTc interval on a manual measurement of their

post-baseline ECG: change from Baseline of >60 msec OR any QTc >450 msec for men or >470 msec for women. (Study drug was to be interrupted while evaluation and treatment of other etiologies was ongoing, and restarted within 5 days if QTc was within normal limits [≤ 450 msec for men, ≤ 470 msec for women]).

- Subjects who required dialysis following randomization, or whose estimated creatinine clearance was < 20 mL/min at any time post baseline.
- Subjects who initiated study drug with the IV formulation and after 3 days on IV could not be switched to oral formulation (never received oral study drug).

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.

Temporary Study Drug Interruption Due to Oral Intolerance or Need for Re-Induction Chemotherapy

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.

Subject Completion Criteria

The following endpoints marked the successful completion of a cycle of prophylaxis with study drug:

- Recovery of ANC to > 500 cells/mm³ ($0.5 \times 10^9/L$) for at least 2 consecutive days. Prophylaxis may have been continued for up to 7 days after the first documented ANC value > 500 cells/mm³ ($0.5 \times 10^9/L$).

Subjects who had recovered from neutropenia but had not achieved a

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clinical complete remission may have continued study drug without interruption if the next scheduled chemotherapy was to be given within 7 days and neutropenia was expected to develop quickly. If the next scheduled chemotherapy was not within 7 days, and the subject had recovered from neutropenia, study drug was to be stopped and end-of-treatment procedures performed. Study drug may have been restarted with the next cycle of chemotherapy, provided that all inclusion/exclusion criteria were still satisfied, and the protocol specified washout periods for prohibited medications were observed.

- Achievement of complete remission of AML with clearance of leukemic cells from the bone marrow, recovery from neutropenia with normal total WBC counts, and platelet counts >100,000 cells/mm³.

Subjects who achieved a complete remission after one induction cycle may have received subsequent cycles of antifungal prophylaxis during consolidation at the approval of the Sponsor.

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Table 23: Schedule of Evaluations: from Study Report P01899, NDA 22-003

	Visit 1 Baseline (Days -7 to 0)	Treatment Phase			Follow-Up	
		Visit 2 (Start of Treatment)	Visit 3 (Fungal Infection Episode Suspected)	Visit 4 (End of Treatment, Study Drug D/C)	Visit 5 +30 Days	Visit 6 100 Days After Randomization
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Comprehensive History Plus Physical Exam	X					
Weight	X	X		X		
Vital Signs	X	X	X	X	X	X
Concomitant Drugs	X	X	X	X	X	X
Safety Labs	X	X	X	X	X	X
Serum Pregnancy Test	X			X		
Fungal Serodiagnostic Testing (polymerase chain reaction [PCR] and Aspergillus antigen)		X	X	X	X	
Screening for Fungal Infections/Problem Focused History and Physical Exam		X	X	X	X	(X)
Surveillance Cultures (Throat, Stool)	X	X	X	X	(X)	(X)
Suspected Infection Site(s) Cultures			X		(X)	(X)
Blood Cultures			X		(X)	(X)
Chest X-Ray	X		X		As clinically indicated	As clinically indicated
Special Diagnostic Exams (CT, magnetic resonance imaging [MRI], bronchoalveolar lavage [BAL], Serology, and Biopsy)			As clinically indicated		As clinically indicated	As clinically indicated
Other X-Ray/CT Scan/Diagnostic Imaging			As clinically indicated		As clinically indicated	As clinically indicated
ECG (12-Lead)	X	X	As clinically indicated	X	As clinically indicated	As clinically indicated
Randomization	X					
Study Drug Dispensing/Treatment		X------(X)				

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Study Drug Compliance/Drug Accountability			X	X		
Adverse Events		X-----(X)			X	X

	Visit 1 Baseline (Days -7 to 0)	Treatment Phase			Follow-Up	
		Visit 2 (Start of Treatment)	Visit 3 (Fungal Infection Episode Suspected)	Visit 4 (End of Treatment, Study Drug D/C)	Visit 5 +30 Days	Visit 6 100 Days After Randomization
Neurologic Exam	X			X	X	
Mucositis Evaluation		X	X	X		
Taste Assessment		X		X		
Pharmacokinetic Specimens			X			

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6.1.4 Efficacy Findings

C98-316

RESULTS

Table 24: Disposition of Patients C98-316

Distribution of Subjects in the Data Subsets Analyzed		
Data Set Analyzed	n (%) of Subjects	
	Posaconazole	Fluconazole
All Randomized Subjects	301 (100)	299 (100)
All Treated *	291 (97)	288 (96)
Efficacy-Evaluable	180 (60)	204 (68)

*Received at least one dose of study medication
 Adapted from Study Report C98-316, NDA 22-003.

Table 25: Reasons Patients excluded from All Randomized Population (to become Efficacy Evaluable or Per Protocol Population)

	Posaconazole N(%)	Fluconazole N (%)
Subject did not receive at least one dose of study medication (capsules or suspension)	10 (3)	11 (4)
Subject did not have “adequate” immunosuppression prior to or within 2 weeks after randomization (See Note)	85(28)	59 (20)
Subject did not have an allogeneic hematopoietic stem cell transplant	0	1 (<1)
Subject did not have GVHD at baseline	1 (<1)	2 (1)
Did not receive more than >80% of study medication*	31 (10)	26 (9)
Subject received prohibited medication*	6 (2)	5 (2)
Subject had IFI prior to first dose	0	1 (,1)

*There is some overlap in these 2 groups
 Adapted from Study Report C98-316, NDA 22-003.

The Division feels that the populations of greatest interest are the All Treated population (often referred to as the Safety population or ITT) and the Efficacy Evaluable population (often referred to as the per protocol population.) The Division will concentrate its analyses on these 2 populations.

MO COMMENT: Sixty-six subjects with acute GVHD in the POS group and 54 in the FLU group received less than 1 mg/kg/day of methylprednisolone equivalent; 7 subjects in each of the POS and FLU groups did not have documentation of the level of dosing. Similarly, for subjects with chronic GVHD, 28 in the POS group and 23 in the FLU group received less than the protocol specified requirement of 0.8 mg/kg every other day (0.4mg/kg/day) of methylprednisolone equivalent, and, in addition, 35 subjects in the POS group and 18 in the FLU group were receiving only one identified immunosuppressive agent at baseline.

The most common reason for exclusion from the Efficacy Evaluable population was a lack of adequate immunosuppression according to the protocol. The protocol was specific as to the amount of immunosuppressive therapy that was required to be included in the Efficacy Evaluable population. The reasons for exclusion were often minor dose reductions in steroid therapy. The DRC and the Division Medical Reviewer did not feel these differences were of clinical significance. However, since two analyses, one ITT with all these patients included and one Per Protocol with them excluded were to be performed the impact of these differences on results could be further evaluated. Later in the Exploratory Analysis section of the Efficacy section of this review there will be a tabular depiction of the effect of immunosuppression by outcome in the 2 groups. No important differences in outcome were detected.

Baseline Characteristics

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The baseline disease characteristics were similar between groups. The most common underlying disease in each group was chronic myelogenous leukemia, in about one-third of the subjects, followed by acute nonlymphocytic leukemia, in about one-quarter of the subjects in each group. About two thirds of the subjects had acute GVHD while about one-third had chronic extensive GVHD. The majority of subjects with acute GVHD had Grade 2 GVHD (45% of randomized subjects in each group). The treatment groups were well balanced with regard to time from transplant to randomization in the study. In both treatment groups, approximately 15% of subjects in the POS group and 12% of subjects in the FLU group were randomized within 30 days after transplant, and about 60% were enrolled prior to day 100 after HSCT; the median time was 63 days for POS and 64 days for FLU. In both treatment arms, 40% of subjects were randomized more than 100 days after HSCT.

MO COMMENT: The risk of systemic fungal infection varies at different time periods post transplant. Most occur after 2 months after transplantation and increase with associated GVHD. The earlier time period is associated with a greater risk of systemic bacterial infection. The treatment groups were well matched in the number of patients at various time periods post transplant.

Few subjects had a prior history of invasive yeast or mould infection. Approximately 1/3 of the population had a positive oral swish for yeast, either persistently or intermittently, during treatment. Fifty-one subjects (10%) had a positive Aspergillus antigen test (defined as a baseline galactomannan index of ≥ 0.5) during the baseline period; in the FLU group more subjects were positive (10%, 30 subjects) vs the POS group (7%, 21 subjects). None of these subjects were considered to have evidence of proven or probable IFI at Baseline.

A nearly identical proportion of subjects in each group received T-cell depleted stem cells at the latest transplant prior to study entry (12% POS, 11% FLU). Almost half of the subjects in each group received body irradiation on or before the transplant date (45% POS, 49% FLU). Very few subjects were neutropenic at baseline (2% POS, <1% FLU) and all but one subject in each group had been treated with systemic corticosteroids at baseline. Approximately half of the subjects were treated with a daily dose greater than 1 mg/kg/day of methylprednisolone or its equivalent, and 11% and 14% of FLU and POS subjects, respectively, received extremely high doses of corticosteroids (2 mg/kg/day or more of methylprednisolone or its equivalent). Other immunosuppressive agents (antithymocyte globulin/OKT3, tacrolimus, sirolimus, mycophenolate mofetil, infliximab, daclizumab, PUVA or extracorporeal photopheresis, or pentostatin) were used in combination with cyclosporine, or as replacement for cyclosporine or high dose corticosteroids according to protocols for management of GVHD. The number of immunosuppressive agents used at baseline was similar between the two groups. All subjects had been treated with antifungal agents prior to baseline and more than half of these in each group (54% POS, 56% FLU) had been treated for more than 14 days. The median number of days of prior therapy was also similar between the two groups (16 POS and 19 FLU); the type and proportion of agents

received was similar. The majority of subjects randomized in this study had at least two or more known risk factors for the subsequent development of IFI.

Baseline Characteristics Study C98-316

Primary Underlying Diagnosis	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)
GVHD Class at Baseline		
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)
Time From Transplant to Baseline Date		
<30 days	45 (15)	37 (12)
30 to 60 days	98 (33)	103 (34)
61 to 100 days	32 (11)	37 (12)
≥101 days	124 (41)	121 (40)
Missing	2 (1)	1 (<1)
Mean (STD)	156.1 (222.2)	171.6 (262.3)
Median	63	64
Range	0 - 1858	0 - 1692
Prior History of Invasive Yeast or Mould	8 (3)	15 (5)

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Oral Swish Positive for Yeast at Baseline	95 (32)	85 (28)
Oral Swish Positive for Yeast During Treatment		
Persistently	27 (9)	29 (10)
Intermittently	84 (28)	77 (26)
Negative	190 (63)	193 (65)
Aspergillus Antigen at Baseline		
Positive (≥ 0.5 at Baseline)	21 (7)	30 (10)

Adapted from Study Report C98-316, NDA 22-003.

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MO COMMENT: There are 3 areas where differences between the groups were noted. The first is the number of patients who were Aspergillus antigen positive upon entry. These data were not available to the investigators during the study. Twenty-one patients or 7% of the Posaconazole group were positive whereas 30 or 10% of the Fluconazole group were positive upon entry. About half as many Posaconazole patients had a prior history invasive yeast or mold (8 to 15 respectively). However, only one of these had a prior history of an Aspergillus infection. The effect of both of these disparities on the outcome of this trial will be further assessed in the exploratory analyses section later in the review.

The third is the level of immunosuppression at entry. The table below looks at these differences. The Division's review of these data agrees with the DRC's opinion that the differences do not constitute an important clinical difference. However, since the results will be analyzed both in the All Treated population and the Per Protocol population it can be examined as to whether this imbalance had an impact on the outcome of the study.

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C/198-316 FINAL
 All Randomized Subjects
 Summary of Risk Factors
 Overall, By Baseline GVHD

	Number (n)							
	Acute		Chronic		None/Missing		Total	
	POSA n=202	FLU n=197	POSA n=98	FLU n=100	POSA n=1	FLU n=2	POSA n=301	FLU n=299
Body irradiation on or before transplant date prior to study entry								
Yes	108 (53)	107 (54)	27 (28)	39 (39)	0	0	135 (45)	146 (49)
No	94 (47)	90 (46)	71 (72)	61 (61)	1 (100)	2 (100)	166 (55)	153 (51)
BL Corticosteroids (mg/kg/day)								
>= 2.0	36 (18)	27 (14)	5 (5)	5 (5)	0	0	41 (14)	32 (11)
< 2.0 but >= 1.0	93 (46)	109 (55)	14 (14)	20 (20)	0	0	107 (36)	129 (43)
< 1.0 but >= 0.4	59 (29)	50 (25)	48 (49)	49 (49)	1 (100)	1 (50)	108 (36)	100 (33)
< 0.4 but >= 0	6 (3)	4 (2)	28 (29)	23 (23)	0	0	34 (11)	27 (9)
Dose unknown	7 (3)	7 (4)	3 (3)	3 (3)	0	0	10 (3)	10 (3)
No corticosteroids	1 (<1)	0	0	0	0	1 (50)	1 (<1)	1 (<1)
Number of Immunosuppressives at BL								
One	29 (14)	29 (15)	35 (36)	18 (18)	0	1 (50)	64 (21)	48 (16)
Two	106 (52)	116 (59)	45 (46)	52 (52)	0	0	151 (50)	168 (56)
Three or more	66 (33)	52 (26)	18 (18)	30 (30)	1 (100)	0	85 (28)	82 (27)
None	1 (<1)	0	0	0	0	1 (50)	1 (<1)	1 (<1)
Cytokine modulation agent on or before BL								
Yes	13 (6)	11 (6)	2 (2)	7 (7)	0	0	15 (5)	18 (6)
No	189 (94)	186 (94)	96 (98)	93 (93)	1 (100)	2 (100)	208 (69)	281 (94)
FUVA photopheresis agent on or before BL								
Yes	1 (<1)	0	4 (4)	3 (3)	0	0	5 (2)	3 (1)
No	201 (100)	197 (100)	94 (96)	97 (97)	1 (100)	2 (100)	296 (98)	296 (99)

‡: Subjects with multiple sources of cells are counted in each source category.
 §: Subjects with multiple primary diagnoses are counted in each primary diagnosis category.

From Study Report C98-316, NDA 22-003.

Duration of study drug and other antifungal therapy

The population being studied has significant comorbidity secondary to post-transplantation and GVHD both of which require multiple concomitant and often poorly tolerated therapies. As such, it is not unusual that a number of adverse events, most unrelated to study drug, would require drug discontinuation. The below table describes the duration of study treatment in both arms. It is important to notice that the duration of therapy for the 2

arms is quite balanced up until about 92 days. After 13 weeks there are about 5 % more posaconazole patients than FLU patients. More FLU patients required discontinuation for any reason. Only 5% of POS patients and 3% of FLU patients received therapy for longer than 16 weeks .

Treatment Duration of Study Drug C98-316

	POS (N=301)	FLU (N=299)
Treatment Duration (Days)		
N	291	288
Mean (SD)	80.3 (42.9)	77.2 (42.7)
Median	111	108
Minimum	1	1
Maximum	138	130
Cumulative Number (%) of Subjects With Indicated Treatment Duration	n (%)	n (%)
≥1 Day	291 (97)	288 (96)
≥22 Days	245 (81)	237 (79)
≥36 Days	218 (72)	215 (72)
≥50 Days	201 (67)	198 (66)
≥64 Days	188 (62)	179 (60)
≥78 Days	178 (59)	169 (57)
≥92 Days	171 (57)	158 (53)
≥106 Days	165 (55)	149 (50)
≥112 Days	139 (46)	122 (41)
≥120 Days	14 (5)	10 (3)
Randomized, not treated	10 (3)	11 (4)

Adapted from Study Report C98-316, NDA 22-003.

The table below shows the use of systemic antifungal medications during the while on treatment phase (from first dose to 7 days after last dose of study drug). For the majority of the cases, the use of systemic antifungal medications occurred after the discontinuation of the study drug but within the 7 days post discontinuation included in the While On Treatment Time Period.

Table 26: Summary of Concomitant Antifungal Medications for Subjects Who Received 4 or More Consecutive Days or 10 or More Total Days of Systemic Antifungal Medication for Empiric Treatment of Invasive Fungal Infection While on Treatment (All Treated Subjects) C98-316

	POS N=291	FLU N=288
Medication	N (%)	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)

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

Adapted from Study Report C98-316, NDA 22-003.

The use of empiric systemic antifungal therapy was prohibited by the study protocol except for the use of one short (<5 days) empiric course, and one short (<5 days) course during a period of study drug interruption (either due to an inability to take oral medication or due to an AE). Use between the treatment groups was similar except that numerically fewer subjects in the POS group (4%, 12/291) used amphotericin B than in the FLU group (6%, 17/288), and more subjects used caspofungin in the FLU group (4 FLU subjects vs 1 POS subject).

Table 27: Days of other antifungal therapy C98-316

	POS N= 291	FLU N=288
none	166	158
Total Yes	125	130
1-3 days	31	32
4-7 days	49	66
>7 days	45	32
Mean	7	6
Median	7	6

Adapted from Study Report C98-316, NDA 22-003.

Measures of Efficacy

Please note that in some analyses presented below the results are reported for the All Randomized Population and in some for the All Treated.

1. Division's Primary Efficacy Analysis

Table 28: Results from C98-316 in Prophylaxis of IFI in All Randomized Patients

	Posaconazole n =301	Fluconazole n = 299
<i>On therapy plus 7 days</i>		
Clinical Failure ^a	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(<i>Aspergillus</i>)	3 (1%)	17 (6%)
(<i>Candida</i>)	1 (<1%)	3 (1%)
(Other)	3 (1%)	2 (1%)
All Deaths	22 (7%)	24 (8%)
Proven / probable fungal infection prior to death	2 (<1%)	6 (2%)
SAF ^{b,c}	27 (9%)	25 (8%)
<i>Through 16 weeks</i>		
Clinical Failure ^{a,d}	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(<i>Aspergillus</i>)	7 (2%)	21 (7%)
(<i>Candida</i>)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths	58 (19%)	59 (20%)
Proven / probable fungal infection prior to death	10 (3%)	16 (5%)
SAF ^{b,c}	26 (9%)	30 (10%)
Event free lost to follow-up ^e	24 (8%)	30 (10%)
<p>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). d: 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%) 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.</p>		

These results show that in this population of post transplant patients over a prespecified period of time from randomization (16 weeks and at the while on therapy + 7 day period the rate of clinical success in the patients randomized to Posaconazole was statistically non inferior to the rate of clinical success in the patients randomized to receive Fluconazole. The definition of clinical failure in this population was: development of proven or probable IFI, death, empiric use of systemic antifungal therapy for > 4 days, lost to follow-up. There were fewer IFIs and especially breakthrough infections with Aspergillus at both time points.

MO COMMENT: The sponsor's proposed analysis for the primary endpoint of incidence of IFI does not take into consideration patients who use any systemic antifungal agents or died. The Review Team had recommended to the Sponsor that these issues be addressed in the analysis of outcomes for the primary endpoint. Patients who receive systemic antifungal agents in addition to study drug and deaths, from all causes, should be considered as "failures" in the analysis of the primary endpoints. The Review division had also requested that the sponsor specify how missing data (early discontinuations of study drug, lost to follow-up) would be counted (failure/success) for the primary endpoints. The Division had recommended that subjects lost to follow-up should be counted as failures in the analysis of the primary endpoints.

Secondary Analyses-

1. Clinical Outcome in the Efficacy Evaluable Population

Table 29: Clinical Failure in the Efficacy Evaluable Subjects During the While on Treatment Period C98-316

	Posaconazole		Fluconazole	
	N	%	N	%
Success	146	81	156	76
Failure	34	19	48	24
Total	180		204	

Table 30: Reasons for Clinical Failure in the Efficacy Evaluable Population during the While on Treatment Period C98-316

	IFI	Empiric use of AF	Died While on Tx
Posaconazole	6	21	12
Fluconazole	18	20	23

When clinical outcome in the Efficacy Evaluable population is assessed only during the time patients actually received study drug (+ 7 days) the results again show numerical superiority but statistical non-inferiority of clinical outcome of those patients who received posaconazole in comparison to those who received fluconazole.

2. Incidence of IFI in All Randomized Population-presented by Sponsor as their primary endpoint

A. Proven or Probable Invasive Fungal Infections During the Primary Time Period (16 weeks from randomization), (All Randomized Subjects) C98-316

POS N=301 n (%)	FLU N=299 n (%)	Difference
16(5%)	27(9%)	3.7%

MO Comment: The above analysis shows that in post transplant patients those randomized to receive Posaconazole had a non-inferior rate of proven or probable invasive fungal infections than patients randomized to Fluconazole during the Primary Time Period. The Sponsor presented this as their primary analysis because they felt there were so many other potentially confounding factors which would affect clinical outcome other than IFI. The Division agrees that this is a very important secondary outcome to analyze. A more pronounced though still non-inferior difference is noted in the incidence of IFI during the while on treatment period shown below.

MO Comment: All cases of Proven/Probable IFI were reviewed by the Medical Officer and the MO concurred with the designations provided. A list of these cases is provided in Appendix 1.

B. Proven or Probable Invasive Fungal Infections During the While on Treatment Period (Oral Treatment + 7days), (All Treated Subjects)

POS N=291	FLU N=288	Difference
7(2%)	22(8%)	6.8%

3. Summary of All DRC-Adjudicated Proven and Probable Invasive Fungal Infections, by Study Period
 (All Randomized Subjects)

	Proven/ Probable (DRC-Adjudicated Invasive Fungal Infections)		
	POSACONAZOLE	FLUCONAZOLE	TOTAL
Primary Time Period (a)	16	27	43
While On Treatment (b)	7	22	29
Post While On Treatment (c)	12	20	32

a: Interval of time which begins on the Randomization Date and ends on the (Baseline Date + 111 days.)
 b: Interval of time which begins on the first day of treatment and ends on the last day of treatment + 7 days.
 c: Interval of time which begins on the last day of treatment + 8 days and ends on the last contact date
 Note: One subject who was randomized to the POS group but never treated with study drug had an IFI on Day 20.

The above table shows that although the incidence of proven/probable IFI is nearly the same in the FLU arm either while on treatment or post treatment in the POS arm there are 12 infections post treatment in the POS arm 7 while on treatment.

2-Death

Time to Death in the Treatment Phase, All Treated Subjects

The time from randomization to death for All Treated Subjects was analyzed using the Kaplan-Meier method during the Treatment Phase; all subjects who did not die, were censored at the end of the Treatment Phase or at the last follow-up observation in the case of premature discontinuation. The cumulative percent of deaths calculated at each time point using the Kaplan-Meier method was similar between the two treatment groups (P=0.6328). There was no overall survival benefit evident from treatment with POS. Deaths can be divided by the time interval during the study when they occurred.

Table 31: Deaths in Study C98-316

Overall Deaths		
Number of Deaths	Posacoanzole N=301	Fluconazole N=299
Deaths during Primary Time Period (16 weeks from R) + 2 months in All Randomized Patients	76	84
Deaths during the Primary Time Period in All Treated Patients	54	58
Deaths during the While on Treatment Period in All Treated Patients	22	24

There were fewer of the overall deaths in the POS group (1% of subjects, 4/301) compared with FLU group (4% of subjects, 12/299) considered related to complications of IFI. Of the 16 IFI-related deaths reported by the investigator, two of the four in the POS group were classified as proven or probable IFIs while the other two were classified as possible IFI, and 11 of 12 in the FLU group were classified as proven or probable IFIs by the DRC with one classified as possible IFI.

Table 32: Deaths by Cause C98-316

Overall Death in All Randomized Patients		
Cause of Death	Posacoanzole N=301	Fluconazole N=299
Total Deaths	76(25%)	84(28%)
AE*	39	37
IFI Related	4	12
Prog of Underlying Disease or GVHD	31	33
Other	2	2

*Adverse Event –most due to complications of underlying disease or its treatment. Only 1 death due to study drug AE-a case of cyclosporine toxicity associated with posaconazole use.

Adapted from Study Report C98-316, NDA 22-003.

MO Comment-Since the autopsy rate was less than 20% there is a lack of reliability of the attribution of cause of death to IFI.

3-Proven/Probable/Possible

This table reveals that Posaconazole had fewer Proven as well as probable invasive fungal infections during the primary and while on treatment time periods. C98-316

Study Period	Proven/ Probable (DRC-Adjudicated Invasive Fungal Infections)						
	PROVEN		PROBABLE		PROV/PROB		PROV/PROB TOTAL
	POS	FLU	POS	FLU	POS	FLU	
Primary Time Period (a)	11	13	5	14	16	27	43
While On Treatment (b)	4	12	3	10	7	22	29
Post While On Treatment (c)	8	8	4	12	12	20	32

a: Interval of time which begins on the Randomization Date and ends on the (Baseline Date + 111 days.)
 b: Interval of time which begins on the first day of treatment and ends on the last day of treatment + 7 days.
 c: Interval of time which begins on the last day of treatment + 8 days and ends on the last contact date
 Note: One subject who was randomized to the POS group but never treated with study drug had an IFI on Day 20.
 Note: In some patients the start of treatment was delayed so that the WOT might extend beyond the PTP- therefore the numbers of WOT+Post WOT might exceed the PTP entries.
 Adapted from Study Report C98-316, NDA 22-003.

If possible IFIs are included in the total IFI incidence the results are similar:

Proven, Probable and Possible IFIs in All Treated Subjects During the While On Treatment Time Period

POS	FLU
N=291	N=288
20 (7%)	41 (14%)

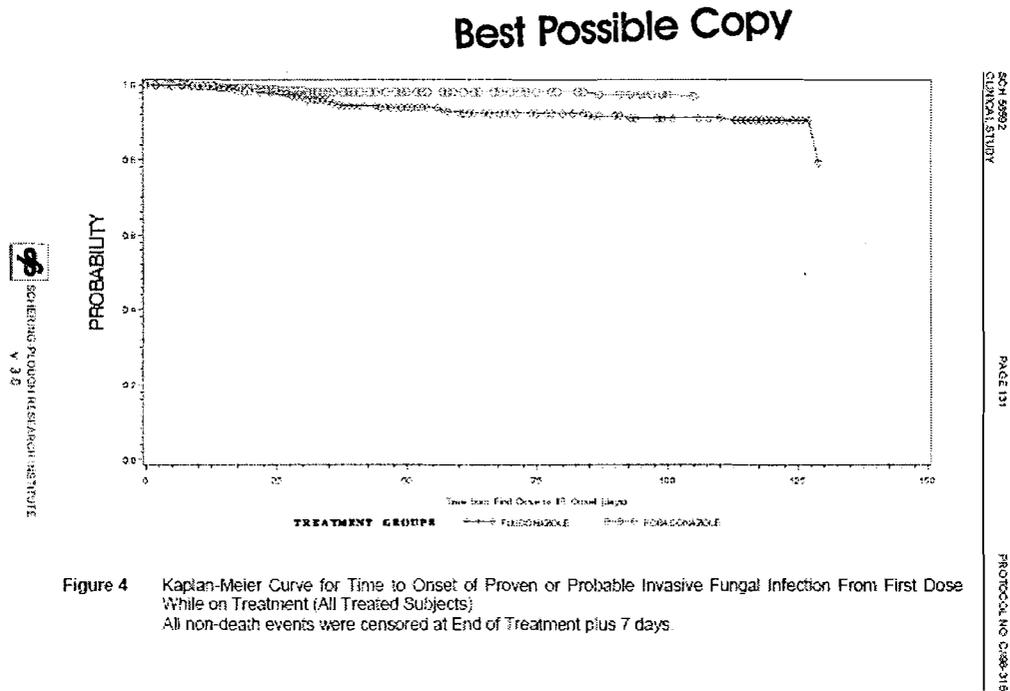
4-Incidence of Aspergillus-Please see Microbiology section below.

5. Time to IFI

Time to onset of proven or probable IFI While on Treatment in All Treated Subjects was analyzed by the Kaplan-Meier method; all subjects were censored at the end of treatment. Figure 4 shows that the time to IFI for subjects treated with POS was statistically different than for subjects treated with FLU (P=0.0034,).

Figure 7: Time to IFI-Kaplan Meier Analysis Study C98-316

From Study Report C98-316, NDA 22-003.



EXPLORATORY ANALYSES

1- Aspergillus Antigen Positivity upon Entry

Table 33: Aspergillus Antigen

	POS	FLU
Total number Aspergillus Ag +	21	30
Asp Ag+ Pt that developed IFI	2	7
Asp Ag+ Pt that developed IFI due to Aspergillus	1	6
Total # of Aspergillus infections seen in the All Treated Population during the Primary Time Period	7	21

As can be seen above there were more patients in the Fluconazole arm who were Aspergillus antigen positive upon entry as opposed to the Posaconazole arm. If one were

to remove these patients from the primary analysis the result of non-inferiority (but numerical superiority) of clinical success for posaconazole does not change. If the patients were removed from the analysis of IFI only in the All Randomized Population during the Primary Time Period there would be 14/299 IFIs in the Posaconazole arm and 20 out of 292 in the Fluconazole arm. This result is consistent with that obtained if these patients are included: noninferiority but numerical superiority for Posaconazole.

Two potential interpretations:

- More Fluconazole patients at higher risk for developing Aspergillus infection.
- Posaconazole better at preventing Aspergillus infection in those who are Aspergillus Ag+

2-History of Prior mould/yeast infection-

There was a history of prior invasive fungal infection at baseline in 8 Posaconazole patients and 15 Fluconazole patients. Only 2 of these patients, both in the fluconazole arm, developed IFIs therefore not significantly affecting the results.

Table 34: Prior history of invasive mould or yeast

Drug	Prot	Center	Subject	History of invasive mould or yeast infection	Proven or probable IFI during the study	IFI Day and diagnosis
POS	I98316	71	000869	Mould	NO	
POS	I98316	12	000061	Yeast	NO	
POS	I98316	12	000068	Yeast	NO	
POS	I98316	20	000010	Yeast	NO	
POS	I98316	20	000015	Yeast	NO	
POS	I98316	51	000382	Yeast	NO	
POS	I98316	51	000392	Yeast	NO	
POS	I98316	52	000560	Yeast	NO	
FLU	I98316	59	000656	Both	NO	
FLU	C98316	34	000180	Mould	NO	
FLU	C98316	35	000219	Mould	NO	
FLU	C98316	35	000220	Mould Fungal Sinusitis 4 years prior to	YES	Day 84(58) <i>Aspergillus Flavus</i>
FLU	I98316	7	000231	Mould	NO	
FLU	I98316	43	000777	Mould	NO	
FLU	C98316	15	000128	Yeast	NO	
FLU	C98316	25	000649	Yeast	NO	
FLU	C98316	43	000501	Yeast	NO	
FLU	C98316	43	000515	Yeast	NO	
FLU	I98316	12	000062	Yeast	NO	
FLU	I98316	12	000078	Yeast	NO	
FLU	I98316	35	000491	Yeast	NO	
FLU	I98316	43	000259	Yeast	NO	
FLU	I98316	44	000600	Yeast (Not specified)	YES	Day 2 <i>C. albicans</i> on

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Drug	Prot	Center	Subject	History of invasive mould or yeast infection	Proven or probable IFI during the study	IFI Day and diagnosis
						esophageal endoscopy

Adapted from Study Report C98-316, NDA 22-003.

3-Effect of Differences in Immunosuppression on Outcome.

The table below reveals that there are not any impressive differences in the incidence of IFI in the 2 arms stratified by the level of immunosuppression produced by immunosuppressive therapies or concomitant CMV infection.

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Table 35: Effect of Immunosuppression on Outcome

	Primary Time Period				While on Treatment			
	Posaconazole (N=301)		Fluconazole (N=299)		Posaconazole (N=291)		Fluconazole (N=288)	
	n	Subjects With IFI n (%)	n	Subjects With IFI n (%)	n	Subjects With IFI n (%)	n	Subjects With IFI n (%)
Baseline Corticosteroids (mg/kg/day)								
≥2.0	41	4 (10)	32	5 (16)	40	2 (5)	32	5 (16)
<2.0 but ≥1.0	107	6 (6)	129	13 (10)	105	3 (3)	126	9 (7)
<1.0 but ≥0.4	108	4 (4)	100	7 (7)	107	1 (1)	98	6 (6)
<0.4 but ≥0	34	0	27	1 (4)	33	0	27	1 (4)
Dose Unknown	10	2 (20)	10	1 (10)	5	1 (20)	5	1 (20)
None	1	0	1	0	1	0	0	0
CMV Positive During Treatment								
Yes	96	7 (7)	78	11 (14)	96	2 (2)	76	10 (13)
No	205	9 (4)	221	16 (7)	195	5 (3)	212	12 (6)
No. of Immunosuppressive Agents at Baseline								
1	64	5 (8)	48	3 (6)	62	2 (3)	45	4 (9)
2	151	6 (4)	168	16 (10)	146	2 (1)	164	12 (7)
3 or more	85	5(6)	82	8 (10)	82	3 (4)	79	6 (8)
None	1	0	1	0	1	0	0	0

Adapted from Study Report C98-316, NDA 22-003.

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MICROBIOLOGICAL RESULTS

Table 36: Proven/Probable IFI by Pathogen-PTP

Distribution of Proven/Probable Invasive Fungal Infections by Pathogen Group During the Primary Time Period (All Randomized Subjects)		
Pathogen or Pathogen Group	No. Subjects With Proven/Probable IFI	
	Posaconazole	Fluconazole
Aspergillus	7	21
Candida	4	4
Other Fungi	5	2
Pseudallescheriaa	1	0
Rhizomucor mieheia	0	1
Trichosporon beigeliia	1	0
Scedosporium prolificansa	1	0
Mould	2	1
All	16	27
a: Specific pathogens under the Other Fungi group are not counted again in the 'All' row.		
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 Adapted from Study Report C98-316, NDA 22-003.		

During both the Primary Time Period (above) and the While on Treatment Period (below) the incidence of Candida infections between the treatment groups is very similar. The difference between the groups primarily occurred in the incidence of proven and probable Aspergillus IFI.

Table 37: Proven/Probable IFI by Pathogen WOT

Distribution of Proven/Probable Invasive Fungal Infections by Pathogen Group While on Treatment (All Treated Subjects)		
Pathogen or Pathogen Group	No. Subjects With Proven/Probable IFI	
	Posaconazole	Fluconazole
Aspergillus	3	17
Candida	1	3
Other Fungia	3	2
Pseudallescheria boydii	1	0
Rhizomucor miehei	0	1
Trichosporon beigelii	1	0
Mould	1	1
All	7	22

Adapted from Study Report C98-316, NDA 22-003.

The tables below separate out the proven and probable IFIs due to Candida or Aspergillus.

Table 38: CANDIDA PROVEN AND PROBABLE INFECTIONS

TIME PERIOD	PROVEN		PROBABLE		TOTAL	
	POS	FLU	POS	FLU	POS	FLU
WOT	1	3	0	0	1	3
PTP-WOT	3	1	0	0	3	1
PTP	4	4	0	0	4	4

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

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

Table 39: ASPERGILLUS PROVEN AND PROBABLE INFECTIONS

TIME PERIOD	PROVEN		PROBABLE		TOTAL	
	POS	FLU	POS	FLU	POS	FLU
WOT	0	7*	3	10	3	17*
PTP-WOT	2	2	2	4	4	6
PTP	2	7	5	14	7	21

*In 2 of these patients the infection occurred either while receiving therapy or within 7 days of discontinuing therapy but after 112 days. Therefore these 2 infections would be considered to have occurred during the WOT period but not the Primary Time Period.

The incidence of breakthrough Candida infections in both arms was quite small and close to identical during the Primary time period and the While on Treatment time periods in the All Treated and Per Protocol populations.

The major numerical difference in incidence is that the incidence of both proven Aspergillus infections and probable Aspergillus infections in the Posaconazole arm are less frequent than in the Fluconazole arm.

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Results for Study P01899

Please see below:

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Populations Analyzed

- **All Randomized Subjects: Subjects who were randomized and signed informed consent.**
- **Modified Intent-to-Treat Subset (also called All Treated): Subjects who were randomized and received at least one dose of oral study drug.**
- **Efficacy-Evaluable Subjects or Per Protocol: A per-protocol subset of All Randomized Subjects who met the following criteria:**
 - o **Met protocol-specified entry criteria.**
 - o **Were compliant with study conduct (i.e. not lost to follow-up.)**
 - o **Were compliant with study treatment (at least 4 days of prescribed oral study drug.)**
 - o **Did not receive unacceptable concomitant medications.**

RESULTS

Disposition of Patients

Summary of Data Subsets Analyzed and Reasons for Exclusion		
Data Set Analyzed	Number (%) of Subjects	
	POS	FLU/ITZ
All Randomized	304 (100)	298 (100)
- Not treated with oral study drug	7 (2)	6 (2)
MITT	297 (98)	292 (98)
- Did not meet entry criteria (b)	0	1 (<1)
- Non-compliance with study conduct (c)	17 (6)	17 (6)
- Unacceptable concomitant medication (d)	1 (<1)	1 (<1)
- Non-compliance with study treatment (e)	18 (6)	13 (4)
Efficacy Evaluable	265 (87)	263 (88)

ANC = absolute neutrophil count; FLU = fluconazole; ITZ = itraconazole; MITT = modified intent-to-treat; POS = posaconazole.

a: Percentage of subjects is based on the All Randomized Subjects population.

b: Includes subjects who did not have a diagnosis of AML or MDS, or subjects who did not receive intensive chemotherapy expected to result in prolonged neutropenia.

c: Includes subjects who did not have at least 7 days of neutropenia (ANC ≤500 cells/mm³), or subjects who received >3 consecutive days or ≥10 cumulative days of IV alternative antifungal study medication.

d: Includes subjects who received medications known to lower the serum concentration of azole antifungals for 5 or more days concurrently with study drug.

e: Includes subjects who received <4 consecutive days of oral study drug.

Adapted from Study Report P01899, NDA 22-003.

BASELINE CHARACTERISTICS

The table below demonstrates that the groups were evenly matched for all of the baseline characteristics of note, especially the degree of neutropenia, the presence of a positive aspergillus antigen upon entry, and the amount of prior antifungal prophylactic therapy.

Table 40: Baseline Characteristics Study P01899

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 ≤100 cells/mm3)	73 (24)	71 (24)
Non-Severe neutropenia (ANC >100 cells/mm3 to ≤500 cells/mm3)	119 (39)	118 (40)
Non-neutropenic (ANC ≥500 cells/mm3)	98 (32)	94 (32)
Missing or unknown	14 (5)	15 (5)
Aspergillus antigen status on or before first date of study drug		
<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		
No mucositis	164 (54)	154 (52)
CTC Grade 1-2	93 (31)	97 (33)

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CTC Grade 3-4	7 (2)	3 (1)
Missing or unknown	40 (13)	44 (15)

Summary of Post-Baseline Characteristics (All Randomized Subjects)

Post-Baseline Characteristic	POS (n=304)	FLU/ITZ (n=298)
	<u>Total Chemotherapy Cycles Before or During the Treatment Phase</u>	
1	174(57)	182 (61)
2	96(32)	89 (30)
3	34(11)	25 (8)
4	0	2 (1)
<u>Worst Neutropenia During the Treatment Phase</u>		
Neutropenic	298 (98)	290 (97)
Severe Neutropenia (ANC ≤100 cells/mm ³)	264 (87)	261 (88)
Non-Severe Neutropenia (ANC >100 cells/mm ³ to ≤500 cells/mm ³)	34 (11)	29 (10)
Non-Neutropenic (ANC >500 cells/mm ³)	1 (<1)	6 (2)
Missing or Unknown	5 (2)	2 (1)
<u>Maximum Consecutive Days of Neutropenia During Treatment Phase</u>		
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)
Mean (SD)	20	18
Median	18	18
<u>Total Days of Neutropenia During Treatment Phase</u>		
0 to 7 days	21 (7)	21 (7)
>7 to 14 days	63 (21)	62 (21)
>14 to 21 days	78 (26)	81 (27)
>21 to 28 days	42 (14)	58 (19)
>28 days	100 (33)	76 (26)
Mean (SD)	25 (17.1)	23 (13.1)
Median	21	20
Minimum-Maximum	0 - 121	0 - 76
<u>SAF Used for Any Reason During The Treatment Phase</u>		
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)

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Median	7	7
Minimum-Maximum	1 - 24	1 - 17

Adapted from Study Report P01899, NDA 22-003.

<u>Use of IV Study Medication (Ampho for POS arm: IV FLU or ITRA for FLU or ITRA arms respectively)</u>	POS (304)	FLU/ITRA(298)
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

Adapted from Study Report P01899, NDA 22-003.

The treatment arms were balanced with respect to the number of chemotherapy cycles and the types of chemotherapy agents used during the Oral Treatment Phase. The majority of subjects (POS, 174/304 [57%]; FLU/ITZ, 182/298 [61%]) received only one cycle of chemotherapy during the Treatment Phase of the study. Approximately one-half of all subjects received growth factors during the Treatment Phase. The median duration of use was slightly longer in the POS arm (11 days; range, 1-67 days) than in the FLU/ITZ arm (9 days; range, 1-57 days); however, this slight difference in duration of growth factor use is not considered to be clinically significant. The treatment arms were also well balanced with respect to the number of subjects who received steroids during the Treatment Phase and in terms of the incidence and severity of neutropenia during the Treatment Phase. Nearly all study subjects had neutropenia during the Treatment Phase. In the vast majority of cases the neutropenia was severe (≤ 100 cells/mm³). The median total number of days of neutropenia during the Treatment Phase was similar in both treatment groups as was the median number of consecutive days of neutropenia. Of note, the POS arm had a higher proportion of subjects with prolonged (>28 consecutive days) neutropenia. The number of subjects with >28 cumulative days of neutropenia was also higher in the POS arm. This higher incidence of cumulative neutropenia in the POS arm may be explained by the fact that more POS subjects completed the Treatment Phase than did FLU/ITZ subjects (52% vs 42%, respectively), and as such, their days of neutropenia continued to be counted until the end of the Treatment Phase or recovery of ANC (>500 cells/mm³), whichever occurred first.

The table shows that more itraconazole/fluconazole patients used SAF for any reason for longer than 3 days (34%) than posaconazole patients (23%). Only 2% of posaconazole used the designated IV study medication (amphotericin) and 4% of fluconazole /itraconazole patients used their IV alternative (fluconazole/itraconazole respectively.) In total, only 17 patients in the posaconazole arm used any amphotericin-11 did so for 3 or less days. Therefore the impact of the opportunity of the patients in the posaconazole arm to receive IV amphotericin if intravenous therapy was needed for oral intolerance was likely small. In the table below copied from the P01899 study report it is shown that patients in the standard azole arm received more

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amphotericin, caspofungin, and voriconazole than patients in the the posaconazole arm, who were given more fluconazole.

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P01899-FINAL
 All Randomized Subjects
 Summary of Systemic Antifungal Medications Taken During the Treatment Phase

	Posaconazole n=504	Standard Azole n=299	Fluconazole n=240	Itraconazole n=58
AMPHOTERICIN B	61/504 (20)	69/299 (23)	50/240 (21)	19/58 (33)
LIPID AMPHOTERICIN B	11/504 (4)	20/299 (7)	17/240 (7)	3/58 (5)
CASPOFUNGIN	14/504 (5)	19/299 (6)	13/240 (5)	6/58 (10)
FLUCONAZOLE	49/504 (16)	37/299 (12)	31/240 (13)	6/58 (10)
INVESTIGATIONAL DRUG	1/504 (<1)	0	0	0
ITRACONAZOLE	12/504 (4)	22/299 (7)	12/240 (5)	10/58 (17)
MICONAZOLE	1/504 (<1)	1/299 (<1)	0	1/58 (2)
TERBINAFINE	0	0	0	0
VORICONAZOLE	13/504 (4)	27/299 (9)	23/240 (10)	4/58 (7)

CLINICAL STUDY

From Study Report P01899, NDA 22-003.

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Table 41: Treatment Duration

Summary of Treatment Duration and Exposure (All Randomized Subjects)	POS (n=304)	FLU/ITZ (n=298)
Treatment Duration (Days)		
N	297	292
Mean (SD)	36.7 (30.3)	32.3 (27.5)
Median	25	21
Minimum	1	1
Maximum	151	112
Cumulative Number (%) of Subjects With Indicated Treatment Duration		
≥7 Days	269 (88)	263 (88)
≥14 Days	212 (70)	194 (65)
≥21 Days	176 (58)	148 (50)
≥28 Days	137 (45)	119 (40)
≥56 Days	83 (27)	64 (21)
≥84 Days	28 (9)	22 (7)
Randomized, not treated	7 (2)	6 (2)
Exposure (Days)		
N	297	292
Mean (SD)	28.9 (21.1)	24.9 (17.2)
Median	23	20
Minimum	1	1
Maximum	110	80

Adapted from Study Report P01899, NDA 22-003.

The average duration of therapy for both arms was less than 30 days, with a range from 1 day to over 100 days. Only about 10% had greater than 84 days. Consequently, the assessment of some outcomes as farther out than 30 days from drug discontinuation may be less valid than measures within a month of treatment discontinuation.

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EFFICACY OUTCOMES

Table 42: Results from Clinical Study 2(P01899) in Prophylaxis of IFI in All Randomized Patients

	Posaconazole n = 304	Fluconazole/Itraconazole n = 298
<i>On therapy plus 7 days</i>		
Clinical Failure ^{a,b}	82 (27%)	126 (42%)
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	17 (6%)	25 (8%)
Proven / probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF ^{c,d}	67 (22%)	98 (33%)
<i>Through 100 days post-randomization</i>		
Clinical Failure ^b	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(<i>Aspergillus</i>)	2 (1%)	26 (9%)
(<i>Candida</i>)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven / probable fungal infection prior to death	2 (1%)	16 (5%)
SAF ^{c,d}	98 (32%)	125 (42%)
Event free lost to follow-up ^e	34 (11%)	24 (8%)
a: 95% confidence interval (posaconazole-fluconazole/ itraconazole) = (-22.9%, -7.8%). 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). e: Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.		

The definition of clinical failure in this population was: development of proven or probable IFI, death, empiric use of systemic antifungal therapy for > 3 days, and lost to follow-up. There were fewer clinically significant failures in the posaconazole arm in comparison to the combined fluconazole-itraconazole arm. There were fewer proven/probable IFIs and especially fewer proven/probable Aspergillus infections in the posaconazole arm. Most of the difference in Aspergillus infection was in the probable Aspergillus cases. Please see Microbiology results below. **Analyses separating outcome by comparator revealed that posaconazole patients had statistically significant lower rates of clinical failure than fluconazole patients but non-inferior rates of clinical failure in comparison to itraconazole patients.**

MO Comment: The sponsor's proposed analysis for the primary endpoint of incidence of IFI does not take into consideration patients who use any systemic antifungal agents or died. The Review Team had recommended to the Sponsor that these issues be addressed in the analysis of outcomes for the primary endpoint. Patients who receive systemic antifungal agents in addition to study drug and deaths, from all causes, should be considered as "failures" in the analysis of the primary endpoints. In addition to those patients who received empiric SAF, six patients in the posaconazole arm and 11 in the fluconazole/itraconazole arm received IV Study drug for 4 or more days. This was amphotericin in the posaconazole arm, fluconazole in the fluconazole arm, and itraconazole in the itraconazole arm. If these numbers are added into the analysis as failures the overall outcome does not change.

Secondary Analyses

Incidence Proven and Probable IFI

The Sponsor presented the incidence of proven and probable IFI during the Oral Treatment Phase as their primary endpoint. They chose this endpoint because the occurrence of so many other adverse events secondary to the underlying disease and or its treatment would make it difficult to examine the effectiveness of the drug in preventing invasive fungal infection. The Division considers this an important secondary endpoint but for reasons listed above still maintains that clinical outcome should be the primary outcome of interest.

MO Comment: The listing of all cases of proven/probable IFI is provided in the first Appendix. The Medical Officer reviewed all these cases and concurred with the DRC results with one possible exception. There was one case of probable Aspergillus infection occurring in a patient assigned to posaconazole who had already been diagnosed with a proven systemic Candida infection 5 days earlier. This patient was considered a proven Candida IFI and not counted again as a probable Aspergillus. The addition of this once case would not have altered the results.

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Table 43: Proven/Probable IFI: POS versus FLU+ITRA P01899 in All Randomized Patients

IFI	POS (304)	FLU/ITRA (298)
Oral Treatment Phase	7/304 (2.3%)	25/298 (8%)
100 Day Phase	14/304 (4.6%)	33/298 (11%)
Post Oral Treatment Phase	10/304 (3%)	9/298 (3%)

Table 44: Proven/Probable IFI: POS versus FLU P01899 in All Randomized Patients

IFI	POS (235)	FLU (240)
Oral Treatment Phase	4/235 (1.7%)	19/240 (7.9%)
100 Day Phase	8/235 (3.4%)	27/240 (11.3%)

Table 45: Proven/Probable IFI: POS versus ITRA P01899 in All Randomized Patients

IFI	POS (65)	ITRA (58)
Oral Treatment Phase	3/65 (4.6%)	6/58 (10.3%)
100 Day Phase	6/65 (9.2%)	6/58 (10.3%)

MO Comment: For the All Randomized populations there was a significantly lower incidence of IFI in the Posaconazole arms when compared to the combined FLU/Itra group or when compared to Fluconazole alone. In the Posaconazole versus Itraconazole analysis the difference is not statistically superior but is noninferior. The incidence of IFI in the posaconazole group at the itraconazole sites is also worse than the the incidence of Posaconazole at the Fluconazole sites possible suggesting the presence of sicker patients at those sites.

Also of note- in the top of the 3 tables above although there is a difference in the Incidence of IFI in the 2 groups (POS vs FLU/ITRA) in the treatment phases there is no difference between the groups in the Post Treatment phase.

Table 46: Proven and Probable IFI Per Protocol (Efficacy Evaluable) Patients P01899

IFI	POS (265)	FLU/ITRA (263)
Oral Treatment Phase	7/265 (2.6%)	24/263 (9.1%)
100 Day Phase	13/265 (4.9%)	29/263 (11%)
Post Oral Treatment Phase	9/265 (3.4%)	6/263 (2.3%)

MO Comment: A similar statistically superior result is seen in the Per Protocol (Efficacy Evaluable) population for the Incidence of Proven/Probable IFI during the treatment phases for POS versus FLU/ITRA.

Proven and Probable IFI's By Organism

Table 47: Proven/Probable IFI by Organism in All Randomized Patients in the Oral Treatment Phase P01899

A=Aspergillus; C=Candida; and O=Other IFI

POSACONAZOLE (N=304)					
PROVEN			PROBABLE		
C	A	O	C	A	O
3	0	1	0	2	1
FLUCONAZOLE (N= 240)					
PROVEN			PROBABLE		
C	A	O	C	A	O
2	1	2	0	14	0
ITRACONAZOLE (N=58)					
PROVEN			PROBABLE		
C	A	O	C	A	O
0	0	0	0	5	1

MO COMMENT: The Incidence of Candida infection was very small in all the arms with very few breakthrough either proven or probable infections detected. Likewise the incidence of proven invasive Aspergillus infection was also similar among patients in the various treatment groups. The important differences are in the incidence of probable Aspergillus infections. This is not very surprising as it is well known that Aspergillus can

be very difficult to definitively diagnose antemortem. However, it would have added additional validity to the conclusions of efficacy had there been a more impressive difference in the incidence of proven IFI due to Aspergillus among the treatment group.

Possible IFIs and DRC vs Investigator Assessments

Table 48: Distribution of Proven, Probable, and Possible Invasive Fungal Infections by Treatment Group (All Randomized Subjects) P01899

	Number (%) of Subjects	
	POS (n=304)	FLU/ITZ (n=298)
IFI Incidence per DRC		
Treatment Phase*	66 (22)	79 (27)
Post-Treatment Phase	23 (8)	20 (7)
IFI Incidence per Investigator		
Treatment Phase*	32 (11)	53 (18)
Post-Treatment Phase	16 (5)	15 (5)

DRC = Data Review Committee

* From randomization to 7 days after end of treatment (oral or IV).

Adapted from Study Report P01899, NDA 22-003.

A higher overall incidence of IFIs was observed when assessed by the DRC, as compared with the investigator assessment, regardless of treatment arm or study period. This finding is not unexpected considering that the DRC review process involved a more focused and systematic review of all of the elements potentially supporting a fungal infection in a selected group of cases which already met the criteria to be considered suspected IFIs. Furthermore, investigators did not have access to the same diagnostic tools as the DRC had (eg, galactomannan levels) at the time of their assessments.

Both the per-DRC and per-investigator incidences of proven/probable/possible IFIs were lower with POS during the Treatment Phase than with FLU/ITZ. In fact, this difference was significant (POS, 32/304 [11%]; FLU/ITZ 53/298 [18%]; P=0.0106) when considering the per-investigator IFI incidence. As one would expect, there was no difference in IFI incidence between treatment arms once study drug was stopped. The findings are consistent with the distribution of DRC-adjudicated proven and probable IFIs for the same time periods

Deaths

A total of 116 deaths (49 POS, 67 FLU/ITZ) were reported during the course of the study, of which 108 deaths (44 POS, 64 FLU/ITZ) occurred during the period from randomization to 100 days post-randomization. The time

from randomization to death was analyzed for the 100-Day Phase using the Kaplan-Meier method. 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. A significant difference ($P=0.0354$) in favor of POS was observed between the treatment groups with respect to time to death during the 100-Day Phase, based on log-rank statistics.

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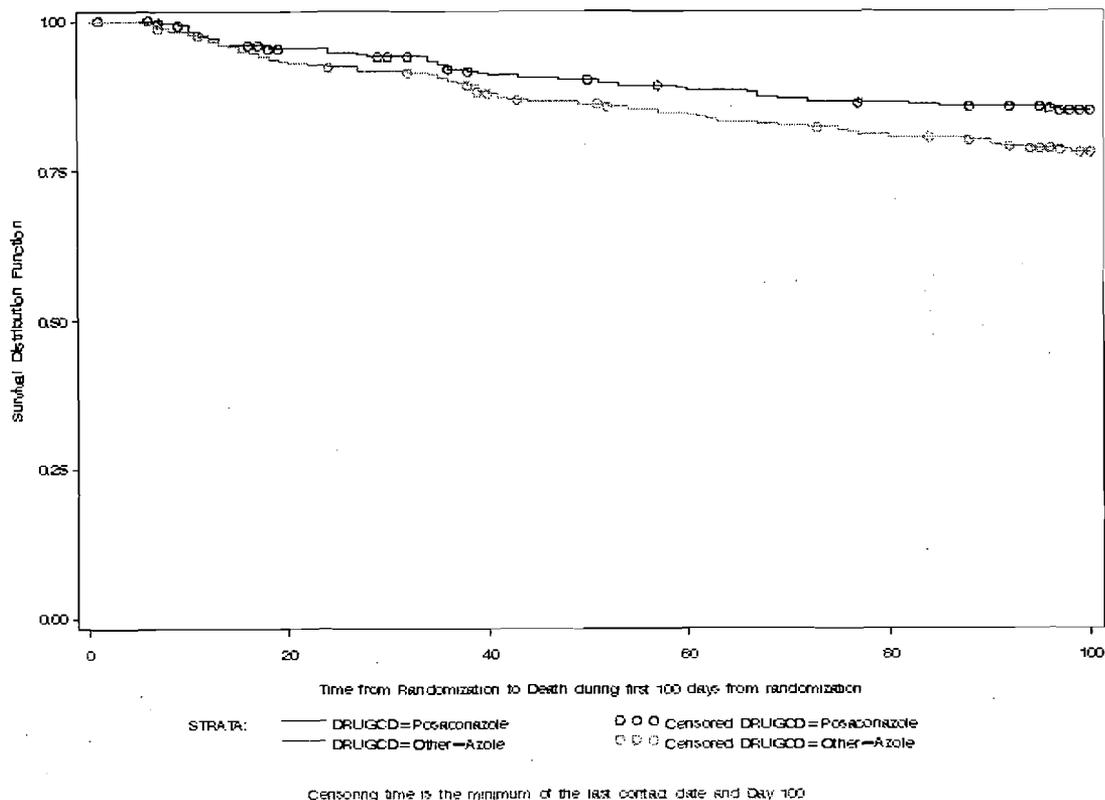
Figure 8: Kaplan-Meier Analysis of Time from Randomization to Death During the 100-Day Phase Study P01899:

Adapted from Study Report P01899, NDA 22-003.

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Study P01899: Posaconazole vs. Other Azoles in the Prophylaxis of Invasive Fungal Infections

FIGURE F-2.1 Kaplan-Meier Analysis of Time from Randomization to Death
 During 100 days from randomization



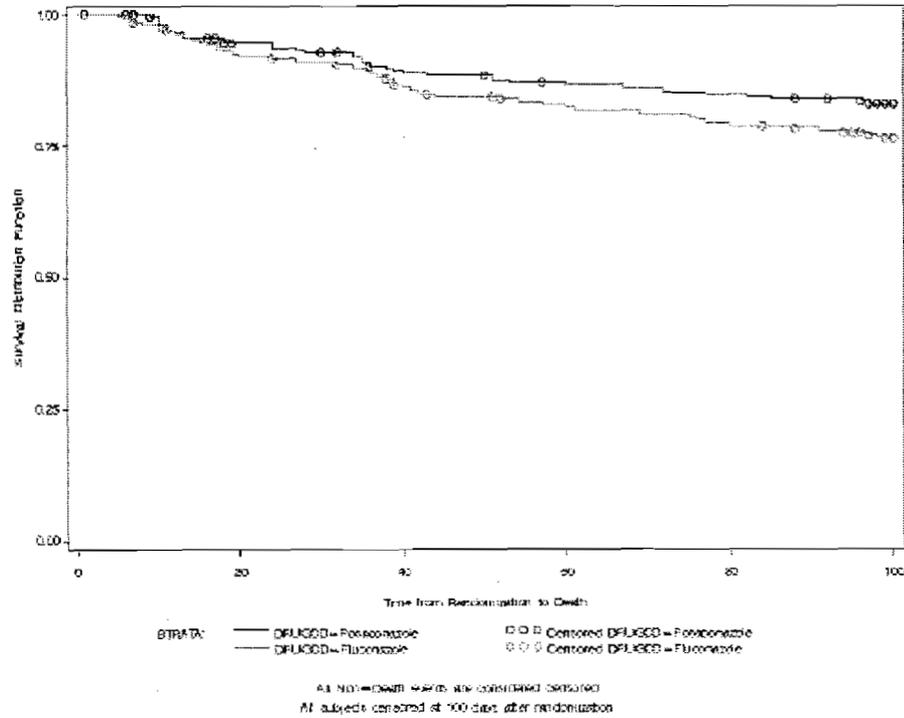
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Below is an analysis which looks at the Time to Death for Posaconazole versus Fluconazole at the Fluconazole sites only. It reveals a similar result to the combined results above.

Figure 9: Kaplan-Meier Analysis of Time from Randomization to Death During the 100-Day Phase Study P01899 for Posaconazole versus Fluconazole at the Fluconazole sites only.

Adapted from Study Report P01899, NDA 22-003.

FIGURE SURVIVAL-F-4.1A Kaplan-Meier Analysis of Time from Randomization to Death by Treatment Group
 Study P01899: Posaconazole vs. Other Azole in the Prophylaxis of Invasive Fungal Infections
 FOR FLUCONAZOLE CITES ONLY

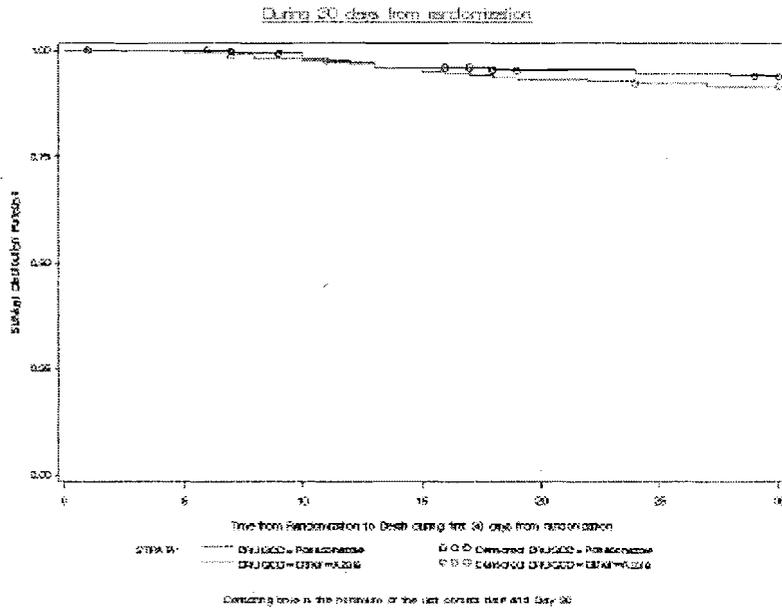


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The average duration of therapy for both arms was less than 37 days, with a range from 1 day to over 100 days. Only about 25 % had greater than 84 days of study drug. Consequently, the assessment of death as far out as 100 days may be less valid for many of the enrollees. Therefore, Time to Death-Thirty Days from Randomization also needs to be examined. There was not a significant difference in death at 30 days post randomization.

Figure 10: Kaplan Meier Analysis Time to Death Thirty Days from Randomization

Study P01899. Adapted from Study Report P01899, NDA 22-003.



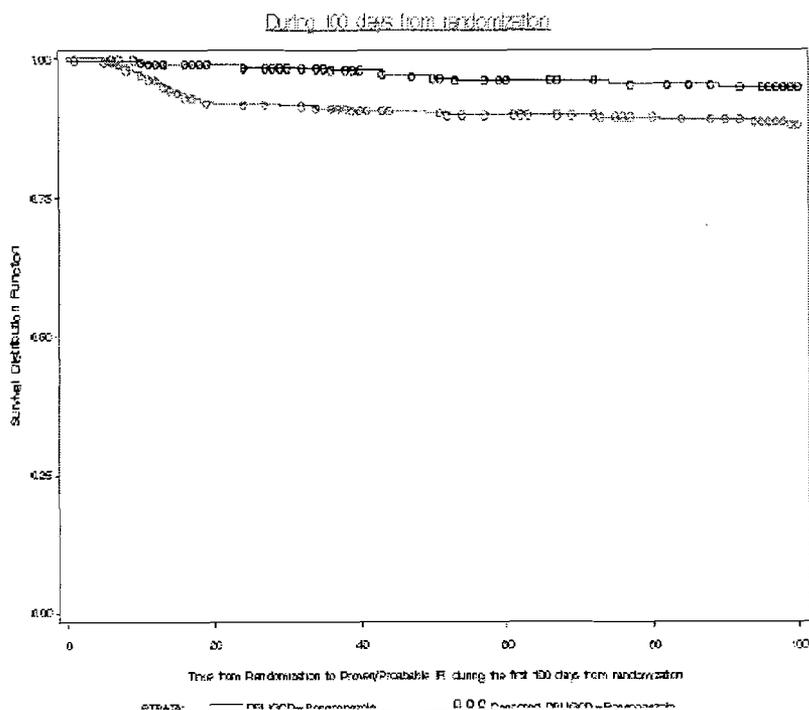
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TIME TO IFI

The time from randomization to onset of proven/probable IFI was analyzed by the Kaplan-Meier method, censoring all subjects who were alive at 100 days postrandomization. A significant advantage was observed with POS vs FLU/ITZ with respect to the time to proven/probable IFI onset for the 100-Day Phase (P=0.0029) based on log-rank statistics (Please see the figure below.) The cumulative percent of IFI at the end of the 100-Day Phase, which was calculated using Kaplan-Meier methods, was lower with POS (5.1%) vs FLU/ITZ (12.0%).

MO Comment: This analysis does not however take into account the other causes of clinical failure such as use of systemic anti-fungal therapy, death, or lost to follow-up.

Adapted from Study Report P01899, NDA 22-003.



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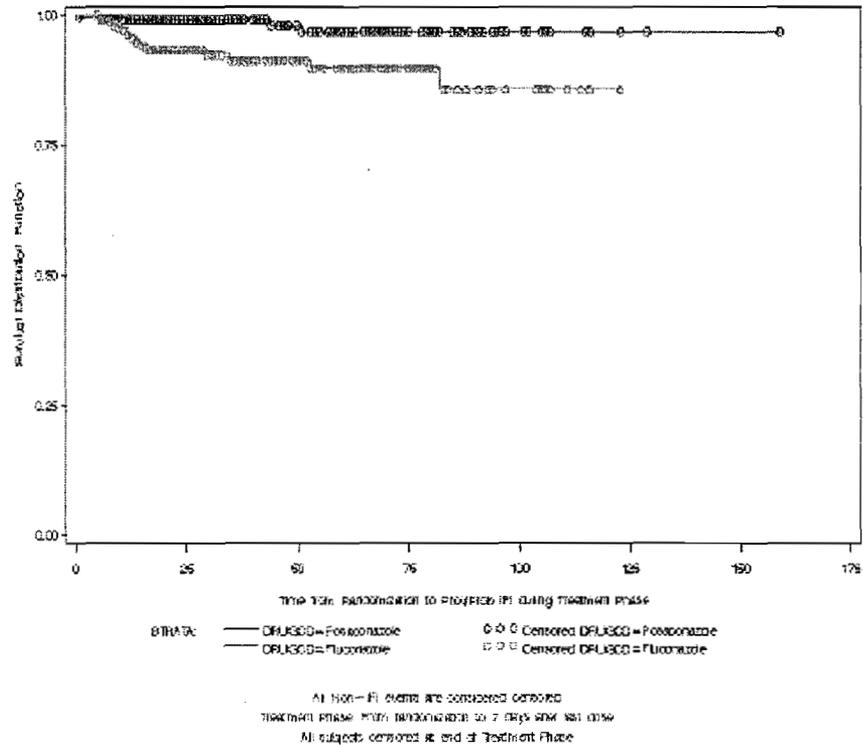
Figure 11: Kaplan Meier Analysis of Time to IFI Study P01899 Posaconazole versus Fluconazole/Itraconazole. Above.

Figure 12: Kaplan Meier Analysis of Time to IFI Study P01899 Posaconazole versus Fluconazole at Fluconazole sites only. Below. Adapted from Study Report P01899, NDA 22-003.

FIGURE IFIF-4.2AA Kaplan-Meier Analysis of Time from Randomization to IFI by Treatment Group

Study P01899: Posaconazole vs. Other Azole in the Prophylaxis of Invasive Fungal Infections
 FOR FLUCONAZOLE SITES ONLY

Only IFI (Proven/Probable) That Occurred During Treatment Phase are Considered Events



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The above Kaplan Meier analysis from time to randomization to IFI looks at the Posaconazole versus Fluconazole patients at the Fluconazole sites only. The results and limitations are similar to that for the combined analysis.

EXPLORATORY ANALYSES

Table 49: Distribution of Proven and Probable Invasive Fungal Infections During the Oral Treatment Phase by Baseline Characteristics (All Randomized Subjects)

Baseline Characteristic	Number (%) of Subjects	
	POS (n=304)	FLU/ITZ (n=298)
Primary diagnosis at study entry		
AML (new diagnosis)	5/213 (2)	20/222 (9)
AML (first relapse)	0/42	3/38 (8)
MDS	2/49 (4)	2/38 (5)
Sex		
Male	3/158 (2)	12/160 (8)
Female	4/146 (3)	13/138 (9)
Race		
Caucasian	5/220 (2)	20/231 (9)
Non-Caucasian	2/84 (2)	5/67 (7)
Black	0/16	1/9 (11)
Asian	1/13 (8)	2/9 (22)
Hispanic	1/51 (2)	2/47 (4)
Other	0/4	0/2
Age (years)		
<18	1/8 (13)	0/8
18 to <65	4/238 (2)	18/223 (8)
≥65	2/58 (3)	7/67 (10)
Severity of baseline neutropenia		
Neutropenic	5/192 (3)	21/189 (11)
Severe neutropenia (ANC ≤100 cells/mm ³)	2/73 (3)	10/71 (14)
Non-severe neutropenia (ANC >100 cells/mm ³ <500cells/mm ³)	3/119 (3)	11/118 (9)
Non-neutropenic (ANC >500 cells/mm ³)	2/98 (2)	3/94 (3)
Missing or unknown	0/14	1/15 (7)
Use of systemic antifungals prophylactically prior to randomization		
No	7/262 (3)	21/256 (8)
Yes	0/42	4/42 (10)
1 to 3 days	0/32	4/31 (13)
4 to 7 days	0/5	0/7
>7 days	0/5	0/4
Mucositis score on or before first date of study drug		
No mucositis	3/164 (2)	19/154 (12)
CTC Grade 1-2	4/93 (4)	4/97 (4)
CTC Grade 3-4	0/7	0/3
Missing or unknown	0/40	2/44

In the table above and the graphic depiction below there were no baseline characteristics identified for which the results were not at least noninferior between the groups.

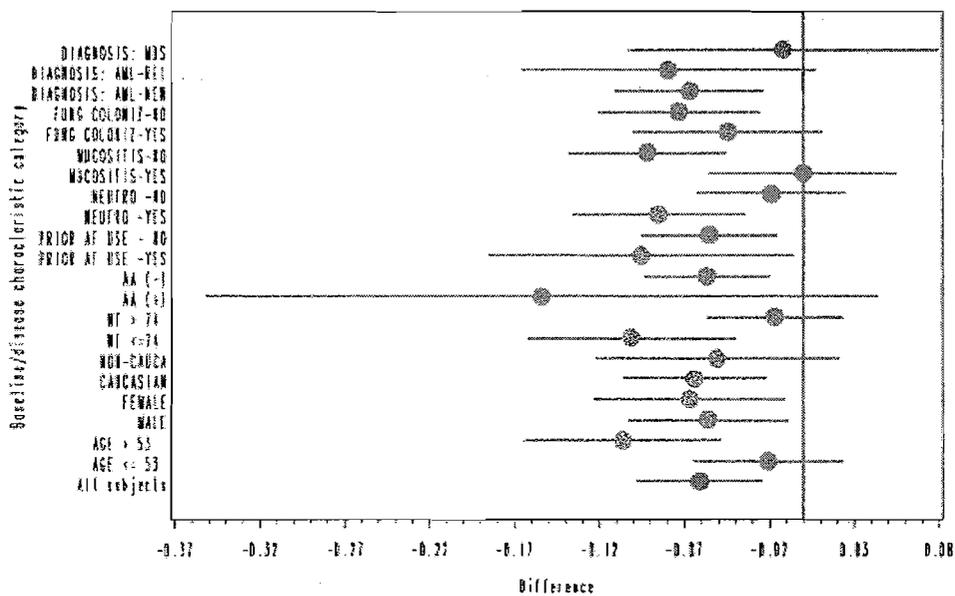


Figure 4 Confidence Interval Plot for the Differences in Proven and Probable Invasive Fungal Infection Rates Between Treatment Groups in the Oral Treatment Phase for Key Baseline or Disease Characteristics (All Randomized Subjects)

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Incidence of IFI by Aspergillus Antigen at Entry

Table 50: Incidence of IFI by Baseline Aspergillus AG

Aspergillus antigen status on or before first date of study drug	POS	FLU/ITRA
<0.5 GMI	6/230 (3)	20/231 (9)
0.5 to 1.5 GMI	0/8	1/7 (14)
>1.5 GMI	0/4	1/6 (17)
Missing or unknown	1/62 (2)	3/54 (6)

Adapted from Study Report P01899, NDA 22-003.

MO Comment: Since there was no imbalance in these factors at enrollment and since the largest incidence is seen in those standard azole (FLU/ITRA) patients with missing or unknown levels no conclusions can be made from these data.

6.1.5 Clinical Microbiology

1. Study C98-316

Table 51: Distribution of Proven/Probable Invasive Fungal Infections by Pathogen Group During the Primary Time Period (All Randomized Subjects)

Pathogen or Pathogen Group	No. Subjects With Proven/Probable IFI	
	Posaconazole	Fluconazole
Aspergillus	7	21
Candida	4	4
Other Fungi	5	2
Pseudallescheria	1	0
Rhizomucor mieheia	0	1
Trichosporon beigeliia	1	0
Scedosporium prolificansa	1	0
Mould	2	1
All	16	27
a: Specific pathogens under the Other Fungi group are not counted again in the 'All' row.		
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.		
Adapted from Study Report C98-316, NDA 22-003.		

MO Comment: During both the Primary Time Period (above) and the While on Treatment Period (below) the incidence of Candida infections between the treatment groups is very similar. The difference between the groups primarily occurred in the incidence of proven/probable Aspergillus IFI.

Table 52: Distribution of Proven/Probable Invasive Fungal Infections by Pathogen Group While on Treatment (All Treated Subjects)

Pathogen or Pathogen Group	No. Subjects With Proven/Probable IFI	
	Posaconazole	Fluconazole
Aspergillus	3	17
Candida	1	3
Other Fungia	3	2
Pseudallescheria boydii	1	0
Rhizomucor miehei	0	1
Trichosporon beigelii	1	0
Mould	1	1
All	7	22

Adapted from Study Report C98-316, NDA 22-003.

The tables below separate out the proven and probable IFIs due to Candida or Aspergillus.

Table 53: CANDIDA PROVEN AND PROBABLE INFECTIONS

TIME PERIOD	PROVEN		PROBABLE		TOTAL	
	POS	FLU	POS	FLU	POS	FLU
WOT	1	3	0	0	1	3
PTP-WOT	3	1	0	0	3	1
PTP	4	4	0	0	4	4

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

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

Table 54: ASPERGILLUS PROVEN AND PROBABLE INFECTIONS

TIME PERIOD	PROVEN		PROBABLE		TOTAL	
	POS	FLU	POS	FLU	POS	FLU
WOT	0	7*	3	10	3	17*
PTP-WOT	2	2	2	4	4	6
PTP	2	7	5	14	7	21

*In 2 of these patients the infection occurred either while receiving therapy or within 7 days of discontinuing therapy but after 112 days. Therefore these 2 infections would be considered to have occurred during the WOT period but not the Primary Time Period.

The incidence of breakthrough Candida infections in both arms was quite small and close to identical during the Primary time period and the While on Treatment time periods in the All Treated and Per Protocol populations.

The major numerical difference in incidence is that the incidence of both proven Aspergillus infections and probable Aspergillus infections in the Posaconazole arm are less frequent than in the Fluconazole arm.

From Division Microbiologist Dr. Suvarna-

(Note Dr. Suvarna evaluated cases in the Efficacy Evaluable Population as opposed to the ITT or MITT populations as used by the MO)

“In study C/I98-316, there were 20 FLZ treated patients and 10 POS treated patients who developed proven or probable IFIs during the primary treatment period (i.e., 16 weeks). In 9 patients (FLZ, n = 5; POS, n = 4) with probable infection, the diagnosis was made using *Aspergillus* antigen test. In 3 of the 9 patients, the diagnosis was based on a single test result using serum or BAL. As discussed previously, positive results should be interpreted in conjunction with clinical and radiological findings. Invasive fungal infections due to *Aspergillus* species (n = 17), *C. glabrata* (n = 1), *Rhizopus miehei* (n = 1) or unidentified mold were identified between 2 to 93 days after starting fluconazole prophylaxis. Similarly, invasive fungal infections due to *Aspergillus* species (n = 4), *C. glabrata* (n = 2), *C. krusei* (n = 1), *Pseudoallescheria boydii* (n = 1), *Scedosporium prolificans* (n = 1), *Trichosporon biegelii* (n = 1) were identified between 9 and 105 days after starting posaconazole prophylaxis. Limited *in vitro* susceptibility testing was performed on breakthrough isolates using CLSI recommended methods. The POS MICs against *Aspergillus* (n = 3) and *Candida* (n = 1) isolates were ≤ 0.125 µg/ml while against 1 *Scedosporium* isolate, the POS MIC was 8 µg/ml.”

STUDY P01899

PROVEN and PROBABLE IFI’s, combined with MICROBIOLOGICAL RESULTS.

Table 55: Proven/Probable IFI by Organism in All Randomized Patients in the Oral Treatment Phase

POSACONAZOLE (N=304)					
PROVEN			PROBABLE		
C	A	O	C	A	O
3	0	1	0	2	1
FLUCONAZOLE (N= 240)					
PROVEN			PROBABLE		
C	A	O	C	A	O
2	1	2	0	14	0

ITRACONAZOLE (N=58)					
PROVEN			PROBABLE		
C	A	O	C	A	O
0	0	0	0	5	1

A=Aspergillus

C=Candida

O=Other

MO COMMENT: The Incidence of Candida infection was very small in all the arms with very few breakthrough either proven or probable infections detected. Likewise the incidence of proven invasive Aspergillus infection was also similarly low among patients in the various treatment groups. The important differences are in the incidence of probable Aspergillus infections in patients who received posaconazole or fluconazole. This is not very surprising as it is well known that Aspergillus can be very difficult to definitively diagnosed antemortem. The difference between the groups would have been more robust had there been a more impressive difference in the incidence of proven IFI due to Aspergillus among the treatment groups.

From Division Microbiologist Dr. Suvarna:

(Note Dr. Suvarna evaluated cases in the Efficacy Evaluable Population as opposed to the ITT or MITT populations as used by the MO)

“In study P01899, 18 FLZ treated patients developed proven or probable IFIs during the oral treatment phase. The majority of invasive fungal infections were due to *Aspergillus* species, *A. fumigatus* or *A. flavus* (n = 14). The remaining infections were due to *Candida* species other than *C. albicans* (n = 2), *Rhizopus arrhizus* (n = 1) or *Pseudoallescheria boydii* (n = 1). The IFIs were identified within 5 to 81 days of FLZ prophylaxis. There were 7 POS treated patients who developed proven or probable invasive fungal infections. The invasive fungal infections were due to *Aspergillus* species (n = 2), *C. glabrata* (n = 2), or mixed infections due to *Candida* species and mold (n = 2). One patient had infection due to *Pneumocystis carinii*. The invasive infections were identified on either the first day of treatment or 53 days after starting POS prophylaxis. None of the patients receiving ITZ prophylaxis developed a proven fungal infection during treatment. Six patients were identified as having probable fungal infections. Of the 6 patients, 4 had infections due to *Aspergillus* species, 1 due to *A. fumigatus* and 1 due to *Pneumocystis carinii*. Probable infections were diagnosed using the *Aspergillus* antigen test in 15 subjects (FLZ, n = 9; POS, n = 2; ITZ, n = 4). Few subjects had only one serum sample that was positive. As discussed previously, the results of the *Aspergillus* antigen test should be interpreted in conjunction with clinical and radiological findings. The baseline *in vitro* susceptibility testing was performed for 6 isolates (4 *Aspergillus* isolates and 2 *Candida* isolates). The POS MICs for all 6 isolates were ≤ 0.125 $\mu\text{g/ml}$. “

EFFICACY CONCLUSIONS

The Sponsor has studied the efficacy of posaconazole in the prevention of invasive fungal infection in 2 different immunocompromised populations.

In patients post stem cell transplantation with GVHD:

- 1. Posaconazole 200 mg po TID was non-inferior to fluconazole in overall clinical outcome and in the prevention of IFI in the ITT analysis and per protocol analyses during the prespecified primary time period of 16 weeks post randomization.**
- 2. Since these patients have significant complications from their underlying disease which often requires discontinuation or interruptions of therapy unrelated to study efficacy or safety, similar analyses were also performed during the While on Treatment period (on therapy + 7 days). In the All Treated population and the Per Protocol populations posaconazole was again non-inferior to Fluconazole in Clinical Outcome.**
- 3. There were less proven/probable IFIs in the Posaconazole arm than the Fluconazole arm both for the Primary time period and the While on Treatment period.**
- 4. Most impressive difference in the incidence of IFI due to Aspergillus.**
- 5. Same results seen with proven IFI only.**
- 6. Same results seen if possible infections added.**
- 7. No significant difference in All Cause Mortality.**
- 8. Time to IFI lower for Posaconazole.**
- 9. Several sensitivity analyses did not change results even with the imbalance in Aspergillus Antigen positivity upon entry.**

In patients with acute hematologic malignancy at high risk for neutropenia:

- 1. A major study limitations is the open label design. The differential use of IV Amphotericin versus either IV FLU in FLU arm or IV ITRA in ITRA arm as the IV study drug if orally intolerant temporarily could have introduced important bias but such therapy was used in such a small number of patients in the posaconazole arm that its effect on outcome was unimportant.**
- 2. Posaconazole was superior in clinical outcome when compared to combined FLU/ITRA or when compared to FLU alone or ITRA alone.**
- 3. Lower incidence of IFI in the Posaconazole arm**
- 4. Marked difference in Aspergillus Proven/Probable IFI**
- 5. Almost all of the difference in IFI incidence between the groups composed of probable Aspergillus infection in the Fluconazole arm.**

- 6. Superiority for Posaconazole for Time to Death at 100 days but not at 30 days post randomization.
- 7. Time to IFI lower for posaconazole .

7 7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Two studies were presented for the evaluation of the safety and efficacy of posaconazole in the prevention of IFI in severely immunocompromised hosts. Please see below.

Table 56: Clinical Studies of Prophylaxis of IFI

Study Number	Type of Study	Population	Study Drug	Control
CI98-316	Randomized, DB	Acute leukemia or Myelodysplastic Syndrome Post HSCT +GVHD	Posaconazole 200mg po TID N=301	Fluconazole 400 mg po qD N=299
P01899	Randomized, OL	Hematologic Malignancy at High Risk for Neutropenia post Chemotherapy	Posaconazole 200mg po TID N=304	Fluconazole 400 mg po qD(N=240) or Itraconazole 200mg po BID (N=58)

The Sponsor had submitted [redacted] for posaconazole [redacted]. On June 12, 2005, Schering received an approvable letter [redacted] for the treatment of the multiple invasive fungal infections in patients 13 years of age or older: The mostly non-comparative safety data from over 1,800 patients was reviewed [redacted].

7.1.1 Deaths

The populations in these studies have a high mortality and frequently experience adverse events based on their underlying diseases (hematologic malignancies either post stem cell transplant or neutropenia inducing chemotherapy) and the primary treatment for those diseases. They are all

on multiple medications, many with very significant toxicities. As such, attributing cause of death to one medication is quite difficult. There were less overall deaths in both studies in the posacoanzole arm than the comparator arms though a significant reduction in overall mortality was only seen at 100 days in study P01899. Review of the deaths in both studies suggested 3 deaths that might be related to therapy with Posaconazole.

Table 57: Deaths in Pooled Prophylaxis Studies

	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58	
	Number (%) of Subjects					
Number of Deaths	125	(21)	142	(26)	9	(16)
Adverse Event *	59	(10)	64	(12)	3	(5)
Invasive Fungal Infection	9	(1)	24	(4)	4	(7)
Underlying Disease Progression	55	(9)	52	(10)	2	(3)
Other	2	(<1)	2	(<1)	0	0

- Adverse Event secondary to therapy for underlying disease, its complications, or drug induced.
- Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

Deaths possibly/probably related to study drug

POS 3
FLU/ITRA 0

The 3 deaths classified by the investigators as probably/possibly related to POS were reviewed by the Medical Officer.

There was one case of death in a 47 yo woman with NHL s/p PBSCT with Grade 3 GVHD who suffered herniation and leukoencephalitis secondary to cyclosporine toxicity (level 313 before POS and 428 after 4 days of POS therapy.) The cyclosporine toxicity was believed secondary to probably related POS therapy.

One of the deaths in study P01899 was a 67 yo male with new AML. The Investigator considered the death possibly related to study drug as hyperbilirubinemia was considered as a potentially contributing factor in the subject's death along with acute leukemia, encephalopathy and pneumonia (suspected fungal). A partial autopsy revealed a micronodular cirrhosis and hemophagocytic syndrome likely related to infectious causes and not related to study drug.. Although the bilirubin continued to increase after stopping study drug, and other potential etiologies such as AML and infectious process were probably contributory, the possible role of POS in this event could not be excluded based on temporal association .

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 Posaconazole (Noxafil) for the Prevention of IFI

The third death was a 19 yo with ALL s/p 13 month prior who was diagnosed with chronic extensive GVHD Day -11. Day 92 the patient developed TTP and HUS leading to multi-organ failure. On Day 101 POS was stopped. On Day 192 the patient died from continued multi-organ failure. This multi-organ failure was considered possibly related to POS.

MO Comment: In the prior NDA submission of posaconazole for the treatment of IFI there were 2 deaths from cyclosporine toxicity that was believed secondary to a drug interaction with Posaconazole. This serious drug interaction should be included in the warning section of the label and specific recommendations on dose reduction will also be included in labeling.

Table 58: Most Common Adverse Events Leading to Death by Body System/Organ Class: Frequency of at Least 1% in the POS or FLU Treatment Groups (All Randomized Subjects)

	Posaconazole n=605	Fluconazole n=539	Itraconazole n=58
Subjects Reporting any Adverse Event	121 (20)	139 (26)	9 (16)
Benign & Malignant Neoplasms (Including Cysts and Polyps)			
Acute Lymphocytic Leukemia	0	4 (1)	0
AML Aggravated	11 (2)	6 (1)	1 (2)
Leukemia	5 (1)	4 (1)	0
Leukemia, Acute Myelogenous	11 (2)	8 (1)	0
Neoplasm Malignant	1 (<1)	3 (1)	0
Body as a Whole - General Disorders			
Disease Progression	0	3 (1)	0
Hypoxia	5 (1)	4 (1)	0
Multiple Organ Failure	21 (3)	11 (2)	1 (2)
Cardiovascular Disorders, General			
Cardiac Failure	6 (1)	3 (1)	0
Cardio-Respiratory Arrest	5 (1)	9 (2)	0
Circulatory Failure	2 (<1)	4 (1)	0
Hypotension	9 (1)	6 (1)	0
Central and Peripheral Nervous System Disorders			
Cerebral Hemorrhage	6 (1)	4 (1)	0
Hemiparesis	0	3 (1)	0
Hemorrhage Intracranial	5 (1)	10 (2)	0
Loss of Consciousness	3 (<1)	3 (1)	0
Disorders of Blood and Lymphatic System			
Febrile Neutropenia	1 (<1)	3 (1)	0
Pancytopenia	4 (1)	0	0
Disorders of the Immune System			
Graft Versus Host Disease	7 (1)	4 (1)	0
Graft vs Host Disease Aggravated	16 (3)	12 (2)	0

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Gastro-Intestinal System Disorders					
Ascites	1	(<1)	3	(1)	0
GI Hemorrhage	6	(1)	5	(1)	1 (2)
Heart Rate and Rhythm Disorders					
Cardiac Arrest	10	(2)	7	(1)	1 (2)
Infection and Infestations					
Aspergillosis NOS	2	(<1)	8	(1)	1 (2)
Bacteremia	4	(1)	5	(1)	1 (2)
Cytomegalovirus Infection	2	(<1)	4	(1)	0
Infection Fungal	5	(1)	6	(1)	0
Pneumonia	10	(2)	11	(2)	1 (2)
Pneumonia Fungal (NOS)	1	(<1)	4	(1)	0
Sepsis	19	(3)	20	(4)	1 (2)
Shock, Septic	11	(2)	10	(2)	2 (3)
Toxoplasmosis	1	(<1)	3	(1)	0

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

MO COMMENT: There were more cases of multi-organ failure (MOF) in the pooled posaconazole patients in comparison to the pooled fluconazole/itraconazole patients. Of those leading to death there were 21 in the posacoanzole group versus 11 in comparators. This difference comes primarily from the C98-316 study as in study P01899 there were 6 cases in POS versus 4 in FLU.

Upon further review of these cases in study C98-316 of MOF by the MO there were 7 cases in the POS arm that occurred after the patient had received at least 1 day of dosing and within 7 days of discontinuing study drug. There were 3 in the same time period in the FLU patients. Of these 7 cases 4 were clearly unrelated to study drug and in 3 of these 4 cases were secondary to overwhelming sepsis. In 2 cases microangiopathy was associated with the multi-organ failure. The incidence of TTP and thrombocytopenia will be addressed in further under Serious Adverse Events of Interest below.

7.1.2 Other Serious Adverse Events

Table 59: Most Common (Greater Than to Equal to 5% in the POS or FLU Treatment Groups) Serious Adverse Events in the Pooled Prophylaxis Safety Analysis: C/I98-316, P01899 All Randomized Subjects (Number (%) of Subjects)

Adverse Event	Posaconazole	Fluconazole	Itraconazole
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Subjects Reporting any Adverse Event	381 (63)	364 (68)	32 (55)
Fever	77 (13)	74 (14)	9 (16)
Thrombocytopenia	70 (12)	52 (10)	9 (16)
Sepsis	1 (7)	45 (8)	5 (9)
Anemia	40 (7)	19 (4)	4 (7)
Diarrhea	36 (6)	25 (5)	0
Graft vs Host Disease Aggravated	36 (6)	29 (5)	0
Bacteremia	35 (6)	38 (7)	4 (7)
Hypotension	35 (6)	45 (8)	4 (7)
Dyspnea	33 (5)	30 (6)	3 (5)
Febrile Neutropenia	33 (5)	37 (7)	4 (7)
Cytomegalovirus Infection	32 (5)	31 (6)	0
Neutropenia	31 (5)	29 (5)	5 (9)
Respiratory Insufficiency	28 (5)	49 (9)	2 (3)

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

More than half of the subjects in the prophylaxis pool reported at least one SAE (63% of POS subjects and 68% of FLU subjects). The overall frequency of subjects reporting SAEs was similar between the POS and FLU treatment groups, although a slightly higher incidence was observed in the FLU group (68%) compared with the POS group (63%). The most common SAE in each treatment group was fever, reported for 13% of subjects in the POS group and 14% of subjects in the FLU group. Other commonly reported SAEs included thrombocytopenia (12% vs. 10%), sepsis (7% vs 8%), anemia (7% vs 4%), diarrhea (6% vs 5%), hypotension (6% vs 8%), GVHD (6% vs 5%), bacteremia (6% vs 7%), dyspnea (5% vs 6%), febrile neutropenia (5% vs 7%), cytomegalovirus infection (5% vs 6%), neutropenia (5% vs 5%), and respiratory insufficiency (5% vs 9%) in the POS and FLU groups, respectively.

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Table 60

	Posaconazole n=605	Fluconazole n=539	Itraconazole n=58
Subjects Reporting Any Adverse Event	59 (10)	33 (6)	2 (3)
Gastro-Intestinal System Disorders			
Nausea	4 (1)	0 0	0 0
Vomiting	4 (1)	1 (<1)	0 0
Liver And Biliary System Disorders			
Bilirubinemia	8 (1)	5 (1)	1 (2)
GGT Increased	5 (1)	3 (1)	0 0
Hepatic Enzymes Increased	9 (1)	2 (<1)	0 0
Hepatic Function Abnormal	0 0	3 (1)	0 0
Hepatocellular Damage	5 (1)	0 0	0 0

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

A total of 59 (10%) subjects in the POS group and 33 (6%) in the FLU group reported SAEs that were considered treatment-related by investigators. The most common ($\geq 1\%$) treatment-related SAEs in these two treatment groups were associated with liver and biliary system disorders and gastrointestinal system disorders. Since these patients have severe underlying illness and were receiving multiple therapeutic agents, many with significant toxicities themselves, it is difficult to ascribe or exclude attributability to study drug.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

As can be seen below most of the discontinuations were due to adverse events, either relating to gastrointestinal or hepatic AEs or to adverse events that were the complications of the underlying disease. In study C98-316 this was aggravation of GVHD, and in P01899 progression of hematologic malignancy. There were relatively few patients who did not wish to continue study. See disposition of patients in Results part of Efficacy section.

7.1.3.2 Adverse events associated with dropouts

Table 61: Most Common Adverse Events Leading to Study Drug Discontinuation by Descending Frequency of at Least 1% in the POS or FLU Treatment Groups (All Randomized Subjects)

Adverse Event	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58	
	202	(33)	208	(39)	26	(45)
Subjects Reporting Any Adverse Event	202	(33)	208	(39)	26	(45)
Nausea	15	(2)	12	(2)	0	
Vomiting	12	(2)	17	(3)	0	
Hepatic Enzymes Increased	11	(2)	5	(1)	0	
Febrile Neutropenia	9	(1)	11	(2)	3	(5)
Infection Fungal	9	(1)	19	(4)	1	(2)
Pneumonia	8	(1)	4	(1)	0	
QTc/QT Prolongation	8	(1)	4	(1)	2	(3)
Bilirubinemia	7	(1)	7	(1)	1	(2)
Fever	7	(1)	13	(2)	2	(3)
Diarrhea	6	(1)	4	(1)	4	(7)
GI Hemorrhage	5	(1)	1	(<1)	0	
Abdominal Pain	4	(1)	6	(1)	0	
Graft vs Host Disease Aggravated	4	(1)	3	(1)	0	
Hepatocellular Damage	4	(1)	0		0	
Leukemia, Acute Myelogenous	4	(1)	0		0	
Nausea Aggravated	4	(1)	1	(<1)	1	(2)
Pulmonary Infiltration	4	(1)	4	(1)	0	
Sepsis	4	(1)	7	(1)	0	
Shock, Septic	4	(1)	3	(1)	0	
Convulsions	3	(<1)	3	(1)	0	
Leukemia	3	(<1)	5	(1)	0	
Pneumonia Fungal (NOS)	3	(<1)	8	(1)	0	
Hemorrhage Intracranial	2	(<1)	4	(1)	0	
Hepatic Function Abnormal	2	(<1)	6	(1)	0	
Respiratory Insufficiency	2	(<1)	4	(1)	0	
Thrombocytopenia	2	(<1)	3	(1)	0	
Aspergillosis NOS	1	(<1)	10	(2)	2	(3)
Dyspnea	1	(<1)	6	(1)	0	
Fibrillation Atrial	1	(<1)	4	(1)	0	
Hypotension	1	(<1)	5	(1)	0	
Hypoxia	1	(<1)	3	(1)	0	
Acute Lymphocytic Leukemia	0		3	(1)	0	
Bronchopulmonary Aspergillosis	0		3	(1)	0	
Dehydration	0		3	(1)	0	
Fungal Test Positive	0		3	(1)	0	
Neutropenia	0		3	(1)	0	

a: Percentages of sex-specific adverse events are based on the number of males/females.

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

7.1.3.3 Other significant adverse events

Hepatic Adverse Events

Hepatic Adverse Events were selected for closer review because of the hepatotoxicity associated with azole antifungals and the previously identified findings of hepatocellular adenomas in mice.

Also in prior studies or compassionate use, cases of serious hepatic toxicity, including hepatic failure and fatalities were seen primarily in patients with serious underlying medical conditions during treatment of refractory or intolerant with posaconazole and occurred after 2 – 200 days of therapy. These Severe hepatic events were seen primarily in subjects receiving the 800 mg QD dose (400 BID) as opposed to the lower 400 mg QD dose. As the data obtained in the more seriously ill population receiving the higher dose was non-comparative, an association with posaconazole treatment could not be excluded. Posaconazole was also associated with mild to moderate elevations in ALT, AST, alkaline phosphatase, and total bilirubin, both during and after treatment with posaconazole. These hepatic reactions were noted to occur mostly in the patients with serious underlying medical conditions (eg, hematologic malignancy) and in those with pre-existing liver dysfunction but also occurred in normal volunteers. Elevations in liver function tests were mostly reversible on discontinuation of therapy and over several weeks,

In the prophylaxis pool, the number of subjects reporting AEs associated with hepatic dysfunction was similar in the POS (30%) and FLU (28%) treatment groups. Within this select category, bilirubinemia, (10% vs 9%), GGT increased (7% vs 7%), hepatic enzymes increased (6% vs 7%), jaundice (6% vs 5%), and SGPT increased (6% vs 6%) were among the most common AEs observed for subjects in the POS and FLU groups, respectively. However, in the hepatic adverse events that were considered by the investigator to be treatment related, there are more adverse events reported for posaconazole in the following categories: bilirubinemia, hepatocellular enzymes altered, and hepatocellular damage. Please refer to the 2 tables below.

The following recommendations will be included in labeling:

Monitoring of hepatic function: Liver function tests should be evaluated at the start of and during the course of Posaconazole therapy. Patients who develop abnormal liver function tests or who experience worsening of pre-existing liver function abnormalities including ALT, AST, Bilirubin, gGT and Alkaline Phosphatase should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of Posaconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to treatment. Posaconazole should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to posaconazole.

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Table 62: Pooled Prophylaxis All Randomized Subjects Treatment Emergent Hepatic Adverse Events

	Posaconazole n=605				Fluconazole n=539				Itraconazole n=58			
	All		Severe/LT		All		Severe/LT		All		Severe/LT	
Liver and Biliary System Disorders	184	(30)	83	(14)	152	(28)	75	(14)	18	(31)	8	(14)
Asterixis	1	(<1)	0		0		0		0		0	
Biliary Sludge	3	(<1)	0		2	(<1)	0		0		0	
Biliary Tract Disorder NOS	0		0		1	(<1)	0		0		0	
Bilirubinemia	59	(10)	24	(4)	51	(9)	27	(5)	11	(19)	6	(10)
Bilirubinemia Aggravated	4	(1)	3	(<1)	4	(1)	3	(1)	0		0	
Bilirubinuria	0		0		1	(<1)	0		0		0	
Cholecystitis	1	(<1)	0		2	(<1)	1	(<1)	2	(3)	1	(2)
Cholelithiasis	5	(1)	1	(<1)	5	(1)	0		2	(3)	0	
Cholestasis	4	(1)	1	(<1)	3	(1)	0		0		0	
Gall Bladder Disorder	1	(<1)	0		1	(<1)	0		0		0	
Gallbladder Cholesterolosis	1	(<1)	0		0		0		0		0	
GGT Increased	42	(7)	21	(3)	38	(7)	22	(4)	4	(7)	0	
Hepatic Disorder NOS	4	(1)	0		1	(<1)	0		0		0	
Hepatic Enzymes Increased	38	(6)	21	(3)	36	(7)	12	(2)	1	(2)	0	
Hepatic Failure	8	(1)	7	(1)	6	(1)	6	(1)	0		0	
Hepatic Function Abnormal	16	(3)	7	(1)	21	(4)	11	(2)	0		0	
Hepatic Necrosis	1	(<1)	1	(<1)	0		0		0		0	
Hepatitis	3	(<1)	1	(<1)	3	(1)	2	(<1)	0		0	
Hepatocellular Damage	9	(1)	8	(1)	3	(1)	0		0		0	
Hepatomegaly	10	(2)	0		5	(1)	0		1	(2)	0	
Hepatosplenomegaly	3	(<1)	0		3	(1)	0		0		0	
Hypertension Portal	1	(<1)	0		2	(<1)	0		0		0	
Jaundice	35	(6)	6	(1)	26	(5)	5	(1)	1	(2)	0	
Jaundice Cholestatic	1	(<1)	0		0		0		0		0	
Liver Abscess	0		0		1	(<1)	1	(<1)	0		0	
Liver Fatty	1	(<1)	0		1	(<1)	0		0		0	
Liver Nodule	1	(<1)	0		0		0		0		0	
Portal Vein Thrombosis 1			(<1)	0			0				0	

	Posaconazole n=605			Fluconazole n=539			Itraconazole n=58					
	All	Severe/LT	All	Severe/LT	All	Severe/LT	All	Severe/LT				
	SGOT Increased	19	(3)	2	(<1)	18	(3)	8	(1)	3	(5)	0
SGPT Increased	39	(6)	14	(2)	30	(6)	16	(3)	3	(5)	1	(2)

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

Table 63: Pooled Prophylaxis All Randomized Subjects Summary of Treatment Related Treatment Emergent Hepatic Adverse Events:

	Posaconazole n=605			Fluconazole n=539			Itraconazole n=58			
	All	Severe/LT	All	Severe/LT	All	Severe/LT	All	Severe/LT		
	Liver And Biliary System Disorders	55	(9)	37	(7)	22	(4)	3	(5)	
Asterixis	1	(<1)	0		0		0			
Biliary Sludge	1	(<1)	0		0		0			
Bilirubinemia	15	(2)	10	(2)	6	(1)	3	(5)	2	(3)
Bilirubinemia Aggravated	2	(<1)	2	(<1)	0		0			
Cholelithiasis	0		1	(<1)	0		0			
Cholestasis	0		1	(<1)	0		0			
GGT Increased	14	(2)	8	(1)	4	(1)	1	(2)		
Hepatic Enzymes Increased	15	(2)	10	(2)	3	(1)	0			
Hepatic Failure	1	(<1)	1	(<1)	1	(<1)	0			
Hepatic Function Abnormal	2	(<1)	1	(<1)	3	(1)	0			
Hepatitis	2	(<1)	1	(<1)	0		0			
Hepatocellular Damage	5	(1)	5	(1)	0		0			
Hepatosplenomegaly	1	(<1)	0		0		0			
Jaundice	5	(1)	2	(<1)	0		0			
SGOT Increased	14	(2)	7	(1)	3	(1)	1	(2)	0	
SGPT Increased	16	(3)	8	(1)	7	(1)	1	(2)	1	(2)

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Visual Disturbances

Reports of some types of visual disturbance have been associated with voriconazole use. Consequently, the following visual disturbances were selected for observation: diplopia, nystagmus, photophobia, photopsia, scotoma, hemianopsia, optic neuritis, uveitis, optic disc disorder NOS, vision abnormal, vision blurred, vision disorder, visual acuity reduced, blindness, optic atrophy, papilledema, and optic neuropathy.

Table 64: Pooled Prophylaxis Safety Analysis: C/I98-316, P01899 All Randomized Subjects Summary of Treatment Emergent Adverse Events: Visual Disturbances Number (%) of Subjects

	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Subjects Reporting any Adverse Event	48 (8)	2 (<1)	50 (9)	3 (1)	7 (12)	1(2)
Disorders of the Eye	48 (8)	2 (<1)	50 (9)	3 (1)	7 (12)	1(2)
Diplopia	1 (<1)	0	3 (1)	1 (<1)	0	0
Nystagmus	0	0	2 (<1)	0	1 (2)	1(2)
Photophobia	6 (1)	0	7 (1)	1 (<1)	0	0
Photopsia	2 (<1)	0	0	0	0	0
Scotoma	3 (<1)	0	0	0	0	0
Vision Abnormal	11 (2)	0	11 (2)	0	1 (2)	0
Vision Blurred	26 (4)	1 (<1)	30 (6)	0	3 (5)	0
Vision Disorder	1 (<1)	1 (<1)	1 (<1)	0	2 (3)	0
Visual Acuity Reduced	4 (1)	0	5 (1)	1 (<1)	0	0

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The most commonly reported visual disturbance TEAE was blurred vision which was reported in 4% of POS subjects and 6% of FLU subjects. Only one of these events was considered severe/LT in a subject treated with POS. Most events in this category were considered to be unrelated to treatment with study drug by investigators. Single occurrences of diplopia, photophobia, and scotoma were each found by the investigator to be possibly related to treatment with POS. Single occurrences of diplopia and vision abnormal were each found to be possibly related to FLU treatment by the investigators. Furthermore, a small number of the reported blurred vision AEs were considered by investigators to be possibly related to treatment in both the POS (n=3) and FLU (n=6) groups. A single report of treatment-related diplopia in subject treated with FLU was severe/LT in nature. Two subjects in the POS group discontinued study drug as a result of a TEAE classified as a visual disturbance.

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Calcium Homeostasis

Preclinical findings of bone thinning/fractures in rats and adrenal medullary tumors in rats (considered a result of altered calcium homeostasis and subsequent proliferation of adrenal medullary cells) warranted an examination of the following specific AEs related to calcium homeostasis (preferred terms): compression fracture, bone fracture, hypocalcemia, fracture pathological, fracture, osteopenia, osteoporosis, renal calculus, renal calculus aggravated.

Table 65: Pooled Prophylaxis Safety Analysis: C/I98-316, P01899 All Randomized Subjects Summary of Treatment: Calcium Homeostasis Number (%) of Subjects

	Posaconazole n=605				Fluconazole n=539				Itraconazole n=58		
	All		Severe/L T		All		Severe/LT		All		Severe/ LT
Subjects Reporting any Adverse Event	67	(11)	13	(2)	59	(11)	5	(1)	5	(9)	1
Injury and Poisoning	7	(1)	5	(1)	2	(<1)	1	(<1)	0		0
Compression Fracture	1	(<1)	1	(<1)	0		0		0		0
Fracture, Bone	6	(1)	4	(1)	2	(<1)	1	(<1)	0		0
Metabolic and Nutritional Disorders	56	(9)	8	(1)	55	(10)	3	(1)	5	(9)	1
Hypocalcemia	56	(9)	8	(1)	55	(10)	3	(1)	5	(9)	1
Musculo-Skeletal System Disorders	2	(<1)	0		3	(1)	1	(<1)	0		0
Fracture Pathological	0		0		1	(<1)	1	(<1)	0		0
Osteopenia	2	(<1)	0		0		0		0		0
Osteoporosis	0		0		2	(<1)	0		0		0
Renal & Urinary System Disorders	4	(1)	0		0		0		0		0
Renal Calculus	4	(1)	0		0		0		0		0

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Gastrointestinal Bleeding

The safety review of serious adverse events observed in the individual prophylaxis studies revealed some events of gastrointestinal (GI) bleeding. For this reason, further examination of the following GI adverse events were performed: diarrhea hemorrhagic, blood in stool,

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hemorrhage rectum, rectal bleeding, GI hemorrhage, hematemesis, melena, duodenitis hemorrhagic, gastric ulcer hemorrhagic, gastritis hemorrhagic, and hematochezia. The table below summarizes TEAEs associated with GI bleeding. Overall, the frequency of GI bleed-related TEAEs was similar among the treatment groups (POS: 13% and FLU: 11%). The most commonly observed AE in this category in the POS and FLU groups was GI hemorrhage, reported by 6% of subjects in the POS group and 4% of subjects in the FLU group. While most TEAEs in this category were mild or moderate in severity, a number of all GI bleeding events were severe/LT in both the POS (5%) and FLU (5%) treatment groups. Five subjects in the POS group and one subject in the FLU group discontinued study drug treatment due to GI hemorrhage. Six subjects in the POS group and 5 subjects in the FLU group died as a result of GI hemorrhage.

Table 66: Treatment Emergent Adverse Events in Gastrointestinal Bleeding

	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Subjects Reporting any Adverse Event	81 (13)	33 (5)	60 (11)	27 (5)	6 (10)	1 (2)
Gastro-Intestinal System Disorders	81 (13)	33 (5)	60 (11)	27 (5)	6 (10)	1 (2)
Blood in Stool	14 (2)	1 (<1)	7 (1)	2 (<1)	1 (2)	0
Diarrhea Hemorrhagic	5 (1)	4 (1)	11 (2)	6 (1)	0	0
Duodenitis Hemorrhagic	0	0	1 (<1)	1 (<1)	0	0
Gastric Ulcer Hemorrhagic	3 (<1)	3 (<1)	1 (<1)	1 (<1)	0	0
Gastritis Hemorrhagic	1 (<1)	1 (<1)	0	0	0	0
GI Hemorrhage	34 (6)	20 (3)	20 (4)	15 (3)	0	0
Hematochezia	2 (<1)	0	3 (1)	1 (<1)	1 (2)	0
Hematemesis	14 (2)	5 (1)	8 (1)	4 (1)	0	0
Hemorrhage Rectum	1 (<1)	1 (<1)	1 (<1)	0	0	0
Melena	15 (2)	4 (1)	12 (2)	2 (<1)	1 (2)	1 (2)
Rectal Bleeding	15 (2)	2 (<1)	6 (1)	1 (<1)	4 (7)	0

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Hematologic Adverse Events

In the preclinical phase disseminated intravascular coagulation was noted in dogs and macrophage hyperplasia in mice. For these reasons and the possible association of azoles with bone marrow suppression adverse events of the hematologic system were closely evaluated. The table below is a summary of TEAEs associated with hematologic and lymphatic function observed in the prophylaxis pool. The overall percentage of subjects in the prophylaxis pool reporting an AE in this category was similar between the POS and FLU treatment groups (57% vs 54% for the "Disorders of the Blood and Lymphatic System" category, and 47% vs 47% for the "Platelet, Bleeding, and Clotting Disorders" category, for the POS and FLU groups, respectively). The most common AEs observed in this special interest category were thrombocytopenia (29% vs 27%), anemia (25% vs 23%), , neutropenia (23% vs 23%), and febrile neutropenia (20% vs 16%), for the POS and FLU groups.

Although the incidence of thrombotic microangiopathy, defined as thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS), was balanced in the combined prophylaxis pool (TTP [1% versus 1%]; HUS [1% vs 1%] in the POS and FLU groups, respectively), it is important to note that all subjects were from the C/198-316 study. There were 6 cases of HUS in the POS arm and 2 in the FLU arm and 5 cases of TTP in the POS arm compared to 3 in the FLU arm. Since all subjects who experienced the AEs of TTP and HUS in the prophylaxis pool were enrolled in Study C/198-316 it is more likely that these AEs are related to the effects of immunosuppressants and the post-procedural sequelae of hematopoietic stem cell transplant.

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Table 67: Treatment Emergent Adverse Events-Hematologic Adverse Events

	Posaconazole n=605				Fluconazole n=539				Itraconazole n=58			
	All		Severe/LT		All		Severe/LT		All		Severe/LT	
Disorders of Blood and Lymphatic System	346	(57)	187	(31)	290	(54)	164	(30)	41	(71)	27	(47)
Anemia	149	(25)	62	(10)	124	(23)	44	(8)	16	(28)	11	(19)
Anemia Aggravated	13	(2)	6	(1)	12	(2)	5	(1)	2	(3)	1	(2)
Anemia Hemolytic	1	(<1)	0		2	(<1)	1	(<1)	0		0	
Aplasia Bone Marrow	1	(<1)	1	(<1)	0		0		0		0	
Blasts Increased	1	(<1)	1	(<1)	0		0		0		0	
Blood Basophil Increased	1	(<1)	1	(<1)	0		0		0		0	
Blood Disorder NOS	1	(<1)	0		1	(<1)	0		0		0	
Blood Neutrophil Count Decreased	5	(1)	2	(<1)	1	(<1)	1	(<1)	1	(2)	0	
Bone Marrow Disorder	1	(<1)	0		0		0		0		0	
Eosinophilia	2	(<1)	0		0		0		0		0	
Erythrocytes Abnormal NOS	1	(<1)	1	(<1)	1	(<1)	0		0		0	
Febrile Neutropenia	118	(20)	49	(8)	85	(16)	40	(7)	23	(40)	7	(12)
Granulocytopenia	1	(<1)	1	(<1)	3	(1)	1	(<1)	0		0	
Hematocrit Decreased	0		0		2	(<1)	1	(<1)	0		0	
Hemoglobin Decreased	7	(1)	2	(<1)	2	(<1)	1	(<1)	1	(2)	1	(2)
Hemolysis	5	(1)	1	(<1)	4	(1)	2	(<1)	0		0	
Hemolytic Uremic Syndrome	6	(1)	5	(1)	3	(1)	1	(<1)	0		0	
Iron Deficiency Anemia	0		0		1	(<1)	0		0		0	
Leukocytosis	4	(1)	1	(<1)	6	(1)	1	(<1)	0		0	
Leukopenia	35	(6)	18	(3)	41	(8)	20	(4)	5	(9)	5	(9)
Lymphadenitis NOS	1	(<1)	0		0		0		0		0	
Lymphadenopathy	10	(2)	1	(<1)	7	(1)	2	(<1)	1	(2)	1	(2)
Lymphadenopathy Cervical	4	(1)	0		4	(1)	1	(<1)	2	(3)	0	
Lymphangitis	1	(<1)	0		1	(<1)	0		0		0	
Lymphocytosis	0		0		1	(<1)	1	(<1)	0		0	
Lymphopenia	0		0		2	(<1)	2	(<1)	1	(2)	0	
Marrow Depression	4	(1)	2	(<1)	2	(<1)	1	(<1)	0		0	

	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Monocytosis	0	0	1 (<1)	0	0	0
Myelodysplastic Syndrome	1 (<1)	1 (<1)	1 (<1)	0	0	0
Neutropenia	141 (23)	93 (15)	122 (23)	78 (14)	23 (40)	19 (33)
Neutropenia Aggravated	4 (1)	2 (<1)	7 (1)	1 (<1)	0	0
Pancytopenia	18 (3)	9 (1)	21 (4)	13 (2)	1 (2)	1 (2)
Polycythemia	0	0	1 (<1)	0	0	0
Spleen Disorder	1 (<1)	0	0	0	1 (2)	0
Splenomegaly	11 (2)	0	7 (1)	1 (<1)	0	0
WBC Abnormal NOS	0	0	1 (<1)	0	0	0
White Blood Cell Count Decreased	3 (<1)	2 (<1)	2 (<1)	0	1 (2)	0
White Blood Cell Count Increased	1 (<1)	0	0	0	0	0
Platelet, Bleeding and Clotting Disorders	282 (47)	159 (26)	251 (47)	134 (25)	29 (50)	16 (28)
Bleeding Time Increased	2 (<1)	1 (<1)	1 (<1)	0	0	0
Bruise	8 (1)	0	3 (1)	0	1 (2)	0
Bruising	9 (1)	0	15 (3)	2 (<1)	0	0
Clot Retraction Retarded	0	0	1 (<1)	0	0	0
Coagulation Disorder	18 (3)	1 (<1)	19 (4)	6 (1)	1 (2)	1 (2)
Coagulation Factor Decreased	1 (<1)	0	1 (<1)	0	0	0
Coagulation Time Decreased	1 (<1)	0	0	0	0	0
Coagulation Time Increased	3 (<1)	0	4 (1)	1 (<1)	0	0
DIC	3 (<1)	2 (<1)	5 (1)	4 (1)	0	0
Fibrinogen Plasma Decreased	1 (<1)	0	1 (<1)	0	1 (2)	0
Fibrinolysis Increased	0	0	1 (<1)	0	0	0
Hematoma	22 (4)	1 (<1)	21 (4)	0	7 (12)	0
Hematoma, Subdural	2 (<1)	1 (<1)	3 (1)	3 (1)	0	0
Hemorrhage NOS	13 (2)	2 (<1)	12 (2)	3 (1)	0	0
Hemorrhage Retroperitoneal	2 (<1)	0	0	0	0	0
INR Increased	4 (1)	0	2 (<1)	0	0	0

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	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Petechiae	64 (11)	2 (<1)	54 (10)	2 (<1)	9 (16)	0
Platelet Count Decreased	9 (1)	3 (<1)	5 (1)	1 (<1)	1 (2)	0
Prothrombin Decreased	6 (1)	0	8 (1)	0	1 (2)	0
Prothrombin Increased	2 (<1)	0	3 (1)	0	0	0
Prothrombin Time Prolonged	3 (<1)	0	9 (2)	1 (<1)	3 (5)	0
Purpura	11 (2)	0	4 (1)	0	2 (3)	0
Rash Purpuric	0	0	1 (<1)	0	0	0
Retinal Hemorrhage	5 (1)	0	6 (1)	1 (<1)	1 (2)	0
Thrombocytopenia	0	0	2 (<1)	1 (<1)	1 (2)	0
Thrombocytopenia	175 (29)	133 (22)	146 (27)	107 (20)	20 (34)	15 (26)
Thrombocytopenia Aggravated	18 (3)	13 (2)	15 (3)	12 (2)	1 (2)	1 (2)
Thrombocytopenic Purpura Aggravated	1 (<1)	1 (<1)	0	0	0	0
Thrombotic Thrombocytopenic Purpura	8 (1)	7 (1)	4 (1)	3 (1)	0	0

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Pulmonary Embolism

Although the absolute number of reports is small, treatment-emergent pulmonary embolism was observed in 7 subjects in the POS group (6 of these in study CI98/316) and was not observed in any subjects treated with FLU in the prophylaxis pool. Two of the 6 cases were observed more than 6 days after discontinuation of POS therapy. Of the 4 that occurred within the While on Therapy time period, all 4 had a central venous catheter in place. One of these patients had a subclavian vein thrombosis believed secondary to the central catheter and whose PE was suspected but not confirmed by radiologic examination. The remaining 3 case narratives are provided below. Only the first of these cases was considered by the investigators to be at least possibly related to treatment with POS. In the Division review of these cases the second appears to be possibly related (actually it is hard to ascribe attribution in this case) but the third is unlikely to be related. The third is believed to be unrelated since the PE occurred in the midst of sepsis and bacteremia with *Pseudomonas* and *Enterobacter*. The PE resolved quickly with therapy and no further thrombotic complications occurred during 3 additional months of POS therapy.

"A 50-year-old Caucasian male subject with a history of chronic myelogenous leukemia, peripheral blood transplant, and acute Grade 2 graft-versus-host disease. His medical history was significant for allergic bronchitis. Concomitant medications at the time of POS (200 mg PO TID) initiation included acyclovir, penicillin, co-trimoxazole, cyclosporine and prednisone. At baseline, laboratory values were as follows: serum glutaminoxaloacetic transaminase (SGOT) 16 U/L; serum glutamic-pyruvic transaminase (SGPT) 25 U/L; lactic dehydrogenase (LDH) 182 U/L; gamma-glutamyl transferase (GGT) 30 U/L; and alkaline phosphatase 55 U/L; and total bilirubin 20 mmol/L. The subject had aching of the left calf and pain in the right leg (D42-D98). He also had moderate dyspnea (D86-D113). The subject was hospitalized due to deep vein thrombosis (DVT) and pulmonary embolus (D99). Ultrasound of the leg confirmed a distal vein thrombosis and ventilation/perfusion lung scintigraphy revealed a single suspected pulmonary embolus. He did not have a central venous catheter in place at the time of diagnosis of the DVT and pulmonary embolus. The subject was treated with low molecular weight heparin and warfarin. He also was noted to have increases in SGOT, SGPT, and alkaline phosphatase (192 U/L, 408 U/L, and 510 U/L, respectively) at this time (D99). The liver enzyme elevations were considered nonserious and possibly related to POS treatment (200 mg PO TID). The subject completed the study. Increased alkaline phosphatase was considered improved and increased SGOT and SGPT remained ongoing. At the last assessment, the pulmonary emboli and the deep vein thrombosis remained ongoing; and the laboratory values were as follows: SGOT 44 U/L and SGPT 89 U/L. The investigator felt leg pain, dyspnea, pulmonary emboli and deep vein thrombosis were possibly related to POS

treatment (200 mg PO TID). He also felt that cyclosporine and prednisone should be considered as cosuspect drugs."

A 41-year-old Caucasian male subject with a history of chronic myelogenous leukemia in remission (), peripheral blood stem cell transplant (unrelated, matched,), and acute Grade 3 graft-versus-host disease (GVHD;) initiated blinded study drug for fungal prophylaxis on 25 FEB 2000. His medical history was significant for diarrhea that was believed to be secondary to GVHD, abdominal discomfort, esophagitis, gastric ulcers, fatigue, weakness, and bronchitis. On the subject was hospitalized with increasing diarrhea. On a colonoscopy showed mucosal inflammatory changes in the rectum, distal sigmoid, and ileum of uncertain etiology; GVHD was considered a possibility. He was treated with octreotide and methylprednisolone; the diarrhea resolved on . On the subject was hospitalized with dyspnea and severe back pain. The subject had a positive blood culture for coagulase-negative *Staphylococcus* which was felt to be a contaminant. On a chest x-ray revealed patchy basilar opacities consistent with basilar pneumonia, and decreased lung volumes consistent with a pulmonary infarct. A CT scan on revealed a large acute pulmonary embolus. The subject was also found to have severe atelectasis. The subject was treated with enoxaparin. The back pain resolved on the dyspnea and pulmonary embolus resolved on and the atelectasis resolved on . The subject was hospitalized with severe pneumonia on . He was treated with ceftriaxone and azithromycin and the pneumonia resolved on . He was hospitalized with bacteremia (coagulase-negative *Staphylococcus*) on . His central venous catheter was replaced with a peripherally inserted central catheter (PICC) and he was treated with vancomycin. A blood culture from on was positive for coagulase-negative *Staphylococcus*. The bacteremia resolved on . The subject completed the study; his last dose of blinded study drug was taken on 14 JUN 2000. The investigator felt that a relationship between the diarrhea and study drug was possible but that a relationship between the other events and study drug was unlikely. After closure of the database, the study was unblinded and the subject was found to have received posaconazole 200 mg PO TID.

A 51 yo Caucasian female with a history of B-cell chronic lymphocytic leukemia (), bone marrow transplant (related, matched,), and Grade 4 graft-versus-host disease (GVHD;), initiated blinded study drug for fungal prophylaxis on 21 SEP 2000. Her medical history was significant for life-threatening neutropenia which was felt to be drug-related (ganciclovir and clotrimazole) and due to GVHD; and skin ulcer. Concomitant medications at the time of study drug initiation included prednisone and cyclosporine; co-trimoxazole; ketoconazole; cefepime; vancomycin; and ganciclovir. At baseline, labs values were white blood cell (WBC) count = $0.6 \times 10^9/L$, and absolute neutrophil count (ANC) = $0.47 \times 10^9/L$. On the subject had Grade 4 neutropenia (WBC = $0.5 \times 10^9/L$), and she started to develop sepsis. Blood

culture was positive for Pseudomonas and the subject was hospitalized. The subject received treatment with flucloxacillin and cefepime. Treatment with G-CSF was also initiated and treatment with co-trimoxazole was discontinued. On _____, skin ulcer culture was positive for Pseudomonas and Enterobacter. On _____ the subject had pulmonary embolism (perfusion lung scan revealed moderate to high probability of a pulmonary embolism), a requiring ventilation and treatment with heparin (IV). Pulmonary embolism was resolved on _____ sepsis and neutropenia were resolved on _____ and the subject was discharged. a Serum aspergillus antigen was >0.500 on 2 consecutive tests on _____ (galactomannan index [GMI] = 1.101) and _____ (GMI = 0.725). The subject completed the study; her last dose of blinded study drug was taken on 09 JAN 2001. The investigator considered the events to be unlikely related to study drug. After closure of the database, the study was unblinded and the subject was found to have received posaconazole 200 mg PO TID.

Thrombotic disease and pulmonary embolism are known complications of malignancy and its treatment. Contributing factors associated with pulmonary embolism include malignancy-associated hypercoagulable state, presence of an indwelling central venous catheter, side effects of antineoplastic treatment, inactivity and immobilization, rapid tumor lysis, thrombogenicity of intravenous hyperalimentation, and platelet microaggregates from transfusions. All of these make the assessment of the role of POS difficult to interpret. Other AEs indicative of thromboembolic disease, such as deep venous thrombosis (POS: 1%; FLU: 2%), embolism-blood clot (POS: 0%; FLU: <1%), arterial embolism (POS: 0%; FLU: <1%), thromboembolism (POS: 0%; FLU: <1%), thrombophlebitis (POS: 1%; FLU: 1%), and thrombosis superior vena cava (POS: 0%; FLU: <1%), in the POS and FLU groups, respectively, were observed slightly more often in subjects in the FLU group than in subjects in the POS group.

In addition, there is no evidence from the OPC safety data in immunosuppressed HIV subjects (who predominantly are not receiving aggressive treatment for underlying malignancy) as well from the healthy volunteer pooled data (Phase 1 studies), that indicates that POS affects coagulation or platelet function.

MO Comment: Since 6/7 cases of PE and all of the cases of TTP or HUS occurred in the post stem cell transplant population who received POS it is possible this may be a result of interaction of posaconazole with other therapies used in this population, especially the immunosuppressants cyclosporine, tacrolimus, and sirolimus. It was also reported above that there were more cases of TTP and HUS in this population and not in study P01899 suggesting that there may be a connection in thrombotic events. Further evaluation of

whether this an association of POS use and these adverse event should be considered in a Phase IV commitment. In addition a Precaution should be added to the label about this potential adverse event.

Hypersensitivity Adverse Events

POS is a new chemical entity and therefore the potential for allergic reaction is unknown. The tables below examine the comparative incidence of reactions that could be related to hypersensitivity either in the immune system category or dermatologic reactions. The overall distributions of AEs in this category were similar between the POS and FLU treatment groups: 22% vs 22% in the "Disorders of the Immune System" category and 53% vs 51% in the "Skin and Subcutaneous Tissue Disorders" category for the POS and FLU groups, respectively. The most commonly reported AEs in this category were rash (19% vs 18%), pruritus (11% vs 12%), erythema (8% vs 7%), and GVHD aggravated (7% vs 9%) in the POS and FLU groups, respectively. The incidence of severe/LT AEs related to hypersensitivity was low in the prophylaxis pool. Only the AEs of GVHD (POS: 2%; FLU: 2%), and GVHD aggravated (POS: 4%; FLU: 5%) were reported with a frequency of greater than 1%. The incidence of hypersensitivity SAEs was comparable between the POS and FLU groups. In the "Disorders of the Immune System" category, SAEs were reported for 9% of subjects in the POS group and 10% of subjects in the FLU group. Similarly, serious dermatologic AEs were reported for 3% of subjects in the POS group and 2% of subjects in the FLU group.

Table 68: Pooled Prophylaxis Safety Analysis: C/I98-316, P01899 All Randomized Subjects Summary of Treatment Emergent Adverse Events: All and Severe/Life Threatening Special Category: Hypersensitivity Adverse Events-Immune System: Number (%) of Subjects

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Clinical Review
 Maureen R. Tierney, MD, MSc.
 NDA 220027
 Posaconazole (Noxafil) for the Prevention of IFI

	Posaconazole n=605				Fluconazole n=539				Itraconazole n=58			
	All		Severe/LT		All		Severe/LT		All		Severe/LT	
Disorders of the Immune System	133	(22)	44	(7)	120	(22)	44	(8)	16	(28)	3	(5)
Allergic Reaction	21	(3)	2	(<1)	17	(3)	2	(<1)	5	(9)	2	(3)
Allergy	6	(1)	0		4	(1)	0		2	(3)	0	
Anaphylactic Reaction	1	(<1)	1	(<1)	2	(<1)	2	(<1)	0		0	
Blood Transfusion Reaction	34	(6)	0		17	(3)	1	(<1)	9	(16)	0	
C-Reactive Protein Increased	5	(1)	1	(<1)	3	(1)	1	(<1)	2	(3)	1	(2)
Gammaglobulins Decreased	7	(1)	1	(<1)	5	(1)	0		0		0	
Graft Versus Host Disease	29	(5)	15	(2)	30	(6)	10	(2)	0		0	
Graft vs Host Disease Aggravated	41	(7)	26	(4)	48	(9)	27	(5)	0		0	
Granulomatous Lesion	3	(<1)	0		0		0		0		0	
Immune System Disorder NOS	1	(<1)	0		1	(<1)	1	(<1)	0		0	
Inflammation, Non- Specific	5	(1)	0		3	(1)	0		1	(2)	0	
Sarcoidosis Aggravated	1	(<1)	0		0		0		0		0	
Transplant Rejection	6	(1)	4	(1)	3	(1)	3	(1)	0		0	

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

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Table 69: Pooled Prophylaxis Safety Analysis: C/I98-316, P01899 All Randomized Subjects Summary of Treatment Emergent Adverse Events: All and Severe/Life Threatening Special Category: Hypersensitivity Adverse Events-Dermatologic Events Number (%) of Subjects

	Posaconazole n=605				Fluconazole n=539				Itraconazole n=58			
	All		Severe/LT		All		Severe/LT		All		Severe/LT	
Bullous Eruption	9	1	2	<1	7	1	1	<1	0			
Dermatitis	12	2	0		6	1	0		0			
Eczema	5	1	0		1	<1	0		0			
Edema Mouth	1	(<1)	0		0		0		0		0	
Edema Periorbital	12	(2)	0		9	(2)	0		1	(2)	0	
Epidermal Necrolysis	2	(<1)	1	(<1)	1	(<1)	0		0		0	
Erythema	51	(8)	1	(<1)	36	(7)	0		4	(7)	0	
Erythema Multiforme	0		0		1	(<1)	0		0		0	
Erythema Nodosum	0		0		0		0		1	(2)	0	
Face Edema	13	(2)	0		11	(2)	0		1	(2)	0	
Mucosal Erosion NOS	2	(<1)	0		3	(1)	0		0		0	
Pain of Skin	6	(1)	1	(<1)	4	(1)	0		0		0	
Palmar Erythema	3	(<1)	1	(<1)	2	(<1)	0		0		0	
Palmar-Plantar Syndrome	4	(1)	0		1	(<1)	0		0		0	
Papule	0		0		1	(<1)	0		3	(5)	0	
Photosensitivity Reaction	1	(<1)	0		2	(<1)	0		0		0	
Pigmentation Abnormal	7	(1)	0		5	(1)	0		0		0	
Prurigo	1	(<1)	0		0		0		0		0	
Pruritus	69	(11)	3	(<1)	62	(12)	2	(<1)	11	(19)	0	
Pruritus Aggravated	0		0		1	(<1)	1	(<1)	1	(2)	0	
Pruritus Ani	2	(<1)	0		0		0		0		0	
Pruritus Genital	1	(<1)	0		1	(<1)	0		0		0	

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Pustule	2 (<1)	0	3 (1)	0	0	0
Rash	113 (19)	4 (1)	96 (18)	2 (<1)	25 (43)	3 (5)
Rash Aggravated	6 (1)	4 (1)	8 (1)	2 (<1)	0	0
Rash Erythematous	9 (1)	1 (<1)	11 (2)	0	1 (2)	0
Rash Follicular	2 (<1)	0	3 (1)	0	0	0
Rash Macular	3 (<1)	0	1 (<1)	0	2 (3)	0
Rash Maculopapular	19 (3)	3 (<1)	10 (2)	0	1 (2)	0
Rash Pruritic	9 (1)	0	13 (2)	2 (<1)	0	0
Rash Pustular	1 (<1)	0	0	0	0	0
Rash Vesicular	4 (1)	0	3 (1)	0	0	0
Skin Discoloration	3 (<1)	1 (<1)	5 (1)	0	0	0
Skin Disorder	11 (2)	1 (<1)	7 (1)	1 (<1)	1 (2)	0
Skin Exfoliation	8 (1)	0	14 (3)	0	1 (2)	0
Skin Lesion NOS	25 (4)	1 (<1)	23 (4)	2 (<1)	3 (5)	0
Skin Necrosis	1 (<1)	0	1 (<1)	0	0	0
Skin Nodule	5 (1)	0	2 (<1)	0	0	0
Skin Striae	0	0	3 (1)	0	0	0
Skin Ulceration	6 (1)	0	2 (<1)	0	0	0
Urticaria	13 (2)	0	12 (2)	0	2 (3)	0

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

Neurologic Adverse Events

The observation of neurophospholipidosis in dog, warranted a closer examination of specific AEs related to neurological function.. The overall distributions of TEAEs related to neurological and psychiatric disorders were similar between the POS and FLU treatment groups. The frequency of AEs related to autonomic nervous system disorders (1% vs 2%), as well as AEs related to psychiatric disorders (35% vs 35%) were similar between the POS and the FLU groups, respectively. The number of subjects reporting AEs related to central and peripheral nervous system disorders in the POS group (27%) was comparable to the number observed for the FLU group (31%). The most common neurologic AEs reported were insomnia (17% vs 17%), anxiety (9% vs 11%), depression (8% vs 8%), tremor (8% vs 8%), confusion (5% vs 6%), and paresthesia (4% vs 5%), among the POS and FLU treatment groups, respectively. It is important to note that the most common AEs in this category were also well balanced between the POS and FLU treatment groups.

Most AEs in this special category were mild or moderate in severity. A small proportion of the reported AEs in this category were deemed to be severe/LT: 8% vs 9% in the "Central and Peripheral Nervous System Disorders" category, and 2% vs 2% in the "Psychiatric Disorders" for the POS and FLU groups, respectively. All AEs reported in the "Autonomic Nervous System Disorders" category were mild or moderate in severity in the prophylaxis pool.

7.1.4 Other Search Strategies

Not Applicable

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Appropriate standard adverse event terms and categories were used by the Sponsor in their study reports and safety summary.

7.1.5.3 Incidence of common adverse events

The most commonly reported TEAEs were: fever (45% vs 47%), diarrhea (42% vs 39%), nausea (38% vs 37%), hypokalemia (30% vs 26%), and vomiting (29% vs 32%), in the POS and FLU groups, respectively.

The most common SAEs were fever (13% vs 14%), thrombocytopenia (12% vs 10%), sepsis (7% vs 8%), anemia (7% vs 4%), bacteremia (6% vs 7%), hypotension (6% vs 8%), and respiratory insufficiency (5% vs 9%) for the POS and FLU groups, respectively.

Analysis of pooled data from the two prophylaxis studies revealed that treatment-emergent AEs (TEAEs) were reported for 98% of subjects in the POS treatment group, 99% of subjects in the FLU treatment group, and 100% of subjects in the ITZ treatment group. Treatment-emergent AEs are defined as those which began during the Treatment Phase, or began prior to Baseline Date and worsened in severity during the Treatment Phase. Any AEs that began prior to Baseline Date or more than 30 days after Stop Date were not classified as treatment-emergent AEs.

The table below summarizes the incidence of the most common TEAEs observed in the POS or FLU treatment groups reported for at least 10% of subjects in either group (ordered by decreasing frequency for the POS group). Fever, the most common TEAE observed in the POS (45%) and FLU (47%) treatment groups, is commonly observed in both recipients of allogeneic progenitor cell transplantation with GVHD and severely neutropenic patients, and is associated with the underlying disease processes and their treatment. Gastrointestinal AEs were among the most commonly reported events in the POS (83%) and FLU (80%) treatment groups, with diarrhea (POS: 42%; FLU: 39%), nausea (POS: 38%; FLU: 37%), and vomiting, (POS: 29%; FLU: 32%) among the most common specific TEAEs reported. These AEs are frequently observed as a result of chemotherapy or GVHD due to the involvement of the GI tract. However, GI-associated AEs may be exacerbated by azole therapy. Other commonly observed TEAEs were balanced between the POS and FLU treatment groups: hypokalemia (POS: 30%; FLU: 26%), thrombocytopenia (POS: 29%; FLU: 27%), abdominal pain (POS: 27%; FLU: 27%), and anemia (POS: 25%; FLU: 23%).

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7.1.5.4 Common adverse event tables

Table 70: Types of Adverse Events by Study Drug in the Prophylaxis Pool (C98-316 and P018999)

	POS N=605	FLU N=539	ITZ N=58
	N(%)	N(%)	N(%)
Treatment Related Adverse Event	595(98)	531 (99)	58 (100)
Treatment Related Treatment Emergent AE	209 (35)	185 (35%)	30 (52)
Serious Adver Events	381 (63)	364 (68)	32 (55)
Treatment Reakted Serious Adverse Events	59 (10)	33(6)	2(3)
AEs Leading to Death	121(20)	139 (26)	9(16)
AEs Leading to Drug Discontinuation	202 (33)	208 (39)	26 (45)

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

Table 71: Common Adverse Event in Pooled Prophylaxis Studies

Adverse Event	Posaconazole n=605	Fluconazole n=539	Itraconazole n=58
Fever	274 (45)	254 (47)	32 (55)
Diarrhea	256 (42)	212 (39)	35 (60)
Nausea	232 (38)	198 (37)	30 (52)
Hypokalemia	181 (30)	142 (26)	30 (52)
Thrombocytopenia	175 (29)	146 (27)	20 (34)
Vomiting	174 (29)	173 (32)	24 (41)
Headache	171 (28)	141 (26)	23 (40)
Abdominal Pain	161 (27)	147 (27)	21 (36)
Anemia	149 (25)	124 (23)	16 (28)
Coughing	146 (24)	130 (24)	14 (24)
Neutropenia	141 (23)	122 (23)	23 (40)
Constipation	126 (21)	94 (17)	10 (17)
Rigors	122 (20)	87 (16)	17 (29)
Dyspnea	121 (20)	116 (22)	15 (26)
Febrile Neutropenia	118 (20)	85 (16)	23 (40)
Rash	113 (19)	96 (18)	25 (43)
Hypomagnesemia	110 (18)	84 (16)	11 (19)

Bacteremia	107	(18)	98	(18)	16	(28)
Hypertension	106	(18)	88	(16)	3	(5)
Mucositis NOS	105	(17)	68	(13)	15	(26)
Insomnia	103	(17)	92	(17)	11	(19)
Fatigue	101	(17)	98	(18)	5	(9)
Musculo-Skeletal Pain	95	(16)	82	(15)	9	(16)
Edema Legs	93	(15)	67	(12)	11	(19)
Anorexia	92	(15)	94	(17)	16	(28)
Herpes Simplex	88	(15)	61	(11)	10	(17)
Hypotension	83	(14)	79	(15)	10	(17)
Cytomegalovirus Infection	82	(14)	69	(13)	0	
Epistaxis	82	(14)	73	(14)	12	(21)
Tachycardia	72	(12)	75	(14)	3	(5)
Pharyngitis	71	(12)	60	(11)	12	(21)
Arthralgia	69	(11)	67	(12)	5	(9)
Pruritus	69	(11)	62	(12)	11	(19)
Hyperglycemia	68	(11)	76	(14)	2	(3)
Dizziness	64	(11)	56	(10)	5	(9)
Petechiae	64	(11)	54	(10)	9	(16)
Back Pain	63	(10)	66	(12)	4	(7)
Dyspepsia	61	(10)	50	(9)	6	(10)
Vaginal Hemorrhagea	24	(10)	20	(9)	3	(12)
Bilirubinemia	59	(10)	51	(9)	11	(19)
Hypocalcemia	56	(9)	55	(10)	5	(9)
Edema	54	(9)	68	(13)	8	(14)

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

Table 72: Pooled Prophylaxis Safety Analysis: C/I98-316, P01899 All Randomized Subjects Summary of Treatment Related Treatment Emergent Adverse Events: All (At Least 2% Incidence in the POS or FLU Treatment Groups) and Severe/Life Threatening Number (%) of Subjects

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58							
	All	Severe/LT	All	Severe/LT	All	Severe/LT						
Subjects Reporting any Adverse Event	209	(35)	81	(13)	186	(35)	53	(10)	30	(52)	6	(10)
Gastro-Intestinal System Disorders												
Abdominal Pain	13	(2)	1	(<1)	15	(3)	2	(<1)	1	(2)	0	
Constipation	4	(1)	0		12	(2)	0		0		0	
Diarrhea	28	(5)	4	(1)	24	(4)	1	(<1)	9	(16)	0	
Dyspepsia	8	(1)	1	(<1)	9	(2)	0		0		0	
Nausea	44	(7)	5	(1)	45	(8)	1	(<1)	8	(14)	0	

Vomiting	27 (4)	4 (1)	29 (5)	3 (1)	6 (10)	0
Heart Rate and Rhythm Disorders						
QTc/QT Prolongation	14 (2)	1 (<1)	6 (1)	0	4 (7)	0
Liver and Biliary System Disorders						
Bilirubinemia	15 (2)	10 (2)	10 (2)	6 (1)	3 (5)	2 (3)
GGT Increased	14 (2)	10 (2)	8 (1)	4 (1)	1 (2)	0
Hepatic Enzymes Increased	15 (2)	11 (2)	10 (2)	3 (1)	0	0
SGOT Increased	14 (2)	2 (<1)	7 (1)	3 (1)	1 (2)	0
SGPT Increased	16 (3)	7 (1)	8 (1)	7 (1)	1 (2)	1 (2)
Metabolic and Nutritional Disorders						
Hypokalemia	11 (2)	2 (<1)	6 (1)	1 (<1)	1 (2)	1 (2)
Skin and Subcutaneous Tissue Disorders						
Rash	12 (2)	1 (<1)	10 (2)	0	1 (2)	0

7.1.5.5 Identifying common and drug-related adverse events

Included in common adverse event section. Drug related adverse events discussed in all the adverse event sections. Extensive evaluation of patients at frequent intervals-detailed Case Report Form.

7.1.5.6 Additional analyses and explorations

Extensive evaluation of patients at frequent intervals-detailed Case Report Form

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7.1.6 Less Common Adverse Events

Included in common adverse event section.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program-



7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

7.1.7.3 Standard analyses and explorations of laboratory data

The most relevant laboratory indicators of potential study drug toxicity were: one measure of renal function (serum creatinine), two measures of serum potassium (hyperkalemia and hypokalemia), and four measures of liver function [alkaline phosphatase, ALT (also referred to as SGPT), AST (also referred to as SGOT), and total bilirubin]. In the pooled prophylaxis data, changes from baseline to endpoint in median values for these selected laboratory test parameters were generally small. The distribution of subjects by grades at baseline and at worst value during treatment for the selected laboratory test parameters is provided in table below. It provides a summary of the changes from Grade 0, 1, or 2 at Baseline to Grade 3 or 4 at any point during the treatment phase. Overall, the proportions of subjects who experienced such shifts in laboratory parameters were similar among the POS and FLU groups. Shifts in creatinine were reported for 2% of subjects in each group. Hypokalemia occurred slightly more frequently in subjects treated with POS (13%) and FLU (10%). The proportions of subjects with at least Grade 1 hyperkalemia were similar among the two groups. Shifts in measures of liver function tests were similar among the POS and FLU groups. It should be noted that nearly half of the subjects treated with POS (44%) or FLU (44%) had abnormal ALT values at baseline. Also, most subjects in the prophylaxis pool were taking concomitant medications and had underlying medical conditions that contributed to increases in liver function test results.

7.1.7.3.1 Analyses focused on measures of central tendency

The analyses of adverse events associated with laboratory values focused on the shift from baseline to Grade 3 or 4 levels. Please see below. Analyses focused on outliers or shifts from normal to abnormal:

Table 73: Pooled Prophylaxis Safety Analysis: C/198-316 and P01899, All Randomized Subjects; Shifts in CTC Grades of Selected Laboratory Test Results From Baseline to Worst Value During Treatment (All Randomized Subjects)

	Baseline CTC Grade	Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Creatinine							
Posaconazole (n = 605)	Grade 0	375 (62)	102 (17)	25 (4)	4 (1)	0	16 (3)
	Grade 1	9 (1)	26 (4)	19 (3)	4 (1)	1 (<1)	3 (<1)
	Grade 2	0	3 (<1)	6 (1)	1 (<1)	0	1 (<1)
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	3 (<1)	6 (1)	1 (<1)	0	0	0
Fluconazole (n = 539)	Grade 0	298 (55)	96 (18)	50 (9)	5 (1)	0	10 (2)
	Grade 1	6 (1)	26 (5)	24 (4)	2 (<1)	0	2 (<1)
	Grade 2	1 (<1)	1 (<1)	5 (1)	0	1 (<1)	1 (<1)
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	6 (1)	2 (<1)	1 (<1)	0	0	2 (<1)
Itraconazole (n = 58)	Grade 0	51 (88)	3 (5)	2 (3)	1 (2)	0	0
	Grade 1	0	0	0	0	0	0
	Grade 2	0	1 (2)	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Hyperkalemia							
Posaconazole (n = 605)	Grade 0	473 (78)	49 (8)	13 (2)	4 (1)	1 (<1)	20 (3)
	Grade 1	10 (2)	5 (1)	0	1 (<1)	0	0
	Grade 2	3 (<1)	0	0	0	0	0
	Grade 3	1 (<1)	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	15 (2)	0	1 (<1)	1 (<1)	0	8 (1)
Fluconazole (n = 539)	Grade 0	404 (75)	60 (11)	21 (4)	6 (1)	1 (<1)	14 (3)
	Grade 1	7 (1)	3 (1)	0	0	0	1 (<1)
	Grade 2	2 (<1)	0	1 (<1)	1 (<1)	0	0
	Grade 3	0	1 (<1)	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	12 (2)	1 (<1)	1 (<1)	0	0	3 (1)
Itraconazole (n = 58)	Grade 0	54 (93)	2 (3)	0	0	0	0
	Grade 1	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0

	Baseline CTC Grade	Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Hypokalemia							
Posaconazole (n = 605)	Grade 0	286 (47)	150 (25)	0	57 (9)	6 (1)	18 (3)
	Grade 1	16 (3) 0	31 (5) 0	0 0	9 (1) 0	1 (<1) 0	2 (<1) 0
	Grade 2						
	Grade 3	0 0	1 (<1) 0	0 0	3 (<1) 0	0 0	0 0
	Grade 4						
Missing	7 (1)	6 (1)	0	2 (<1)	2 (<1)	8 (1)	
Fluconazole (n = 539)	Grade 0	277 (51)	124 (23)	0 0	41 (8) 7	2 (<1) 2	14 (3) 1
	Grade 1	23 (4)	24 (4)		(1)	(<1)	(<1)
	Grade 2	0	0	0	0	0	0
	Grade 3	4 (1) 0	1 (<1) 1	0 0 0	1 (<1) 0	0 0 0	0 0 3 (1)
	Grade 4	10 (2)	(<1) 3		1 (<1)		
Missing		(1)					
Itraconazole (n = 58)	Grade 0	13 (22)	24 (41)	0	11 (19)	2 (3)	0
	Grade 1	3 (5) 0	2 (3) 0	0 0	0 0	1 (2) 0	0 0
	Grade 2						
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
Missing	1 (2)	0	0	0	1 (2)	0	
Alkaline Phosphatase							
Posaconazole (n = 605)	Grade 0	293 (48)	100 (17)	14 (2)	6 (1) 2	0 0 0 0	25 (4) 4
	Grade 1	23 (4) 0	60 (10)	18 (3)	(<1) 5		(1) 1 (<1)
	Grade 2	0	9 (1) 0	12 (2) 5	(1) 5 (1)		0
	Grade 3			(1)			
	Grade 4	0	0	0	0	0	0
Missing	11 (2)	9 (1)	0	2 (<1)	0	1 (<1)	
Fluconazole (n = 539)	Grade 0	260 (48)	82 (15)	15 (3)	3 (1)	0	19 (4)
	Grade 1	24 (4) 0	62 (12)	16 (3)	4 (1) 2	0 0 0 0	6 (1) 3
	Grade 2	0 0	9 (2) 0 0	13 (2) 0	(<1) 1		(1) 1 (<1)
	Grade 3			0	(<1) 0		0
	Grade 4						
Missing	9 (2)	6 (1)	1 (<1)	0	0	3 (1)	
Itraconazole (n = 58)	Grade 0	33 (57)	18 (31)	1 (2) 0 0	1 (2) 0 0	0 0 0	1 (2) 0 0
	Grade 1	1 (2) 0	3 (5) 0				
	Grade 2						
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
Missing	0	0	0	0	0	0	

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

	Baseline CTC Grade	Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Alanine Aminotransferase (ALT)							
Posaconazole (n = 605)	Grade 0	165 (27)	108 (18)	26 (4)	14 (2)	2 (<1)	12 (2)
	Grade 1	23 (4) 3	60 (10)	31 (5)	24 (4)	4 (1) 0 2	6 (1) 3
	Grade 2	(<1) 0 0	22 (4) 7	19 (3) 9	21 (3)	(<1) 1	(<1) 1
	Grade 3		(1) 0	(1) 1	18 (3) 0	(<1)	(<1) 0
	Grade 4			(<1)			
	Missing	6 (1)	5 (1)	6 (1)	1 (<1)	0	5 (1)
Fluconazole (n = 539)	Grade 0	139 (26)	94 (17)	20 (4)	11 (2)	3 (1) 1	11 (2) 7
	Grade 1	27 (5)	53 (10)	25 (5)	19 (4)	(<1)	(1)
	Grade 2	2 (<1) 2	25 (5) 3	23 (4)	20 (4)	0 1 (<1)	4 (1) 1
	Grade 3	(<1) 0 3	(1) 0 5	14 (3) 1	19 (4) 0	0 2 (<1)	(<1) 0 2
	Grade 4	(1)	(1)	(<1) 0	2 (<1)		(<1)
	Missing						
Itraconazole (n = 58)	Grade 0	32 (55)	10 (17)	3 (5)	1 (2)	0	0
	Grade 1	4 (7) 0 0	5 (9) 0 0	0 1 (2) 0	0 0 0	0 0 0	0 0 0
	Grade 2						
	Grade 3						
	Grade 4	0	0	0	0	0	0
	Missing	0	2 (3)	0	0	0	0
Aspartate Aminotransferase (AST)							
Posaconazole (n = 605)	Grade 0	261 (43)	103 (17)	24 (4)	12 (2) 3	0 2 (<1)	16 (3) 4
	Grade 1	32 (5) 2	52 (9)	28 (5)	(<1) 3	1 (<1) 0	(1) 4 (1)
	Grade 2	(<1) 2	10 (2) 4	10 (2) 1	(<1) 2		0
	Grade 3	(<1)	(1)	(<1)	(<1)		
	Grade 4	0	0	0	0	0	0
	Missing	5 (1)	6 (1)	2 (<1)	2 (<1)	0	14 (2)
Fluconazole (n = 539)	Grade 0	208 (39)	97 (18)	23 (4)	2 (<1)	2 (<1)	18 (3)
	Grade 1	32 (6) 6	59 (11)	20 (4)	10 (2) 2	1 (<1) 0	6 (1) 0 1
	Grade 2	(1) 0 0	13 (2) 1	12 (2) 2	(<1) 0 0	0 0	(<1) 0
	Grade 3		(<1) 0	(<1) 0			
	Grade 4						
	Missing	4 (1)	3 (1)	3 (1)	2 (<1)	0	12 (2)
Itraconazole (n = 58)	Grade 0	38 (66)	12 (21)	0 1 (2) 0	1 (2) 0 0	1 (2) 0 0	0 0 0
	Grade 1	1 (2) 1	2 (3) 1				
	Grade 2	(2)	(2)				
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

	Baseline CTC Grade	Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Total Bilirubin							
Posaconazole (n = 605)	Grade 0	279 (46)	79 (13)	46 (8)	13 (2)	4 (1)	16 (3)
	Grade 1	24 (4)	18 (3)	19 (3)	11 (2)	2 (<1)	3 (<1)
	Grade 2	4 (1)	9 (1)	22 (4)	11 (2)	3 (<1)	2 (<1)
	Grade 3	0	0	4 (1)	8 (1)	2 (<1)	0
	Grade 4	0	0	0	2 (<1)	1 (<1)	2 (<1)
	Missing	6 (1)	3 (<1)	6 (1)	2 (<1)	2 (<1)	2 (<1)
Fluconazole (n = 539)	Grade 0	283 (53)	50 (9)	26 (5)	18 (3)	2 (<1)	15 (3)
	Grade 1	18 (3)	24 (4)	17 (3)	11 (2)	1 (<1)	4 (1)
	Grade 2	9 (2)	15 (3)	9 (2)	4 (1)	3 (1)	2 (<1)
	Grade 3	0	0	2 (<1)	8 (1)	3 (1)	1 (<1)
	Grade 4	0	0	0	0	2 (<1)	1 (<1)
	Missing	4 (1)	3 (1)	0	2 (<1)	0	2 (<1)
Itraconazole (n = 58)	Grade 0	20 (34)	13 (22)	6 (10)	2 (3)	1 (2)	1 (2)
	Grade 1	3 (5)	4 (7)	2 (3)	2 (3)	0	0
	Grade 2	1 (2)	0	1 (2)	2 (3)	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

Abnormalities in hematologic lab values are included above in a discussion of hematologic adverse events.

7.1.7.3.2 Marked outliers and dropouts for laboratory abnormalities

This information is included in the section on drug discontinuation for an adverse event above. The 3 most common lab value abnormalities of clinical importance associated with drug discontinuation were LFT elevations, thrombocytopenia, and hypokalemia.

7.1.7.4 Additional analyses and explorations-see above

7.1.7.5 Special assessments

See Other Significant Adverse Events 7.1.3.3

See under other significant adverse events

7.1.8 Vital Signs

Overview of vital signs testing in the development program

Overview of vital signs testing in the development program

In two preclinical cardiovascular safety pharmacology studies, a 1-month oral gavage study in male rats (90 mg/kg) and a 7-day IV study in male monkeys (40 mg/kg), an increase in systolic (10 to 23 mmHg) blood pressure was observed.

The analysis of vital was challenging because of the complicated clinical course of subjects in the rIFI and OPC Pools, therefore the data from the five studies in healthy volunteers in which posaconazole was administered at the proposed clinical dose (800 mg BID) for at least 7-8 days

was analyzed to assess the potential effects of posaconazole on blood pressure () although these studies were not designed to specifically evaluate blood pressure changes, and therefore the timing of the vital sign measurements was not the same across studies.

The applicant's table below summarizes the mean, minimum, and maximum blood pressure measurements at screening and postdose (5 – 8 days). Overall, no clinically significant increase in mean systolic or diastolic blood pressure was observed following administration of POS relative to the screening values. The only mean increase in systolic blood pressure was observed in Study _____, in which a mean increase of 2.3 mmHg was observed. A maximum increase in systolic blood pressure (40 mmHg) was observed in a 72-year-old woman from the age/sex study _____ Subject 405). At steady-state (8 days after dosing) this subject's blood pressure was 164/90 mmHg. The measurement was not repeated to verify the value; however, on the previous 3 days, her blood pressure was lower and ranged from 112/74 to 138/90 mmHg.

The most common AEs in the rIFI and OPC populations were from the cardiovascular system and included both hyper and hypotension. For further details see MOR of cardiac safety.

In general, posaconazole did not appear to cause significant increases or decreases of the systolic or diastolic blood pressure of healthy volunteers or patients at the proposed 800 mg QD dose.

Table 74: Summary of Blood Pressure Changes in the 5 Healthy Volunteer Studies in which Posaconazole Oral Suspension was Administered at 400 mg BID With Food

Study	Mean (SD) Systolic Blood Pressure - mm Hg				
	Screening	Postdose	Difference	Min	Max
Placebo (n=17)	123 (14.5)	117 (20)	-6 (15)	-34	28
(n=12)	113 (5.7)	116 (7.3)	2.3 (7.3)	-8	16
(n=53)	122 (15.8)	120 (16.6)	-2.2 (16.7)	-40	40
(n=56)	130 (8.0)	130 (8.7)	0 (12)	-25	25
(n=23)	112 (9.5)	107 (8.1)	-5 (10)	-22	14
(n=35)	115 (11.5)	107 (8.9)	-8 (9.7)	-30	10

Study	Mean (SD) Diastolic Blood Pressure - mm Hg				
	Screening	Postdose	Difference	Min	Max
Placebo (n=17)	78 (10.3)	73 (8.3)	-5 (9.8)	-28	10
(n=12)	77 (5.9)	77 (7.7)	0 (10.2)	-14	16
(n=53)	79 (10.3)	73 (10.8)	-6 (11.3)	-32	22
(n=56)	78 (6.0)	75 (7.1)	-3 (7.8)	-15	18
(n=23)	74 (6.7)	71 (6.1)	-3 (8.1)	-24	12
(n=35)	73 (9.9)	70 (7.8)	-3 (9.6)	-22	20

From MO Review of Safety

7.1.8.1 Selection of studies and analyses for overall drug-control comparisons

7.1.8.2 Standard analyses and explorations of vital signs data

7.1.8.2.1 Analyses focused on measures of central tendencies

No clinically meaningful abnormalities attributable to POS or FLU were noted on physical examination or vital sign measurements in either prophylaxis study.

7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.2.3 Marked outliers and dropouts for vital sign abnormalities

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Preclinical Evaluation of Cardiac safety:

Non-clinical *in vitro* and *in vivo* data were gathered to examine the potential for posaconazole to cause cardiac arrhythmia.

In vitro effects of posaconazole on ventricular repolarization were evaluated by measuring both the action potential and the recombinant hERG channel current. In Purkinje fibers isolated from dog heart exposure to posaconazole at measured concentrations of 25 ng/mL (36 nM), 69 ng/mL (98 nM) and 365 ng/mL (521 nM) induced a small (<10%) but statistically significant increase in action potential duration at 60% (APD60) and/or 90% (APD90) repolarization. There were no posaconazole-related effects on other action potential parameters including resting membrane potential, maximum rate of depolarization and upstroke amplitude.

Mouse L-929 cells stably transfected with the human α -subunit (hERG) of the cardiac delayed rectifier, IKr, were also used to evaluate the potential for ventricular repolarization effects of posaconazole. A measured concentration of 770 ng/mL (1.1 microM) posaconazole decreased hERG current by 7% relative to vehicle control. Posaconazole is 98.5% bound to plasma proteins. Accounting for this protein binding, the drug concentration in the hERG assay was 18-times the free posaconazole Cmax value in healthy volunteers.

At an oral (gavage) dose of 90 mg/kg in rats, posaconazole was associated with a minimal increase in systolic (13 to 23 mm Hg) and mean arterial (10 to 19 mm Hg) blood pressures after four weeks of dosing; there were no changes in heart rate. After four weeks of dosing, rats given posaconazole had a decreased intraventricular systolic diameter and increased fractional shortening, which may be indicative of increased cardiac contractility. However, there was no concomitant increase in stroke volume. No other echocardiographic indices of cardiac function were altered by posaconazole. Heart weights were significantly increased at the end of dosing. The specific mechanism whereby posaconazole caused an increase in blood pressure in the rat was not determined in this study. The applicant postulated that the blood pressure change was most likely a response to increased vascular resistance (increased afterload). However, a direct positive inotropic effect on cardiac contractility cannot be ruled out with certainty from the available data. There was no indication of a posaconazole induced reduction in cardiac contractility or of cardiac decompensation in this study in rats.

Cardiovascular parameters in monkeys were assessed in two safety pharmacology studies with the lipid-containing intravenous formulation of posaconazole. No posaconazole related effects on heart rate, arterial blood pressure, ECG intervals (RR, PR, QRS, QT, QTc), or ECG morphology and rhythm were observed following seven days of dosing at doses up to 40 mg/kg. At a dose of

40 mg/kg, increased arterial pressure (9 to 14 mm Hg) was seen during the one-hour infusion period on the first day of dosing. This change was not seen after the end of the infusion period on Day 1, but did occur at the 3- to 8-hour postdose measurements (i.e., around the period of postinjection nC_{max}) on subsequent days of data collection, Days 4 and 7. The range of increases in systolic and arterial pressure was 11 to 29 mm Hg. These effects persisted for 120 hours after the seventh day of IV drug administration. This persistence correlated with sustained presence of plasma drug concentrations because of the long half-life of posaconazole. The increases in systolic and arterial pressures occurred at mean plasma concentrations of 7.85 to 18 microg/mL. The lowest mean AUC (0-24 hr) was observed on Day 1 and was 141 microg.hr/mL, which is 2.4-fold human AUC exposure of 59 microg.hr/mL.

In a one-month oral toxicity study in dogs, electrocardiographic changes consisting of increased QT intervals, reversal of T waves in leads rV2 and V10, STj point depression in lead V2, deep negative T waves in lead V2, and increased U wave amplitude in precordial leads, occurred in dogs in the 45 and 90 mg/kg groups. There were no abnormal arrhythmias or conduction disturbances. These doses caused severe toxicity, including mortality and the coagulopathy syndrome produced in dogs by posaconazole. Of greater relevance to the ECG changes, moderate decreases in serum potassium occurred in dogs in the 45 and 90 mg/kg groups. The range of serum potassium in the affected dogs was 2.9-3.9 mEq/L. The electrocardiographic changes that occurred in this study are all consistent with the effects of hypokalemia, which reduces the intracellular versus extracellular electro-potential gradient in myocytes and thereby slows cardiac repolarization.

Histopathologic changes occurred in the heart in dogs at the 45 and 90 mg/kg dose levels in the one month dog study, including myocarditis, hemorrhage and hemorrhagic infarcts, vascular fibrinoid necrosis, vasculitis, and endocarditis. The nature of the histopathologic changes indicates that they were secondary to vascular injury related to the coagulopathy syndrome and not a direct toxic effect of posaconazole on myocardium. These histopathologic changes may have contributed to the occurrence of electrocardiographic abnormalities. At the end of an eightweek recovery period there were no posaconazole-related changes in electrocardiograms, serum potassium, heart weight and heart histopathology in the 45 mg/kg dosed dogs.

No electrocardiographic abnormalities occurred in six- or twelve-month oral toxicity studies in dogs. There were no posaconazole-related histopathologic findings in the heart in either of these studies. The high dose in both studies was 30 mg/kg. Therefore, the no-effect-level for electrocardiographic changes in the heart in dogs was 30 mg/kg, which produced a mean AUC (0-24 hr) plasma concentration of 192 microg.hr/mL, 3.25 times the plasma concentration in healthy volunteers given 400 mg BID and fed a high fat meal (AUC [0-24 hr] = 59 μ g.h/mL). In a one-month oral toxicity study in monkeys, there were no electrocardiographic changes at doses up to 180 mg/kg posaconazole. The no-effect dose of 180 mg/kg in monkeys produced AUC (0-24 hr) plasma concentrations of 149 and 111 microg.hr/mL in males and females, respectively, which are 2.52 and 1.88 times the highest anticipated plasma concentration in humans.

To conclude it appeared as if the following were noted *in vitro* and *in vivo*:

Positive HERG and Purkinje fiber assays indicative of a delay in repolarization.

Increased QT interval in one month dog study (attributed to hypokalemia)

No increased QT interval in a 7 day monkey study at 4 fold the human dose

Increases in systolic and diastolic BP in rats and monkeys.

Increased heart weights in mice and dogs.

Focal myocarditis in rats and mice.

Cardiac toxicity in humans:

Electrocardiogram evaluations:

Multiple, time-matched ECGs were recorded from 189 healthy volunteers in five clinical pharmacology studies (Study 1, 2, 3, 4, and 5) designed to maximize the exposure to posaconazole, by taking into consideration its pharmacokinetic characteristics such as its slow absorption and the dose proportional increases in exposure up to 800 mg/day as well as the fact that the AUC is 4 times higher when administered with a high-fat meal (~50 gm) relative to the fasted state (Study 1). In these studies, POS was administered as oral suspension at a dose of 400 mg BID with a high-fat meal. Median Tmax is approximately 5 hours and time matched ECGs were recorded in all studies at predose, 2, 4, 5, 6 and 12 hours after the morning dose on Day -1 and following 7 to 8 days of multiple-dose administration of posaconazole or placebo (additional ECGs were collected in some studies, eg, Study 1). One of the five studies (Study 1) had a placebo group (n=16) included for comparative purposes. All time matched ECGs were centrally read by a blinded, external, third party, and evaluated individually by study. In the analysis of each study, the absolute QT interval, QTc interval (Fridericia and Bazett), PR, RR, QRS, and ventricular rate, including changes from baseline, were listed and summarized using descriptive statistics. The primary pharmacodynamic endpoint for each analysis was the QTc interval change from baseline. Both the Bazett (QTc [B]) and Fridericia (QTc [F]) correction methods were used in each analysis; however, only the QT correction using the Fridericia calculation was presented in this summary. The FDA BioPharm reviewers agreed with this method of reporting. The methods used to evaluate the potential for posaconazole to prolong the QTc interval included an analysis of central tendency and a categorical analysis. As part of this analysis of central tendency, a mean time-matched QTc interval change over a 12-hour interval was calculated.

In the placebo-controlled Study 1, 64 healthy volunteers received posaconazole or placebo in a 3:1 ratio (48 posaconazole: 16 placebo) for a total of 8 days. The summary statistics (mean, median, minimum, and maximum) of the mean QTc (F) interval change per time point over a 24-hour postdose period showed no clinically significant changes. There were no positive increases in the mean QTc (F) interval changes from baseline when evaluated by time point. Overall, the change in the time-averaged QTc (F) interval from 2 to 24 hours postdose was -6.59 msec (95% confidence interval [CI], -10.1 to -3.05 msec) in subjects administered posaconazole and -3.14 msec (95% CI, -7.79 to 1.52 msec) in placebo subjects. All subjects administered posaconazole, regardless of age or sex, had mean time-matched QTc(F) interval changes less than or equal to 30 msec. Overall, the largest QTc(F) time-matched interval change (increase) from baseline was 83 msec in the placebo group (in an elderly female subject) and 57 msec in the posaconazole group (in a young male subject). The largest QTc (F) interval change (decrease) in any individual subject was -120 msec after posaconazole dosing (in an elderly female subject) and -45 msec in the placebo group after dosing (in an elderly male subject). The majority of subjects

administered posaconazole (29 of 48, 60%) had maximum QTc(F) interval changes between 0 to <30 msec, four subjects (8%) had QTc(F) interval changes between 30 to <60 msec, and no subject had a maximum QTc(F) interval change \geq 60 msec. Eleven placebo subjects (69%) had maximum QTc(F) changes of between 0 and <30 msec and 1 subject (6%) had a change between 30 to <60 msec. One subject (6%) in the placebo group had a maximum QTc (F) interval change \geq 60 msec.

In addition to the placebo-controlled study [redacted], there were four additional studies [redacted] collecting multiple time-matched ECGs. The ECG data from all five clinical pharmacology studies were pooled for a total database of 189 healthy volunteers (posaconazole treated=173, placebo treated=16). There were a number of female subjects (38%) and elderly subjects (14%) administered posaconazole in these studies. The summary statistics (mean, median, minimum, and maximum) of the mean QTc interval change over the 12-hour postdose period in each study were consistent across studies with no clinically significant changes after posaconazole administration. Overall, the changes in QTc interval showed a mean and median change in QTc (F) interval of approximately -5 msec. The maximum mean time-matched QTc (F) interval change was higher in the 16 subjects administered placebo compared to all subjects administered posaconazole (change of 33 msec vs. 25 msec, respectively). The results of the pooled analysis suggest that posaconazole does not prolong the QTc interval in healthy volunteers and the changes are within normal QTc interval variability. For the categorical analysis of the pooled data, the mean baseline values were divided into categories of normal and borderline and each individual subject's maximum post-treatment QTc (F) interval change was grouped into categories. All but two subjects had a mean baseline QTc (F) interval within the normal range; these two male subjects' mean baseline values were slightly above normal (437 and 434 msec).

In a comparison of the maximum change of QTc (F) interval from mean baseline, the majority of subjects had a maximum change in their QTc (F) interval between 0 and 30 msec (74%), and no subject had a change greater than or equal to 60 msec. In addition, a comparison of mean QTc change to mean baseline showed that all subjects had changes <30 msec after posaconazole administration.

To determine if the change from baseline in the QTc interval could be related to posaconazole plasma concentration, summary statistics for each subject's QTc (F) interval change at the time of their maximum plasma concentration (Tmax) were calculated by the applicant. The mean and median QTc (F) interval change at Tmax (-4 msec) were comparable to the overall pooled mean change (approximately -5 msec) across all studies. Therefore, this change in the QTc interval was not considered to be associated with an increase in posaconazole exposure.

There was no relationship between individual plasma concentrations and QTc (F) changes from baseline. In addition, there was no relationship between the derived AUC values and the individual's mean change from baseline (slope of the linear regression = 0.000085) and no relationship between an individual's Cmax value and time-matched change from baseline at Tmax (slope of the linear regression = 0.00115). As per the applicant, based on these results, the potential for posaconazole to prolong the QTc interval is considered minimal at the concentrations anticipated in the clinic.

In the Phase I dataset of 449 subjects (normal volunteers and special population), five subjects had changes in their ECGs, which were considered unrelated to treatment administration in 4 of

the 5 subjects.

One subject in the single-dose, 4-way cross-over, food-effect study () experienced a flattening of their T wave and a prolonged QTc interval after receiving 200 mg posaconazole while fasted (Subject 19, a 56-year-old woman). This subject was discontinued from the study and her ECG tracings subsequently evaluated by an independent, external cardiologist, who concluded that although a relationship to posaconazole could not be excluded, the ECG deviations observed at baseline may have predisposed the subject to aspecific non-drug related changes in the ST segment, occurring due to diurnal variations and/or heart rate changes. The subject's QTc (B) interval returned to normal by 9 hours postdose and a flattened T wave was not seen on the follow-up ECG tracing performed at 72 hours postdose. The changes led to discontinuation in this subject. These ECG findings did not occur in this subject during the highfat arm of the study and this subject's exposure in the fasted period was similar to the concentrations observed in other subjects receiving the same regimen.

Cardiac Events Phase II/III (prior Phase III studies)

To assess cardiac safety in the rIFI and OPC Pools, all AEs of the general cardiovascular system and all AEs of heart rate and rhythm disorders were reviewed.

In the rIFI Pool, 158/428 subjects (37%) had general cardiovascular AEs, regardless of causality. The most common cardiovascular AEs were hypotension (15%, 64/428), hypertension (12%, 53/428), cardiorespiratory arrest (4%, 18/428), cardiac failure (4%, 15/428), hypertension aggravated (3%, 12/428), and pericardial effusion (3%, 14/428). Most of these events with the exception of 2 reports each of cardiorespiratory arrest, hyper and hypotension, and ventricular hypertrophy as well as one report each of MI, MV disease and AV sclerosis were considered by the investigator to be unlikely related to study drug. Heart rate or rhythm disorders were reported 117/428 subjects (27%). Tachycardia, the most commonly reported event (13%/57/428), was more prevalent in the BMT group (23%) than the non-BMT group (9%).

Commonly reported heart rate or rhythm AEs included atrial fibrillation (18/428, 4%), QTc/QT prolongation (11, 3%), and supraventricular tachycardia (14/428, 3%) arrhythmia, arrhythmia aggravated, ECG abnormal and ECG abnormal specific, cardiac arrest, ventricular tachycardia, ventricular fibrillation, and aggravated tachycardia were reported for <1%-2% of subjects.

Grade 3 or Grade 4 cardiovascular AEs were reported for 40 (9%) and 35 (8%) of subjects in the overall rIFI Pool, most of which were considered by the investigator to be unlikely related to treatment. Grade 3 and Grade 4 treatment related cardiovascular AEs were reported in less than 1% of subjects. The most common Grade 3 or Grade 4 AEs were hypotension and cardiorespiratory arrest. The Grade 3 or Grade 4 AEs possibly indicative of a negative inotropic effect (eg, cardiac failure, various terms for edema) occurred in <1%-2% of subjects. Grade 3 or Grade 4 cardiac failure led to death in six subjects, all of which were considered by the investigators to be unlikely related to posaconazole. There were no cases of edema that led to discontinuation or death.

Grade 3 or Grade 4 AEs of heart rate/rhythm disturbances were reported in 22 (5%) and 13 (3%) of the subjects, the most common of these were supraventricular tachycardia (Grade 3 in 2% of subjects, n = 7) and cardiac arrest (Grade 4 in 2% of subjects, n = 9), with other events reported as Grade 3 or Grade 4 in 1% of subjects. Grade 3 treatment-related heart rate/rhythm disturbances were reported in less than 1% of subjects; there were no treatment related Grade 4 heart rate/rhythm disturbances. A total of 35 subjects (8%) in the rIFI Pool had general

cardiovascular AEs and 17 (4%) had heart rate and rhythm disturbances that resulted in death or discontinuation. Two deaths were attributed to cardiovascular events considered by the investigator to be possibly related to posaconazole treatment, one due to cardiorespiratory arrest (P00041-89/8902) and one due to multi-organ failure and cardiorespiratory arrest subsequent to a prolonged seizure (P00041-19/1904). However, as noted in the section of the MOR pertaining to deaths, there were many possible factors contributing to these deaths.

A total of 70 subjects (16%) had general cardiovascular SAEs. Hypotension (8%), cardiorespiratory arrest (4%), and cardiac failure (3%) were the more common of these events. A total of 42 subjects (10%) had heart rate or rhythm SAEs. Cardiac arrest (2%) and supraventricular tachycardia (2%) were the most common. Few of these SAEs were treatment related.

Tachycardia and QTc/QT prolongation were reported as SAEs for five subjects and three subjects, respectively; none of these events led to discontinuation or death. Each subject with an AE with the preferred term of "QTc/QT prolongation", regardless of severity or relationship to treatment, is summarized in tables that follow.

Reports of QTc/QT prolongation for all but one subject were classified as mild or moderate in severity, and no subjects discontinued from the study due to QTc/QT prolongation. None of the subjects with AEs of QTc/QT prolongation had QTc intervals greater than or equal to 500 msec, based on the Fridericia correction formula (QTcF), during the treatment phase. For 8 of 11 subjects, the changes from baseline in the QTcF interval were less than 60 msec; however, for 3 subjects, the change from baseline was greater than 60 msec (Subjects P01893-01-78, P00041-75/7501, and P00041-104/10401). Additional reports of AEs with the preferred terms of "ECG abnormal" or "ECG abnormal specific" were examined and these cases showed no evidence of prolongation of the QTc interval with posaconazole.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Both prophylaxis studies were randomized comparative trials which included ECG data in their standard safety evaluations.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Table 75: Median QTc Changes from Baseline by Study Drug

Variable	n	QTcF (msec)				
		Mean	SD	Median	Minimum	Maximum
Posaconazole (N=605)						
Baseline Value	500	402.5	37.7	405	47	579
Change from Baseline at Endpoint	500	-1.8	41.3	-1	-419	426
Maximum Value - Change from Baseline During the Treatment Phase	500	7.7	36.9	9	-234	426
Fluconazole (N=539)						
Baseline Value	430	403.5	38.5	407	40	589

Change from Baseline at Endpoint	430	-6.3	41.2	-5	-217	322
Maximum Value - Change from Baseline During the Treatment Phase	430	3.7	38.2	5	-217	322
Itraconazole (N=58)						
Baseline Value	54	415.7	24.4	419	360	479
Change from Baseline at Endpoint	54	8.0	30.5	7	-67	78
Maximum Value - Change from Baseline During the Treatment Phase	54	19.6	29.4	19	-51	81

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

The mean change from baseline for QTc was less than 0 in the Posaconazole arm.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 76: QTc Increases of >60msec or Absolute QTc of >500msec by Study Drug

Values and Changes in Values	Number (%) of Subjects		
	Any QTc Correction	Bazett Correction	Fridericia Correction
Posaconazole			
All Posaconazole Subjects			
Any Increase From Baseline ≥ 60 msec-a	26/500 (5)	22/500 (4)	15/500 (3)
Any Value ≥ 500 msec During Treatment Phase-b	8/515 (2)	7/515 (1)	3/515 (1)
Male			
Any Value ≥ 450 msec During Treatment Phase-b	80/304 (26)	76/304 (25)	37/304 (12)
Any Increase From Baseline ≥ 60 msec to a Value ≥ 450 msec During Treatment Phase-a	11/296 (4)	9/296 (3)	3/296 (1)
Female			
Any Value ≥ 470 msec During Treatment Phase-b	13/211 (6)	12/211 (6)	6/211 (3)
Any Increase From Baseline ≥ 60 msec to a Value ≥ 470 msec During Treatment Phase-a	5/204 (2)	5/204 (2)	4/204 (2)
Any Condition Met-b	101/515 (20)	96/515 (19)	51/515 (10)
Fluconazole			
All Fluconazole Subjects			
Any Increase From Baseline ≥ 60 msec-a	25/430 (6)	24/430 (6)	17/430 (4)
Any Value ≥ 500 msec During Treatment Phase-b	5/440 (1)	4/440 (1)	2/440 (<1)
Male			
Any Value ≥ 450 msec During Treatment Phase-b	73/260 (28)	73/260 (28)	27/260 (10)

Any Increase From Baseline ≥ 60 msec to a Value ≥ 450 msec During Treatment Phase-a	10/251 (4)	10/251 (4)	4/251 (2)
Female			
Any Value ≥ 470 msec During Treatment Phase-b	11/180 (6)	10/180 (6)	3/180 (2)
Any Increase From Baseline ≥ 60 msec to a Value ≥ 470 msec During Treatment Phase-a	3/179 (2)	3/179 (2)	0/179
Any Condition Met-b	96/440 (22)	94/440 (21)	43/440 (10)

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

All Itraconazole Subjects			
Any Increase From Baseline ≥ 60 msec-a	6/54 (11)	1/54 (2)	6/54 (11)
Any Value ≥ 500 msec During Treatment Phase-b	1/54 (2)	0/54	1/54 (2)
Male			
Any Value ≥ 450 msec During Treatment Phase-b	18/29 (62)	17/29 (59)	10/29 (34)
Any Increase From Baseline ≥ 60 msec to a Value ≥ 450 msec During Treatment Phase-a	3/29 (10)	1/29 (3)	3/29 (10)
Female			
Any Value ≥ 470 msec During Treatment Phase-b	4/25 (16)	4/25 (16)	2/25 (8)
Any Increase From Baseline ≥ 60 msec to a Value ≥ 470 msec During Treatment Phase-a	2/25 (8)	0/25	2/25 (8)
Any Condition Met-b	22/54 (41)	21/54 (39)	13/54 (24)
a:	These data are presented in the form X/Y, where X represents the number of subjects who met the criterion as indicated, and Y represents the number of subjects who had a baseline value and at least one value in the Treatment Phase.		
b:	These data are presented in the form X/Y, where X represents the number of subjects who met the criterion as indicated, and Y represents the number of subjects who had at least one value in the Treatment Phase.		

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

Similar results were obtained in the posaconazole and fluconazole arms. In the posaconazole arm 5% of patients had at any time during the study a >60 msec increase in QTc from baseline and 2% a QTc of >500 msec. There were 6% and 1% of fluconazole patients reporting the same events respectively.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Two cases of Torsades de Pointes occurred during the 2 Phase 3 Prophylaxis studies both of which were in patients with severe underlying conditions associated with TdP.

“A 21-year-old Caucasian female, was randomized to the POS group after receiving idarubicin and cytarabine for AML. The subject had a history of palpitations, hypokalemia, and hypomagnesemia. This subject also had a history of QTc prolongation associated with hypokalemia. At baseline, QTc was 430 milliseconds (msec) and T-wave abnormalities consistent with hypokalemia were noted. On Day 18 of

treatment, palpitations followed by syncope occurred and torsades de pointes was observed on telemetry (D21). On Day 19 of therapy, QTc was 566 msec (D22). The subject was found to be hypomagnesemic. The symptoms resolved following treatment with lidocaine, magnesium, and potassium. POS was discontinued; no further episodes were reported. The investigator considered the events to be possibly related to study drug treatment (POS). The sponsor considers the events to be possibly related to study drug with the proarrhythmic effects of hypokalemia, hypomagnesemia, and potential latent cardiotoxicity from anthracycline therapy playing a contributory role. hypokalemia. At baseline, QTc was 430 milliseconds (msec) and T-wave abnormalities consistent with hypokalemia were noted. On Day 18 of treatment, palpitations followed by syncope occurred and torsades de pointes was observed on telemetry (D21). On Day 19 of therapy, QTc was 566 msec (D22). The subject was found to be hypomagnesemic. The symptoms resolved following treatment with lidocaine, magnesium, and potassium. POS was discontinued; no further episodes were reported. The investigator considered the events to be possibly related to study drug treatment (POS). The sponsor considers the events to be possibly related to study drug with the proarrhythmic effects of hypokalemia, hypomagnesemia, and potential latent cardiotoxicity from anthracycline therapy playing a contributory role.”

“A 19-year-old Hispanic male with a history of hypocalcemia received cytarabine and idarubicin for AML. QTc was 453 msec on baseline ECG. The subject was randomized to receive FLU for antifungal prophylaxis. FLU was discontinued due to *Aspergillus* pneumonia after 17 days of dosing (D25-D54). Twenty-two days after last dose of FLU, the subject developed severe respiratory failure requiring assisted ventilation (D43-D54). Hypovolemic shock (D44-D46) and hemothorax (D44-D47) were reported on the following day and torsades de pointes was noted 2 days later (D46-D54). The subject died one week later due to progression of fungal pneumonia (D54). The event of torsades de pointes was considered unlikely related to FLU treatment.

MO Comment: Posaconazole may have a low potential for induction of QTc prolongation, similar to that observed with Fluconazole. As noted with other azoles, Posaconazole is a potent inhibitor of the CYP3A4 enzyme pathway and thus other drugs that are metabolized through this pathway, and are known to cause QTc prolongation, should be administered with caution. In addition, close attention needs to be made to the serum potassium level in these patients.

7.1.10 Immunogeneticity

A series of immunotoxicology studies was performed in CD-1 mice. Mice were dosed for one or three months with 10, 30 or 90 mg/kg posaconazole, with a one-month recovery period. Two functional assays (antibody forming cell assay and natural killer cell assay) and an immunophenotyping study were performed. In the antibody forming cell assay, a T cellMOR dependent antigen (sheep red blood cells) was used. The antibody forming cell assay is an indication of the function of macrophages (presentation of antigen), T lymphocytes (T celldependent antigen) and B lymphocytes (production of antibody). The natural killer cell assay indicates the function of natural killer cells isolated from spleen.

After one or three months of dosing, a slight decrease in the antibody forming cell response and a slight increase in natural killer cell activity were seen in the 30 and 90 mg/kg groups, but not in the 10 mg/kg group. A dose of 10 mg/kg in mice yields a mouse-to-human exposure multiple of 1.51-fold. At the end of the one month recovery period, there were no changes in immunologic function. There were minimal effects on the natural killer cell, monocytes and lymphocyte populations evaluated in the blood and spleen. Absolute numbers of lymphocytes were minimally higher than concurrent control in blood of males in the 30 and 90 mg/kg groups after three months of dosing. Males and females in the 30 and 90 mg/kg groups had minimally lower splenic lymphocytes after one month of dosing. Splenic monocytes were minimally higher in males and females in the 90 mg/kg group after three months of dosing. At the end of the one month recovery period, there were no changes in blood cell populations and only a minimally higher number of one splenic lymphocyte population in females in the 90 mg/kg group. It appeared as if posaconazole as other azoles had minimal effects on the immune system and what changes there were reversible.

7.1.11 Human Carcinogenicity

Two carcinogenicity studies of posaconazole were performed in mice at the high dose (60 mg/kg from Weeks 1 to 5, 90 mg/kg from Weeks 6 to 23, and diet only Weeks 24 to 56). In the first carcinogenicity study in mice, there were no posaconazole-related changes in the incidence of any tumors. In the repeat carcinogenicity study in mice, females (5/49) in the high-dose group (90 mg/kg from Weeks 1 to 48 and 60 mg/kg from Week 49 to termination) had a drug-related increase in hepatocellular adenomas.

Histopathologic findings in the liver of mice in the high-dose group included diffuse hepatocellular hypertrophy, anisocytosis, intranuclear inclusions, hepatocellular mitotic figures and regenerative hepatocellular hyperplasia, and hepatocellular adenomas. Increases in liver tumors, including hepatocellular adenomas, have been reported with other azoles, including fluconazole and voriconazole. The tumors observed after administration of posaconazole

occurred at a dose level that exceeded the maximum tolerated dose (MTD) based on mortality. No posaconazole-related tumors were seen at 30 mg/kg; the exposure to posaconazole at 30 mg/kg in mice is 3.69-fold higher than the human exposure. In the first carcinogenicity study in mice, enlarged lymph nodes were seen beginning in Week 13 in high-dose groups. The incidence of these masses subsequently increased and then also occurred in the control, low dose (10 mg/kg) and mid-dose (30 mg/kg) groups. The incidence was generally dose-related. At necropsy, the enlargement was observed in internal and peripheral lymph nodes. Microscopically, the lymph node change was characterized by hyperplasia and hypertrophy of stromal fixed histiocytes in lymph nodes, spleen and, occasionally, bone marrow. Kupffer cells of the liver were also hypertrophied and hyperplastic. The histiocytes were oval or polygonal to elongate, with a moderate amount of eosinophilic cytoplasm and were primarily arranged in coalescing cords and sheets. The nucleus was mildly pleomorphic and lacking a conspicuous nucleolus. Mitotic figures were infrequent. Ultrastructurally, there were large interdigitating cells containing primary and secondary lysosomes and nuclear euchromatin. There was no evidence of an infectious agent and no evidence of phospholipidosis within the proliferative cell population. Moderate to intense cytoplasmic staining for lysozyme histochemically, confirmed the histiocytic origin of the cells. Lymphoid elements were not affected. This lymph node finding was not observed in rats at up to two years of dosing, in dogs at up to twelve months of dosing, or monkeys in a one-month oral toxicity study.

7.1.12 Special Safety Studies

There were no additional special safety studies submitted with this NDA.

7.1.13 Withdrawal Phenomena or Abuse Potential

Not applicable

7.1.14 Human Reproduction and Pregnancy Data

Non-clinical studies of reproductive function showed that posaconazole had no effect on fertility of male or female rats.

In studies of embryo and fetal development in the rat at doses of 3, 9 or 27 mg/kg, the highest dose caused skeletal malformations, while the no-effect dose was 9 mg/kg. In the rabbit, the no effect dose was 20 mg/kg, while high doses of 40 and 80 mg/kg caused a reduction in the body weight gain of females and in litter size, and an increase in resorptions. No malformations were noted in rabbits. In a peri- and post-natal study, adverse reproductive effects including dystocia, prolonged parturition, reduced F1 mean live litter size and reduced F1 post-natal viability occurred at doses of 18 mg/kg and above, but not at 6 mg/kg.

Embryo resorptions, post-implantation losses, delayed parturition, and fetal skeletal malformations and variations are class effects of azole antifungal drugs and may be due to azole-related alterations in female sex hormone levels, such as reductions in estradiol and/or progesterone levels.

There were two reports of maternal drug exposure in women enrolled in the clinical studies with posaconazole, one in Study C/198-316 and one in Study P02095. One subject (Subject I98316-51/388) was found to be pregnant at a follow-up visit approximately 1 month after the completion of a full 16-week treatment period per protocol. The subject had a healthy full-term male infant via cesarean section. The treatment assignment for this subject remains blinded. One unintended pregnancy was reported for a female subject (Subject P02095-11/004), who was being treated with posaconazole 800 mg/day for disseminated coccidioidomycosis; the pregnancy ended in an elective termination due to concerns regarding the effect of pregnancy on her fungal infection. No examination of the fetus was reported. In addition, a male study subject

Subject P02095-19/001) reported that his female partner had become pregnant, which resulted in the delivery of an infant with a small congenital ventricular septal defect, considered unlikely related to posaconazole exposure in the father.

7.1.15 Assessment of Effect on Growth

Not applicable

7.1.16 Overdose Experience

Clinical experience in doses exceeding 800 mg/day (this is the dose studied for the treatment of IFI), from Phase 2/3 studies, is summarized below.

In the dose-finding study in rIFI (Study P01893), 31 subjects were treated with orally administered posaconazole 400 mg QID for 2 days, followed by 600 mg BID for up to 6 months. The safety of posaconazole in these subjects was similar to that observed in subjects treated with posaconazole 800 mg/day. There was no suggestion of an increased risk of AEs with the increased dosage possible because exposure to posaconazole in these subjects was lower than the exposure achieved in subjects administered posaconazole 400 mg twice daily.

In the rIFI Pool, one subject was accidentally administered posaconazole 2400 mg/day for 6 days (Subject P00041-05/524) and two subjects were administered posaconazole 1600 mg/day for approximately 2 months (Subjects P00041-05/0502 and P00041-08/0802). There was no indication of an increased risk of adverse events in these subjects during the time of the overdosing. One subject in the Refractory OPC Pool had an AE of drug toxicity (literal term was surdosage). During the first 3 days of treatment, Subject I97330-12/003 took posaconazole 1200 mg twice daily; thereafter, the dose was reduced to 400 mg once daily until Day 30. No other AE

was reported for this subject during the first 3 days of posaconazole treatment. Grade 4 neutropenia was reported on Day 7, considered by the investigator to be unrelated to posaconazole therapy, and was treated with filgrastim (baseline WBC for this subject was $1.21 \times 10^9/L$ and Week 1 WBC was $3.98 \times 10^9/L$).

Data from pharmacokinetic studies demonstrate that exposure to orally administered posaconazole appears to be limited at the 800 mg dose, which may explain the lack of increased risk in subjects who were administered posaconazole doses greater than 800 mg. Results of Study P01940 showed that posaconazole was not removed by hemodialysis. Therefore, hemodialysis should not be used in cases of overdose.

7.1.17 Postmarketing Experience

Not Applicable

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 77: Clinical Studies of Prophylaxis of IFI

Study Number	Type of Study	Population	Study Drug	Control
CI98-316	Randomized, DB	Acute leukemia or Myelodysplastic Syndrome Post HSCT +GVHD	Posaconazole 200mg po TID N=301	Fluconazole 400 mg po qD N=299
P01899	Randomized, OL	Hematologic Malignancy at High Risk for Neutropenia post Chemotherapy	Posaconazole 200mg po TID N=304	Fluconazole 400 mg po qD(N=240) or Itraconazole 200mg po BID (N=58)

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7.2.1.2 Demographics

Table 78: Demographics of the Pooled Prophylaxis of IFI Studies

	Posaconazole n=605	Fluconazole n=539	Itraconazole n=58
Sex (n,%)			
Female	244 (40)	224 (42)	26 (45)
Male	361 (60)	315 (58)	32 (55)
Race (n,%)			
Caucasian	479 (79)	428 (79)	49 (84)
Non-Caucasian	126 (21)	111 (21)	9 (16)
American Indian	4 (1)	2 (<1)	0
Asian	22 (4)	13 (2)	6 (10)
Black	28 (5)	25 (5)	2 (3)
Hispanic	70 (12)	70 (13)	1 (2)
Other ^a	2 (<1)	1 (<1)	0
Age (years)			
Mean (SD)	45.7 (14.6)	44.8 (15.1)	51.6 (14.2)
Median	47.0	45.0	54.0
Range	13 - 82	13 - 79	20 - 81
Age (n,%)			
13 - <18	12 (2)	16 (3)	0
18 - <65	530 (88)	460 (85)	49 (84)
65 or Older	63 (10)	63 (12)	9 (16)
Weight (kg)			
Mean (SD)	73.21 (17.64)	74.39 (17.57)	76.15 (14.33)
Median	71.00	72.10	76.35
Range	34.0 - 150.4	39.0 - 160.0	50.0 - 112.9
Missing	10	18	0
Height (cm)			
Mean (SD)	169.89 (10.56)	169.60 (10.16)	168.60 (7.78)
Median	170.00	170.00	168.00
Range	139.5 - 198.1	137.0 - 198.0	152.0 - 185.0
Missing	22	28	1

a: Includes Indian, Native American, and mixed race.
 cm = centimeters; kg = kilograms; SD = standard deviation.

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

7.2.1.3 Extent of exposure (dose/duration)

In both studies the dose of posaconazole was 200 mg po TID:

Table 79: C98-316 Treatment Duration of Study Drug

	POS (N=301)	FLU (N=299)
Treatment Duration (Days)		
N	291	288
Mean (SD)	80.3 (42.9)	77.2 (42.7)
Median	111	108
Minimum	1	1
Maximum	138	130
Cumulative Number (%) of Subjects With Indicated Treatment Duration	n (%)	n (%)
≥1 Day	291 (97)	288 (96)
≥22 Days	245 (81)	237 (79)
≥36 Days	218 (72)	215 (72)
≥50 Days	201 (67)	198 (66)
≥64 Days	188 (62)	179 (60)
≥78 Days	178 (59)	169 (57)
≥92 Days	171 (57)	158 (53)
≥106 Days	165 (55)	149 (50)
≥112 Days	139 (46)	122 (41)
≥120 Days	14 (5)	10 (3)
Randomized, not treated	10 (3)	11 (4)

Adapted from Study Report C98-316, NDA 22-003

Table 80: Study P01899 Summary of Treatment Duration and Exposure (All Randomized Subjects)

	POS (n=304)	FLU/ITZ (n=298)
Treatment Duration (Days)		
N	297	292
Mean (SD)	36.7 (30.3)	32.3 (27.5)
Median	25	21
Minimum	1	1
Maximum	151	112
Cumulative Number (%) of Subjects With Indicated Treatment Duration		
≥7 Days	269 (88)	263 (88)
≥14 Days	212 (70)	194 (65)
≥21 Days	176 (58)	148 (50)
≥28 Days	137 (45)	119 (40)
≥56 Days	83 (27)	64 (21)
≥84 Days	28 (9)	22 (7)
Randomized, not treated	7 (2)	6 (2)

Adapted from Study Report P01899, NDA 22-003

In the prior submission 195 patients had received posaconazole 800 mg po daily for the treatment of various invasive fungal infections for between 91 and 365 days and 57 received this dose for longer than 365 days. The longest any patient received posaconazole was 1061 days.

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7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies-

Please see listing of studies in _____ which are referred to here in aggregate in the safety section

7.2.2.2 Postmarketing experience

Not Applicable

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience was adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See Pharm/Toxicology Review

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology review-will recommend Phase 4 commitment to assess the reasons for and the outcome of low serum levels of posaconazole and to determine the value TDM (therapeutic drug monitoring) in the use of posaconazole for prevention of IFI.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The incidence of TTP, HUS, and PE was higher in the posaconazole arm than the fluconazole arm in study C98-316. This was not seen in study P01899. It is unclear whether this is due to the underlying disease state of post stem cell transplantation with GVHD, the therapies for these conditions or the interaction of posaconazole either with those therapies or with the underlying condition. Close surveillance of these events on a quarterly basis will be necessary to better understand these potentially drug related adverse events.

7.2.8 Assessment of Quality and Completeness of Data

The data was of good quality and complete.

7.2.9 Additional Submissions, Including Safety Update

None at this time.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Repeated Table 81: Types of Adverse Events by Study Drug in the Prophylaxis Pool (C98-316 and P018999)

	POS N=605	FLU N=539	ITZ N=58
	N(%)	N(%)	N(%)
Treatment Related Adverse Event	595(98)	531 (99)	58 (100)
Treatment Related Treatment Emergent AE	209 (35)	185 (35%)	30 (52)
Serious Adver Events	381 (63)	364 (68)	32 (55)
Treatment Reakted Serious Adverse Events	59 (10)	33(6)	2(3)
AEs Leading to Death	121(20)	139 (26)	9(16)
AEs Leading to Drug Discontinuation	202 (33)	208 (39)	26 (45)

Adapted from Pooled Prophylaxis Safety Summary NDA 22-003

In summary, posaconazole is a relatively well tolerated azole with some of the same safety concerns as other members of the azole class and some unique safety issues. Overall the potential benefits of this agent in the reduction of invasive fungal infections in severely immunocompromised patients outweighs its potential risks.

There were 3 deaths considered by the investigators to be possibly or probably related to posaconazole therapy. One of the deaths was felt to be probably related to a posaconazole drug interaction producing severe neurologic cyclosporine toxicity and death. The other 2 were possible related-one secondary to multi-organ failure and the other partly due to persistent hyperbilirubinemia and liver failure with micronodular cirrhosis found at autopsy. All of these cases are described in more detail in the Deaths section above. There were more serious adverse events that were considered to be treatment related in the posaconazole arms than the comparator arms (10 versus 6%) but fewer adverse events leading to death or discontinuation than in the posaconazole arm.

Some of the possible adverse events of concern are:

- 1-increase in hepatic adverse events including elevation in liver function tests and rare cases of severe liver injury in patients with severe underlying comorbidity
- 2-drug interaction with cyclosporine which can lead to severe, even fatal cyclosporine toxicity. Similar interactions might also be possible with tacrolimus or sirolimus.
- 3-inhibitor of CYP3A4-such interactions could result in effects on QTc and in reduced levels of posaconazole which may result in subtherapeutic effect.
- 4-similar rates of increase of >60msec of QTc from baseline and QTC over 500 msec in prophylaxis patients as those who received fluconazole. No similar events recorded in healthy subjects. One case of Torsades de Pointes in prophylaxis pool of patients with severe electrolyte abnormalities.
- 5-Mild increase in incidence of hypokalemia (13%) in comparison to fluconazole(10%.) which may influence changes in QTc.
- 6-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 to 0.)
- 7-mild increase in TTP (and overall thrombocytopenia) and HUS in the post stem cell transplant patients with GVHD who received Posacoanzole in comparison to Fluconazole. These events may be related to toxicity with cyclosporine, tacrolimus, and sirolimus.
- 8-Most common adverse events that were likely to be drug related were gastrointestinal-nausea, vomiting, diarrhea, and hepatic.

Recommendations:

Include in labeling:

- Warning about cyclosporine interaction (and potential interactions with tacrolimus and sirolimus) and potentially fatal toxicity. Recommend initial cyclosporine, tacrolimus, or sirolimus dose reduction when posaconazole therapy is begun and monitor levels more frequently.
- Precaution about QT effects and interaction with CYP3A4 drugs with QT prolonging potential.
- Warning about hepatic adverse events and recommendation for hepatic enzyme monitoring
- Precaution about Pulmonary embolus, TTP, HUS, and thrombocytopenia in post stem cell transplant patients with GVHD

-Recommendation to measure K+, platelets frequently

Phase 4 safety study:

Detailed quarterly adverse event reports of TTP, HUS or PE should be filed with the Agency to better elucidate the occurrence of thrombotic or microangiopathic events.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Data was not pooled in the efficacy analysis since the populations in the 2 study populations were very different. Consequently, the efficacy outcomes of the 2 studies were evaluated individually.

7.4.1.2 Combining data-

Data were combined in the safety analyses to better determine the overall safety pattern when posaconazole was used in the prophylaxis of IFI. When pertinent, safety data from the pooled treatment of IFI experience was used. Also there were certain adverse events which were more common in one of the prophylaxis populations (eg. TTP and HUS in the post stem cell transplant population). IN such a case the safety data from the individual studies would be presented.

7.4.2 Explorations for Predictive Factors

Not performed

7.4.2.1 Explorations for dose dependency for adverse findings

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Table 82: Incidence of treatment-emergent and drug-related (Possible and Probable) AEs (%) in the All Treated population in 4 quartiles of average plasma concentration POS (C_{avg}) (N=450; Studies C98-316 and P01988).

	1 st Q (n=119)	2 nd Q (N=121)	3 rd Q (N=120)	4 th Q (N=120)	P value ^b
C_{avg} (ng/mL) ^a	205±105 [2.51-355]	498±77.1 [355-626]	835±138 [626-1118]	1751±538 [1118-3650]	
Diarrhea	3.36%	4.96%	8.33%	6.67%	0.4378
Nausea	7.56%	6.61%	10%	12.5%	0.3746
Vomiting	3.36%	4.96%	7.5%	6.67%	0.4639
Discontinuation	8.4%	7.44%	14.2%	17.5%	0.0595
Bilirubinemia	1.68%	3.31%	4.17%	3.33%	0.4787
SGOT increased	1.68%	2.48%	4.17%	3.33%	0.4016
SGPT increased	1.68%	3.31%	5%	3.33%	0.4911
Hepatic enz. increased	1.68%	3.31%	4.17%	3.33%	0.4787
Hypokalemia	0.84%	1.65%	4.17%	2.5%	0.4818
Rash	0.84%	1.65%	4.17%	3.33%	0.1739

^a: Mean±SD [range]

^b: Logistic regression for the relationship between the incidence of treatment-related adverse events and C_{avg} . Datasets from Study C98-316 and P01899 were pooled for these analyses.

It is unclear why there is an increase with discontinuation with dose escalation. This can be further examined in a phase 4 study performed to better understand low levels of absorption, dose response, and the potential benefits of therapeutic drug monitoring.

7.4.2.2 Explorations for time dependency for adverse findings

Not performed

7.4.2.3 Explorations for drug-demographic interactions

None performed

7.4.2.4 Explorations for drug-disease interactions

In study C98-316, pulmonary embolus, TTP and HUS occurred more frequently in the posaconazole arm than the fluconazole arm. This pattern was not evident in the P01899 study.

Consequently further evaluation of the potential interaction of posaconazole with either the post transplant state or its therapy will be proposed for the post marketing phase.

7.4.2.5 Explorations for drug-drug interactions

Please see below in Drug Interactions

7.4.3 Causality Determination

Not applicable

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Posaconazole is to be administered as an oral suspension of 200 mg (5 mL) three times a day. Each dose of Posaconazole will need to be given with a full meal or with a liquid nutritional supplement in patients who cannot eat a full meal in order to enhance the oral absorption of posaconazole and optimize plasma concentrations. The duration of therapy is based on recovery from neutropenia or immunosuppression. The safety of posaconazole used as prophylaxis has been assessed for up to 4 months only.

In the prior submission — 195 patients had received posaconazole 800 mg po daily for the treatment of various — invasive fungal infections for between 91 and 365 days and 57 received this dose for longer than 365 days. The longest any patient received posaconazole was 1061 days.

8.2 Drug-Drug Interactions

Effect of Other Drugs on Posaconazole

Posaconazole is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. A summary of drugs studied clinically, which affect posaconazole concentrations, is provided below.

Table 83: Summary of the Effect of Co-administered Drugs on Posaconazole in Healthy Volunteers

Co-administered Drug (Postulated Mechanism of Interaction)	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Posaconazole		Recommendations
			Change in Mean Cmax (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)	
Rifabutin (UDP-G Induction)	300 mg QD x 7 days	200 mg (tablets) QD x 10 days	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)	Avoid concomitant use unless the benefit outweighs the risks.
Phenytoin (UDP-G Induction)	200 mg QD x 10 days	200 mg (tablets) QD x 10 days	↓ 41% (0.59; 0.44-0.79)	↓ 50% (0.50; 0.36-0.71)	Avoid concomitant use unless the benefit outweighs the risks.
Cimetidine (Alteration of Gastric pH)	400 mg BID x 10 days	200 mg (tablets) QD x 10 days	↓ 39% (0.61; 0.53-0.70)	↓ 39% (0.61; 0.54-0.69)	Avoid concomitant use unless the benefit outweighs the risks.

* Ratio Estimate is the ratio of co-administered drug plus posaconazole to posaconazole alone for Cmax or AUC.

Coadministration of these drugs listed above with posaconazole may result in lower plasma concentrations of posaconazole.

No clinically relevant effect on posaconazole bioavailability and/or plasma concentrations was observed when administered with an antacid, glipizide, ritonavir, H2 receptor antagonists other than cimetidine, or proton pump inhibitors; therefore, no posaconazole dose adjustments are required when used concomitantly with these products.

Effect of Posaconazole on Other Drugs

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole. A summary of the drugs studied clinically, for which plasma concentrations were affected by posaconazole, is provided below.

Table 84: Summary of the Effect of Posaconazole on Co-administered Drugs in Healthy Volunteers and Patients

Co-administered Drug (Postulated Mechanism of Interaction)	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Co-administered Drugs		Recommendations
			Change in Mean Cmax (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)	
Cyclosporine (Inhibition of CYP3A4 by posaconazole)	Stable maintenance dose in heart transplant recipients	200 mg (tablets) QD x 10 days	↑ cyclosporine whole blood trough concentrations. Cyclosporine dose reductions of up to 29% were required		At initiation of posaconazole treatment, reduce the cyclosporine dose to approximately three-fourths of the original dose. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly.
Tacrolimus (Inhibition of CYP3A4 by posaconazole)	0.05 mg/kg single oral dose	400 mg (oral suspension) BID x 7 days	↑ 121% (2.21; 2.01-2.42)	↑ 358% (4.58; 4.03-5.19)	At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly.
Rifabutin (Inhibition of CYP3A4 by posaconazole)	300 mg QD x 7 days	200 mg (tablets) QD x 10 days	↑ 31% (1.31; 1.10-1.57)	↑ 72% (1.72; 1.51-1.95)	Avoid concomitant use unless the benefit outweighs the risks. If the drugs are coadministered, frequent monitoring of rifabutin adverse effects (e.g. uveitis, leukopenia) should be performed.

Co-administered Drug (Postulated Mechanism of Interaction)	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Co-administered Drugs		Recommendations
			Change in Mean Cmax (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)	
Midazolam (Inhibition of CYP3A4 by posaconazole)	Single 30 min IV infusion of 0.05 mg/kg	200 mg (tablets) QD x 10 days	NA**	↑ 83% (1.83; 1.57-2.14)	Frequent monitoring of adverse effects of benzodiazepines metabolized by CYP3A4 should be performed and dose reduction of these benzodiazepines should be considered during coadministration with posaconazole.
Phenytoin (Inhibition of CYP3A4 by Posaconazole)	200 mg PO x 10 days	200 mg (tablets) QD x 10 days	↑ 16% (1.16; 0.85-1.57)	↑ 16% (1.16; 0.84-1.59)	Frequent monitoring of phenytoin concentrations should be performed while co-administered with posaconazole and dose reduction of phenytoin should be considered.
*Ratio Estimate is the ratio of co-administered drug plus posaconazole to posaconazole alone for Cmax or AUC. **NA: Not applicable if administered as an IV					

Additional clinical studies demonstrated that no clinically significant effects on phenytoin, zidovudine, lamivudine, ritonavir, indinavir, or caffeine were observed when administered with posaconazole; therefore, no dose adjustments are required for these co-administered drugs.

Posaconazole administration with glipizide does not require a dose adjustment in either drug; however, glucose concentrations decreased in some healthy volunteers administered the combination. Therefore, glucose concentrations should be monitored in accordance with the current standard of care for patients with diabetes when posaconazole is co-administered with glipizide.

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Table 85: Summary of the Effect of Co-administered Drugs on Posaconazole.

Co-administered Drug	Recommendations
Cimetidine	Avoid concomitant use unless the benefit outweighs the risks
Rifabutin	Avoid concomitant use unless the benefit outweighs the risks
Phenytoin	Avoid concomitant use unless the benefit outweighs the risks

Coadministration of these drugs listed in Table 5 with posaconazole may result in lower plasma concentrations of posaconazole.

Table 86: Summary of the Effect of Posaconazole on Co-administered Drugs

Co-administered Drug	Recommendations
Cyclosporine	Increased cyclosporine concentrations resulted in cyclosporine dose reductions in heart transplant patients co-administered posaconazole. At initiation of posaconazole treatment, reduce the cyclosporine dose to approximately three fourths of the original dose. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly.
Tacrolimus	Posaconazole has been shown to increase C _{max} and AUC of tacrolimus significantly. At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly.
Rifabutin	Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. However, if they are required to be administered concomitantly, frequent monitoring of full blood counts and adverse events due to increased rifabutin levels (e.g., uveitis) is recommended.
Midazolam	Frequent monitoring of adverse effects of benzodiazepines metabolized by CYP3A4 should be performed and dose reduction of these benzodiazepines should be considered during coadministration with posaconazole.

Co-administered Drug	Recommendations
Phenytoin	Frequent monitoring of phenytoin concentrations should be performed while co-administered with posaconazole and dose reduction of phenytoin should be considered.

Although not studied *in vitro* or *in vivo*, posaconazole may affect the plasma concentrations of the drugs or drug classes described in the table below. Appropriate precautions for the co-administration of these drugs with posaconazole are provided..

Table 87: Drugs Not Studied in vitro or in vivo but Likely to Result in Significant Drug Interactions

Drug or Drug Class (CYP3A4 Substrates)	Recommendations
Terfenadine, Astemizole, Pimozide, Cisapride, Quinidine	Increased plasma concentrations of these drugs can lead to QT prolongation with rare occurrences of torsade de pointes. Co-administration with posaconazole is contraindicated. See CONTRAINDICATIONS .
Ergot Alkaloids	Posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism. Co-administration of posaconazole with ergot alkaloids is contraindicated. See CONTRAINDICATIONS .
Vinca Alkaloids	Posaconazole may increase the plasma concentrations of vinca alkaloids (eg, vincristine and vinblastine) which may lead to neurotoxicity. Therefore, it is recommended that the dose adjustment of the vinca alkaloid be considered.
Sirolimus	Frequent monitoring of sirolimus whole blood trough concentrations should be performed upon initiation, during coadministration, and at discontinuation of posaconazole treatment, with sirolimus doses reduced accordingly.
HMG-CoA reductase inhibitors (statins) metabolized through CYP3A4	It is recommended that dose reduction of statins be considered during co-administration. Increased statin concentrations in plasma can be associated with rhabdomyolysis.
Calcium Channel Blockers metabolized through CYP3A4	Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during co-administration. Dose reduction of calcium channel blockers may be needed.

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8.3 Special Populations

Of the 605 patients randomized to posaconazole in the prophylaxis clinical trials, 63 (10%) were ≥ 65 years of age. In addition, 48 patients treated with ≥ 800 mg/day posaconazole in another indication

were ≥ 65 years of age. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

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8.4 Pediatrics

There were 28 pediatric subjects (ranging in age from 13 to 17 years) in the prophylaxis pool. Baseline demographic (sex and race) and underlying disease characteristics for these pediatric subjects were similar to those observed for the overall prophylaxis pool, and similar proportions of pediatric subjects experienced SAEs or other clinically significant AEs compared with the subjects in the prophylaxis pool overall. The prophylaxis pool contained 12 pediatric subjects treated with POS and 16 pediatric subjects treated with FLU. Of the 12 pediatric subjects in the POS group, 9 completed the treatment phase. Two pediatric subjects in the POS treatment group died for reasons unlikely related to study drug treatment, as determined by investigators. One died as a result of the AE of intracranial hemorrhage 14 days following the end of treatment with POS. Another died as a result of the progression of the underlying disease, AML, 8 days following the end of treatment with POS.) Of the 16 pediatric subjects treated with FLU, 5 completed the treatment phase. Three pediatric subjects in the FLU treatment group died for reasons unlikely related to FLU treatment, as determined by the investigator.

8.5 Advisory Committee Meeting

None

8.6 Literature Review

In a study by Goodman, et al, (6) in the *New England Journal of Medicine* fluconazole was compared to placebo for the prevention of IFI in patients post bone marrow transplantation. In this study 15.8% of the patients in the placebo arm experienced proven systemic fungal infection versus 2.8% in the fluconazole arm. A similar study was reported by Slavin (16). In this study 18% of placebo patients had a proven systemic fungal infection versus 7% with fluconazole.

Similar studies were performed in patients with hematologic malignancies with neutropenia from cancer chemotherapy. Menichetti (13) reported that the rate of proven and suspected IFI in the placebo arm was 33% and 24% in the fluconazole arm. Winston (19) reported only proven IFIs with rates of 8% in placebo patients and 4% in fluconazole patients.

8.7 Postmarketing Risk Management Plan

The Division has requested quarterly detailed reports of all patients with thrombotic or microangiopathic events such as TTP, HUS, or PE, etc. for 3 years.

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

In double-blind clinical study C98-316 in patients post hematopoietic stem cell transplant with GVHD, posaconazole was shown to be noninferior to fluconazole in clinical outcome defined as the occurrence of proven or probable invasive fungal infection, death, or use of systemic anti-fungal therapy for greater than 4 days during both the While on Treatment period (oral therapy plus 7 days) or the prespecified primary time period of 16 weeks (where lost to followup was also included as clinical failure.). Mortality was similar between the groups. The majority of deaths were secondary to the underlying disease, its complications or its primary therapy. The incidence of IFI, especially *Aspergillus* infection, was lower in the posaconazole arm. Please see the table below. Placebo rates of the incidence of proven/probable IFI in this population range from 15 to 18%. (6, 16.)

Table 88: Results from Blinded Clinical Study C98-316 in Prophylaxis of IFI in All Randomized Patients with hematopoietic stem cell transplant (HSCT) and graft-vs-host disease (GVHD)

	Posaconazole n = 301	Fluconazole n = 299
<i>On therapy plus 7 days</i>		
Clinical Failure ^a	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(<i>Aspergillus</i>)	3 (1%)	17 (6%)
(<i>Candida</i>)	1 (<1%)	3 (1%)
(Other)	3 (1%)	2 (1%)
All Deaths	22 (7%)	24 (8%)
Proven / probable fungal infection	2 (<1%)	6 (2%)

prior to death		
SAF ^{b,c}	27 (9%)	25 (8%)
Through 16 weeks		
Clinical Failure ^{a,d}	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(<i>Aspergillus</i>)	7 (2%)	21 (7%)
(<i>Candida</i>)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths	58 (19%)	59 (20%)
Proven / probable fungal infection prior to death	10 (3%)	16 (5%)
SAF ^{b,c}	26 (9%)	30 (10%)
Event free lost to follow-up ^e	24 (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). d: 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%) 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.		

In the second open label study in patients with hematologic malignancy with prolonged neutropenia from cancer chemotherapy posaconazole was superior to the combined standard azole arm (either fluconazole or itraconazole depending on the site but 4/5 of the control patients received fluconazole) in clinical outcome (defined as defined as the occurrence of proven or probable invasive fungal infection, death, or use of systemic anti-fungal therapy for greater than 3 days during both the Treatment Phase (oral therapy plus 7 days) or 100 days post randomization. Posaconazole performed better against fluconazole than itraconazole (superior to fluconazole in clinical outcome and IFI incidence and noninferior for these same parameters against itraconazole but the number of patients enrolled at these sites was much smaller.) Mortality was similar between the groups at the end of treatment but was lower in the posaconazole arm at 100 days post randomization. The incidence of IFI especially *Aspergillus* infection was lower in the posaconazole arm. Most of the difference between the posaconazole arm and fluconazole/itraconazole arm in this study was in probable *Aspergillus* infection. Rates for proven *Aspergillus* infection were low and similar among the groups. Placebo rates for this population range from 8% in one study which included only proven IFIs to 33% when proven and probable IFIs are included. (19, 13) Please see the table below.

Table 89: 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
On therapy plus 7 days		
Clinical Failure ^{a,b}	82 (27%)	126 (42%)
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	17 (6%)	25 (8%)
Proven / probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF ^{c,d}	67 (22%)	98 (33%)
Through 100 days post-randomization		
Clinical Failure ^b	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(<i>Aspergillus</i>)	2 (1%)	26 (9%)
(<i>Candida</i>)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven / probable fungal infection prior to death	2 (1%)	16 (5%)
SAF ^{c,d}	98 (32%)	125 (42%)
Event free lost to follow-up ^e	34 (11%)	24 (8%)
a: 95% confidence interval (posaconazole-fluconazole/ itraconazole) = (-22.9%, -7.8%). 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). e: Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.		

An exposure-response relationship analysis was performed by Dr. Jang. In this analysis it was shown that for the first study (C98-316) at lower serum levels of posaconazole (<700 ug/ml) there was a higher incidence of IFI than at levels above 700 ug/ml. This association was not as apparent for the second study (P01899.) Please see tables below.

Table 90. Incidence of Proven/Probable IFIs between those patients whose POS C_{avg} was ≤700 ng/mL and those patients whose POS C_{avg} was >700 ng/mL (Study C98316).

C _{avg} (ng/mL)	≤700 ng/mL (N=92)	>700 ng/mL (N=160)
Incidence of Prove/Probable IFIs	6.52% (6/92)	1.88% (3/160)
Incidence of Aspergillosis	4.35% (4/92)	0.63% (1/160)

Table 91: Incidence of Proven/Probable IFIs between those patients whose C_{avg} was ≤700 ng/mL and those patients whose C_{avg} was >700 ng/mL (Study P01899).

C _{avg} (ng/mL)	≤700 ng/mL (N=155)	>700 ng/mL (N=60)
Incidence of Prove/Probable IFIs	3.87% (6/155)	0% (0/60)

Even though a mortality advantage was shown only in the second study, the demonstration of a consistent pattern of at least non-inferiority in clinical outcome and IFI in the 2 studies and the demonstration of an exposure response relationship in at least one of the studies supports the efficacy of posaconazole in the prophylaxis of IFI due to *Candida* and *Aspergillus*. Since the mortality rate is very high due to the underlying disease and the complications of its treatment in the populations studied here it is difficult in this population to demonstrate a mortality advantage. However, since IFI due especially to *Aspergillus* and other molds has a high mortality rate, one can conclude that reducing the incidence of such infections would translate into a mortality benefit in clinical practice. A decreased incidence of IFI may also allow patients to receive more therapy for their underlying disease. The presence of an active fungal infection may reduce the ability for the patient to receive further immunosuppressing therapy that might be necessary in combating the underlying malignancy or transplant rejection.

Safety

There were 3 deaths considered by the investigators to be possibly or probably related to posaconazole therapy. One of the deaths was felt to be probably related to a posaconazole drug interaction producing severe neurologic cyclosporine toxicity and death. The other 2 were possibly related—one secondary to multi-organ failure and the other partly due to persistent hyperbilirubinemia and liver failure with micronodular cirrhosis found at autopsy. There were more serious adverse events that were considered to be treatment related in the posaconazole arms than the comparator arms (10 versus 6%) but fewer adverse events leading to death or discontinuation in the posaconazole arm than in comparators.

Some of the possible adverse events of concern were:

- 1-Increase in hepatic adverse events including elevation in liver function tests and rare cases of severe liver injury in patients with severe underlying comorbidity;
- 2-Drug interaction with cyclosporine which can lead to severe, even fatal, cyclosporine toxicity. Similar interactions might also be possible with tacrolimus or sirolimus;
- 3-Inhibition of CYP3A4—such interactions could result in effects on QTc and in reduced levels of posaconazole which may result in subtherapeutic effect;
- 4-Similar rates of increase of >60 msec of QTc from baseline and QTC over 500 msec in prophylaxis patients as those who received fluconazole. No similar events recorded in healthy subjects. One case of Torsades de Pointes in prophylaxis pool of patients with severe electrolyte abnormalities;
- 5-Mild increase in incidence of hypokalemia (13%) in comparison to fluconazole(10%.) which may influence changes in QTc;
- 6-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 to 0.);
- 7-Mild increase in TTP and HUS in the post stem cell transplant patients with GVHD who received Posaconazole in comparison to Fluconazole. These events may be related to toxicity with cyclosporine, tacrolimus, and sirolimus;

8-Most common adverse events that were likely to be drug related were gastrointestinal-nausea, vomiting, diarrhea, and hepatic.

Recommendations:

1. Include in labeling:

- Warning about cyclosporine interaction (and potential interactions with tacrolimus and sirolimus) and potentially fatal toxicity. Recommend initial cyclosporine, tacrolimus, or sirolimus dose reduction when posaconazole therapy is begun and monitor levels more frequently.
- Precaution about QT effects and interaction with CYP3A4 drugs with QT prolonging potential.
- Warning about hepatic adverse events and recommendation for hepatic enzyme monitoring
- Precaution about Pulmonary embolus, TTP, HUS, and thrombocytopenia in post stem cell transplant patients with GVHD
- Recommendation to measure K⁺, platelets frequently.

2. Phase 4 safety reports:

- Quarterly detailed reports of the occurrence of thrombotic or microangiopathic events including TTP, HUS or PE should be filed with the Division.

In summary, posaconazole is a relatively well tolerated azole with some of the same safety concerns as other members of the azole class and some unique safety issues. Overall the potential benefits of this agent in the reduction of invasive fungal infections in severely immunocompromised patients outweigh its potential risks.

9.2. Recommendation on Regulatory Action

The Division and the Medical Officer recommend that posaconazole in a dose of 200mg given by oral suspension three times daily be used in the prevention of invasive fungal infection (IFI) due to *Aspergillus* and *Candida* in patients with severe immunocompromise such as post stem cell transplant patients with graft versus host disease (GVHD) or patients with hematologic malignancies with prolonged neutropenia be approved. The duration of therapy will depend upon the length of time the patient remains at risk for IFI. However, the safety of this dose used as prophylaxis for IFI has been assessed for up to 4 months only.

9.2.1 Risk Management Activity

The Division has requested quarterly detailed reports of all patients with thrombotic or microangiopathic events such as TTP, HUS, or PE, etc. for 3 years.

9.2.2 Required Phase 4 Commitments

The Division requests that a study be performed to look at low levels of posaconazole absorption and clinical outcome using different dosing strategies and the potential benefit of TDM.

The Division has requested quarterly detailed reports of all patients with thrombotic or microangiopathic events such as TTP, HUS, or PE, etc. for 3 years.

9.2.3 Other Phase 4 Requests

Utilization including indication where known biannually for 3 years

9.3 Labeling Review-see inclusion of final negotiated label in the Appendix

9.4 Comments to Applicant

Please see Phase 4 and Risk Management above.

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10 APPENDICES

10.1 Review of Individual Study Reports-

Both study reports included in main part of review. Included here are the listing of Proven/Probable IFIs in each study referred to in the text of the review.

Table 92: Study C98-316: Listing of Patients with Proven/Probable IFI's During WOT (Treatment + 7 days)

Subject	IFI Phase	Trt. Arm	Pathogen	IFI Proven or Probable	Treatment Duration (Days)	Study Day of IFI Onset	Subject Disposition at EOT
C20/120	W, P	POS	Mould	Proven	4	9 (5)	Adverse Event
C25/030	W, P	POS	Candida glabrata	Proven	17	14	Treatment Failure
I66/618	W, P	POS	Trichosporon biegeleii	Proven	25	22	Treatment Failure
C30/079	W, P	POS	Aspergillus	Probable	45	26	Adverse Event
C15/137	W, P	POS	Pseudoallescheria boydii	Proven	29	31 (2)	Treatment Failure
I54/475	W, P	POS	Aspergillus	Probable	86	87 (1)	Adverse Event
C09/341	W, P	POS	Aspergillus	Probable	112	105	Completed
I44/600	W, P	FLU	Candida albicans	Proven	2	2	Adverse Event
I11/740	W, P	FLU	Aspergillus	Probable	11	14 (3)	Adverse Event
C51/538	W, P	FLU	Aspergillus	Proven	14	17 (3)	Adverse Event
I46/200	W, P	FLU	Aspergillus fumigatus	Probable	16	18 (2)	Adverse Event
C04/195	W, P	FLU	Aspergillus	Probable	14	18 (4)	Adverse Event
I28/785	W, P	FLU	Aspergillus	Probable	23	24 (1)	Treatment Failure
C35/205	W, P	FLU	Mould	Proven	28	28	Treatment Failure
C25/034	W, P	FLU	Aspergillus	Probable	57	28	Adverse Event
C31/279	W, P	FLU	Aspergillus fumigatus	Proven	27	31 (4)	Treatment Failure
I05/521	W, P	FLU	Candida glabrata	Proven	28	31 (3)	Treatment Failure
I02/868	W, P	FLU	Aspergillus	Probable	113	35	Completed
C46/260	W, P	FLU	Candida krusei	Proven	36	36	Treatment Failure
C12/014	W, P	FLU	Aspergillus fumigatus	Probable	37	37	Treatment Failure
C46/259	W, P	FLU	Aspergillus	Probable	39	38	Treatment Failure
I43/783	W, P	FLU	Aspergillus terreus	Probable	80	45	Treatment Failure
I19/033	W, P	FLU	Aspergillus fumigatus	Probable	58	57	Treatment Failure
C31/280	W, P	FLU	Aspergillus flavus	Proven	56	58 (2)	Treatment Failure
I45/440	W, P	FLU	Rhizomucor miehei	Proven	60	61 (1)	Treatment Failure
C12/006	W, P	FLU	Aspergillus flavus	Proven	85	85	Treatment Failure
C15/130	W, P	FLU	Aspergillus fumigatus	Proven	115	93	Adverse Event
C35/217	Pf	POS	Candida	Proven	0	(20)	Adverse Event

Subject	IFI Phase	Trt. Arm	Pathogen	IFI Proven or Probable	Treatment Duration (Days)	Study Day of IFI Onset	Subject Disposition at EOT
C15/672	P	POS	Aspergillus fumigatus	Proven	2	18 (16)	Adverse Event
I04/048	P	POS	Aspergillus	Probable	13	48 (35)	Adverse Event
C09/342	P	POS	Candida krusei	Proven	7	48 (41)	Adverse Event
I60/948	P	POS	Aspergillus fumigatus	Proven	42	62 (20)	Treatment Failure
C25/022	P	POS	Candida glabrata	Proven	33	75 (42)	Adverse Event
I21/301	P	POS	Aspergillus	Probable	66	78 (42)	Non-compliance with protocol
I71/953	P	POS	Scedosporium prolificans	Proven	14	80 (66)	Adverse Event
C43/516	P	POS	Mould	Proven	4	104 (100)	Subject did not wish to continue
I05/535	P	FLU	Aspergillus	Probable	14	23 (9)	Adverse Event
I12/076	P	FLU	Candida parapsilosis	Proven	7	30 (23)	Adverse Event
I35/495	P	FLU	Aspergillus	Probable	6	57 (51)	Subject did not wish to continue
C19/340	P	FLU	Aspergillus	Probable	32	79 (47)	Adverse Event
C16/083	P	FLU	Aspergillus niger	Proven	20	79 (59)	Adverse Event
I12/071	P	FLU	Aspergillus	Probable	45	80 (35)	Adverse Event
C35/220	P	FLU	Aspergillus flavus	Proven	26	84 (58)	Adverse Event
I15/807	W e	FLU	Aspergillus fumigatus	Proven	114	113	Treatment Failure
C35/211	W e	FLU	Aspergillus	Proven	125	129 (4)	Completed
C12/664	T	POS	Aspergillus	Probable	72	119 (47)	Adverse Event
C17/639	T	POS	Candida	Proven	122	132 (10)	Completed
C35/207	T	POS	Candida glabrata	Proven	138	165 (27)	Completed
C50/419	T	POS	Aspergillus	Probable	114	173 (59)	Completed
I54/474	T	FLU	Aspergillus	Probable	39	117 (78)	Non-compliance with protocol
I71/367	T	FLU	Aspergillus fumigatus	Probable	76	118 (42)	Treatment Failure
C12/009	T	FLU	Aspergillus fumigatus	Proven	47	120 (73)	Treatment Failure
C43/517	T	FLU	Aspergillus fumigatus, Aspergillus niger	Probable	110	132 (22)	Completed
I43/766	T	FLU	Candida	Proven	112	135 (23)	Completed
C12/002	T	FLU	Candida glabrata	Proven	116	143 (27)	Treatment Failure; Proven Aspergillus on Autopsy (Day 182). Probable Aspergillus on Day 116
C3/458	T	FLU	Aspergillus	Probable	1	144 (143)	Non-compliance with protocol
I20/009	T	FLU	Aspergillus	Probable	113	145 (32)	Completed
I66/617	T	FLU	Aspergillus fumigatus	Probable	112	161 (49)	Completed
C43/520	T	FLU	Candida glabrata	Proven	113	168 (55)	Completed
C42/497	T	FLU	Candida glabrata	Proven	114	172 (58)	Completed

C12/662 T FLU Aspergillus fumigatus Probable 107 179 (72) Completed

Table 93: Study P01899-Listing Of Patients with Proven/Probable IFI in the Oral Treatment Phase (oral therapy + 7 days)

Subject	Treatment Arm	Pathogen	IFI Proven or Probable	Treatment Duration (Days)	Study Day of IFI Onset
41/1329	POS	Candida tropicalis	Proven	5	1
57/1492	POS	Candida glabrata	Proven	12	11
15/1415	POS	Candida glabrata	Proven	48	44
2/1271	POS	Pneumocystis cariniic	Proven	45	51 (6)
10/1371	POS	Mould	Probable	9	12 (2)
54/1468	POS	Aspergillus sp.	Probable	92	44
15/1239	POS	Aspergillus sp.	Probable	54	54
50/1155	FLU	Rhizopus arrhizus	Proven	6	6
148/1248	FLU	Candida krusei Candida parapsilosis	Proven Proven	12	12 14 (1)
57/1498	FLU	Pseudallescheria boydii	Proven	12	17 (4)
74/1493	FLU	Candida glabrata	Proven	27	30 (2)
3/1284	FLU	Aspergillus sp.	Proven	52	53 (1)
2/1211	FLU	Aspergillus sp.	Probable	5	6 (1)
2/1103	FLU	Aspergillus sp.	Probable	12	8
3/1563	FLU	Aspergillus sp.	Probable	3	9 (5)
8/1352	FLU	Aspergillus sp.	Probable	12	9
102/1342	FLU	Aspergillus flavus	Probable	20	10
41/1510	FLU	Aspergillus sp.	Probable	10	11 (1)
41/1242	FLU	Aspergillus flavus	Probable	18	12
41/1215	FLU	Aspergillus sp.	Probable	16	13
68/1560	FLU	Aspergillus sp.	Probable	12	14 (1)
139/1081	FLU	Aspergillus sp.	Probable	12	14 (1)
41/1461	FLU	Aspergillus sp.	Probable	20	15
2/1307	FLU	Aspergillus sp.	Probable	10	16 (5)
2/1045	FLU	Aspergillus fumigatus	Probable	37	35
79/1380	FLU	Aspergillus sp.	Probable	82	82
15/1517	ITZ	Aspergillus sp.	Probable	7	9
10/1425	ITZ	Aspergillus sp.	Probable	9	11
15/1279	ITZ	Aspergillus sp.	Probable	17	17
84/1179	ITZ	Pneumocystis cariniic	Probable	16	18 (1)
96/1146	ITZ	Aspergillus fumigatus	Probable	19	19
125/1109	ITZ	Aspergillus sp.	Probable	96	21

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