



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

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A Randomized Open-Label Trial of Posaconazole Versus Micafungin for Prophylaxis Against Invasive Fungal Infections During Neutropenia in Patients Undergoing Chemotherapy for Acute Myelogenous Leukemia, Acute Lymphocytic Leukemia, or Myelodysplastic Syndrome

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Genovefa Papanicolaou, MD	Medicine/Infectious Disease
Co-Principal Investigator(s)/Department:	Rana Kaplan , MD	Medicine/Pulmonary
Investigator(s)/Department:	Ellin Berman, MD Renier Brentjens, MD, PhD Ross Levine, MD Peter Maslak, MD David Scheinberg, MD, PhD Virginia Klimek, MD Martin Tallman, MD Jae Park, MD Dan Douer, MD Susan Seo, MD Mini Kamboj, MD Ying Taur, MD Kent Sepkowitz, MD Monika Shah, MD Katherine Panageas, DrPh Omar Abdel-Wahab, MD Stephen Chung, MD Marco Davila, MD Joo Yeon Lee, MD	Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Infectious Disease Medicine/ Infectious Disease Medicine/ Infectious Disease Medicine/ Infectious Disease Medicine/ Infectious Disease Biostatistics Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Infectious Disease
Consenting Professional(s)/Department:	Genovefa Papanicolaou, MD Ellin Berman, MD Renier Brentjens, MD, PhD Ross Levine, MD Peter Maslak, MD David Scheinberg, MD, PhD Virginia Klimek, MD Martin Tallman, MD Jae Park, MD Dan Douer, MD Susan Seo, MD Mini Kamboj, MD Ying Taur, MD Kent Sepkowitz, MD Monika Shah, MD Elizabeth Halton, NP Omar Abdel-Wahab, MD Stephen Chung, MD Marco Davila, MD Christina Baldwin, NP Jamila N. Brutus, NP Hilda Quintanilla, NP Gaelle Senatus, NP Michelle G. Turner, NP Joo Yeon Lee, MD	Medicine/Infect. Dis Medicine/Leukemia Medicine/Leukemia Medicine/Leukemia Medicine/Leukemia Medicine/Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Infectious Disease Medicine/ Infectious Disease Medicine/ Infectious Disease Medicine/ Infectious Disease Medicine/ Infectious Disease Medicine/Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Leukemia Medicine/ Infectious Disease

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065



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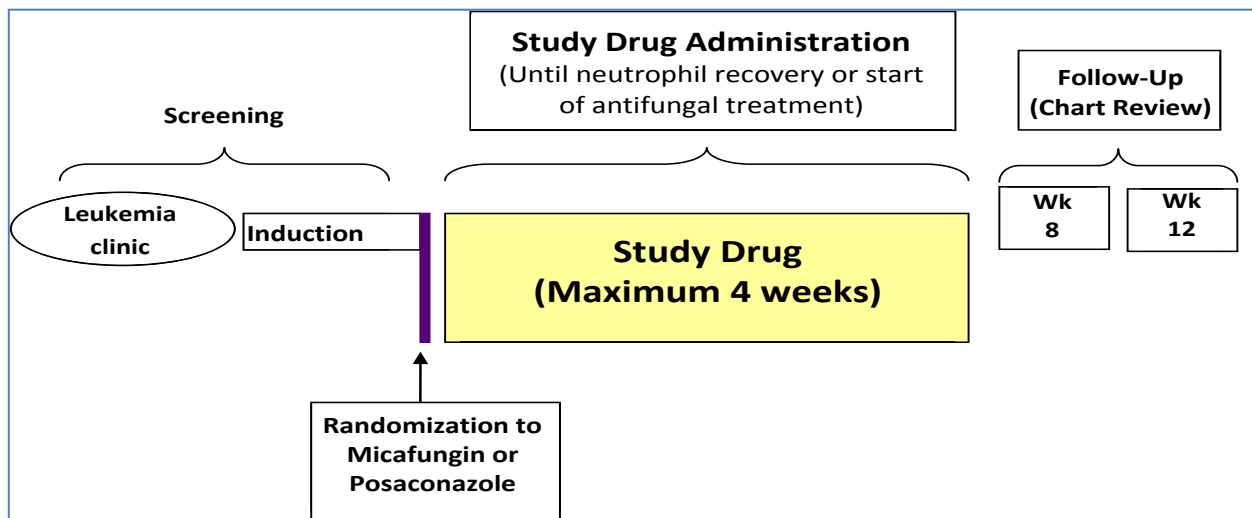
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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Background: Induction chemotherapy for acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) is associated with a high risk of invasive fungal infection due to *Candida* and *Aspergillus* species. Posaconazole, an oral broad spectrum azole, is currently approved for chemoprophylaxis during induction chemotherapy. Posaconazole is available only as oral formulation and requires food intake for optimal absorption thus limiting its utility in patients unable to tolerate oral intake. Micafungin, an echinocandin with antifungal activity against *Candida* and *Aspergillus* species is approved for the prevention of invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Micafungin is available as intravenous formulation and has an excellent safety profile. Micafungin has not been evaluated as prophylaxis against fungal infection in patients undergoing induction chemotherapy for AML/ALL/MDS. We hypothesize that micafungin would be a safe and effective alternative to posaconazole as antifungal prophylaxis in patients at high risk for invasive fungal infections due to neutropenia after induction chemotherapy for AML/ALL/MDS.

Proposed Study design: This is a single-center, open-labeled, randomized, controlled trial. One hundred and fourteen patients undergoing induction chemotherapy for newly diagnosed acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), myelodysplastic syndrome (MDS) or re-induction chemotherapy for first relapse of AML at MSKCC will be randomized 1:1 to receive micafungin 100mg IV daily or posaconazole 400 mg orally 2 times a day. Patients will be stratified by stage of disease ie newly diagnosed AML/ALL/MDS or AML in first relapse. Prophylaxis will start 24-48 hours after the last dose of chemotherapy and will be continued until neutrophil recovery (ANC>500/mm³ on 2 consecutive days) or maximum of 4 weeks. If the patients develop suspected or proven fungal infection the study drug will be discontinued and patients will receive antifungal treatment with AmBisome according to the standards of care at MSKCC. The patients will be followed up through chart review for a total of 12 weeks to assess survival and if applicable outcome of fungal infection.

A schema of the study design is shown below:





2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary

- To compare rates of clinical failure between patients who receive posaconazole and those who receive micafungin at 4 weeks from randomization.

Clinical failure is defined as: 1) need for systemic antifungal therapy (AmBisome) for > 3 consecutive days for presumptive fungal infection, toxicity or intolerance of study medication or 2) death.

Secondary

- To compare the number of days on study drug between patients who receive posaconazole and patients who receive micafungin. The maximum number of days on study drug is 28 days (4 weeks).
- To compare the incidence of possible, probable or proven IFI between patients who receive posaconazole and those who receive micafungin during treatment phase at 4 weeks from start of study drug.
- To compare the incidence of possible, probable or proven IFI between patients who receive posaconazole and those who receive micafungin at 12 weeks from randomization.
- To compare the rates of discontinuation of study medication for any reason between patients who receive posaconazole and those who receive micafungin.
- To compare overall survival rates at 6 weeks (12 weeks) from randomization between the two treatment arms.

3.0 BACKGROUND AND RATIONALE

Invasive fungal infections (IFI) are a significant cause of morbidity and mortality in patients with hematologic malignancies. Of all hematologic malignancies, patients with AML appear to be at greatest risk for an IFI. In a large autopsy series [1], 42% of all IFIs were identified in patients with AML and 77% of all IFIs were believed to have contributed to the cause of death. Yet, in almost 75% of cases, the IFI was not diagnosed antemortem. Upon review of almost 12,000 patients with hematologic malignancies from 18 centers in Italy during 1999-2003, IFI were most commonly seen in patients with AML (69% of all proven or probable IFIs identified) [2]. Even more striking was that greater than 12% of all patients with AML had a proven or probable IFI. Among the 3,012 patients with AML, the attributable mortality from Aspergillosis and Candidiasis was 35-40% [2]. Such infections were most commonly seen in patients receiving initial chemotherapy to treat active hematologic malignancies rather than in those having been treated with multiple rounds of myelosuppressive chemotherapy. The true incidence of IFIs in AML is probably underestimated due to our inability to establish the diagnosis of by the percentage of patients with a “proven” or “probable” Mortality rates for candidiasis and aspergillosis in high risk patients such as those with AML and MDS range between 10-49% and 32-87% respectively [3-4].

Several trials have evaluated the utility of antifungal prophylaxis in patients undergoing induction chemotherapy. Winston et al conducted a prospective-randomized double blinded placebo-controlled study in 256 patients 124 of which received fluconazole and 132 of whom received placebo. Fluconazole prophylaxis prevented fungal colonization and superficial fungal infections caused by



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most *Candida* species. Significantly fewer patients who received fluconazole experienced a proven fungal infection. There was no significant difference between the groups in the overall incidence of IFI, use of empiric therapy or in overall mortality [5]. Based on these results, fluconazole prophylaxis has been used in patients undergoing remission-induction chemotherapy for acute leukemia, even though advantages with respect to morbidity or mortality have not been proved and there was no consensus among clinicians regarding its use in these high-risk patients [6].

Morgenstern et al conducted a prospective-randomized open labeled study in 445 neutropenic patients with leukemia 227 of which received fluconazole 218 of whom received itraconazole. Itraconazole and fluconazole were equally effective in preventing IFI. Itraconazole was more effective in preventing aspergillosis. Fewer patients receiving itraconazole received empiric amphotericin B compared with patients receiving fluconazole. There was a higher incidence of withdrawal caused by side-effects in patients receiving itraconazole [7].

Although the use of itraconazole seemed to reduce the incidence of proven invasive fungal infections [8] it did not confer a significant survival benefit over fluconazole in large trials, and has been associated with greater toxicity [5, 9].

Mattiuzzi et al conducted a prospective-randomized open labeled study in 200 neutropenic patients with acute leukemia 92 of which received itraconazole IV and 108 of whom received Caspofungin. Prophylaxis with caspofungin appeared to be as effective and tolerable as prophylaxis with IV itraconazole. No statistically significant differences in treatment-related adverse events were noted [10]. This study suggests that the echinocandins may be a suitable alternative to the azoles for prophylaxis in high risk patients with leukemia.

Most recently, Cornely and colleagues conducted a randomized, multicenter, open-label, non-inferiority study to assess the efficacy of posaconazole versus standard triazole therapy for prophylaxis of IFIs in 602 high-risk, neutropenic patients with AML/MDS in which 304 patients were randomly assigned to receive posaconazole, and 298 patients were randomly assigned to receive fluconazole or itraconazole. Patients received posaconazole 200 mg oral suspension three times daily or standard triazole therapy (fluconazole 400 mg orally daily or itraconazole 200 mg oral solution twice daily) with each chemotherapy cycle. The study agents were administered until patients were no longer neutropenic or until the occurrence of an IFI, up to 84 days after randomization. The primary endpoint was the occurrence of proven or probable IFI during the treatment phase (from randomization until 7 days after last dose of study drug). Probable or proven IFIs occurred in 2% of posaconazole treated patients and 8% of fluconazole- or itraconazole-treated patients ($P = 0.0009$). All-cause mortality rates were lower in the posaconazole group than in the standard triazole therapy group (16% vs 22%, $P = 0.048$). In summary, posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival. There were more serious adverse events possibly or probably related to treatment in the posaconazole group [11]. A patient's ability to swallow is rarely compromised immediately after induction chemotherapy, but oral intake may decrease owing to mucositis later in the course of treatment. The study was therefore limited in its ability to provide data on the usefulness of azole prophylaxis in patients who have severe mucositis and are unable to eat or take oral medication.

Micafungin is an echinocandin with antifungal activity against *Candida* and *Aspergillus* species and *Pneumocystis carinii* [12-13]. Micafungin is given intravenously thus achieving reliable serum levels in patients unable to tolerate oral intake. A randomized, double-blind study compared micafungin to fluconazole for prophylaxis against invasive fungal infections in 882 neutropenic stem-cell transplant recipients [14]. Patients were treated with either fluconazole or micafungin during the period of neutropenia or up to a maximum of 42 days after transplant. Successful prophylaxis (absence of a



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proven, probable or suspected IFI) was documented in 80.7% of patients receiving micafungin compared to 73.7% of those receiving fluconazole (absolute difference 7%, 95% confidence interval 1.5-12.5%). Overall, 4.2% of micafungin-treated patients died during the study period compared to 5.7% of fluconazole-treated (p=NS). Micafungin is the first echinocandin approved for prophylaxis.

A smaller study performed in Japan suggested that pre-emptive IFI treatment with micafungin was safe and effective [15]. A multinational, non-comparative study utilizing an open-label design examined the efficacy of micafungin alone or in combination with another systemic antifungal agent as primary or salvage therapy for proven or probable (pulmonary only) *Aspergillus* species infection in a wide variety of patient populations. Micafungin proved efficacious and safe in high-risk patients with IA, although patient numbers were small in the micafungin-only groups [16].

Based on its excellent safety profile and pharmacology, micafungin is promising as an alternative to posaconazole as antifungal prophylaxis in patients with AML/MDS. We propose a randomized, open label, single center clinical trial to compare micafungin with posaconazole for prevention of invasive fungal infections during neutropenia in patients with AML/ MDS who are undergoing induction chemotherapy.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single institution (MSKCC), randomized, open-label comparative trial of micafungin and posaconazole administered as prophylaxis against fungal infections during neutropenia following induction chemotherapy for AML/ALL/MDS. One hundred and fourteen patients will be randomized 1:1 on either treatment arm. See schema in section 1.

4.2 Intervention

Patients will be randomized to one of two arms:

1. Micafungin 100 mg intravenously once daily.

or

2. Posaconazole 400 mg orally twice daily.

Randomized treatment will be initiated 24-48 h after completion of the last dose of chemotherapy.

Patients will receive the assigned treatment until the earliest of any of the following:

- Reach absolute neutrophil count (ANC) of ≥ 500 cells/mm³ for 2 consecutive days;
- Completion of 4 weeks on study drug
- Proven , probable, or suspected invasive fungal infection;
- Unacceptable drug toxicity;



- Adverse event requiring discontinuation;
- Death;
- Withdrawal from study participation (patient's decision);
- Clinically documented mucositis or colitis precluding the administration of oral medication or nutritional supplement is considered intolerance to posaconazole since it posaconazole is administered orally.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1. MICAFUNGIN

5.1.1. Overview

Micafungin (Mycamine[®], Astellas) is an echinocandin antifungal with activity against a broad range of yeast and mold, including fluconazole-susceptible and fluconazole-resistant *Candida*, *Aspergillus spp.* including species resistant to amphotericin and others [17-20]. The primary mechanism of action is the inhibition of 1,3- β -D-glucan synthase, an enzyme utilized in the synthesis of 1,3- β -D-glucan. Glucan comprises 30–60% of the cell wall of *Candida* and a lesser percentage of the cell wall of *Aspergillus* and is an excellent target for antifungal activity as mammalian cells lack cell walls. There is little human toxicity attributed to the mechanism of action, because glucan polymers are not components of mammalian cells.

In time-kill studies, micafungin demonstrates fungicidal activity against *C. albicans*, *C. krusei*, *C. parapsilosis*, and *C. glabrata* at multiples of the MIC [19]. In animal studies, micafungin demonstrates dose- and concentration-dependent fungicidal activity in reducing tissue burdens of *Candida* in rabbits treated over an eight-fold dosage range and in the mouse thigh model of *Candida* infection. The effect of echinocandins on tissue burden of *Candida* and *Aspergillus* differs: *Candida* may be completely eradicated from tissue, while *Aspergillus* tends to persist, perhaps because echinocandins work on the branch points and advancing tips of hyphae, while other cells of the hyphal structure may remain viable. These differences in pharmacologic effects may indicate that echinocandins will be more effective for prophylaxis against, rather than treatment of, aspergillosis.

5.1.2. Pharmacokinetics

The pharmacokinetic parameters of micafungin were assessed in healthy subjects and in adult and pediatric patient populations [21-23]. Micafungin is not appreciably absorbed when administered orally. In adults and children >2 years of age, steady-state plasma concentrations are achieved by day 4 with repeated dosing. Pharmacokinetic parameters indicate dose proportionality for doses up to 50 mg (adults) and 1 mg/kg (children) [24]. Plasma concentrations of micafungin are well described by a linear 2-compartment model with first-order input. The volume of distribution is approximately 0.2 L/kg, and total protein binding of micafungin is at least 99%.

5.1.3. Indications and usage

Micafungin is FDA-approved for the:

- Treatment of patients with candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses.



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- Treatment of patients with esophageal candidiasis
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

Micafungin is the first echinocandin approved for prophylaxis.

5.1.4. Formulation and labeling

Vials contain 50mg of sterile micafungin. The diluent to be used for reconstitution and dilution is 0.9% sodium chloride injection, USP (without a bacteriostatic agent). Alternatively, 5% Dextrose Injection, USP, may be used for reconstitution and dilution of micafungin.

5mL of 0.9% sodium chloride injection, USP, should be added to a 50mg vial of micafungin to yield a preparation containing approximately 10mg/mL. Reconstituted micafungin should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. To minimize excessive foaming, gently dissolve the micafungin powder by swirling the vial and do not vigorously shake. The diluted solution should be protected from light and further diluted in 100ml normal saline for injection before administration. It is not necessary to cover the infusion drip chamber or the tubing.

5.1.5. Adverse effects

- Micafungin has been studied in over 3500 subjects in 41 clinical trials and is found to have a safety profile comparable to fluconazole.
- Clinically supported details regarding the safety profile of micafungin can be found at: <http://www.mycamine.com/about/intro.php>

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with micafungin. Elevations in BUN and creatinine have also been reported. In controlled trials, the incidence of drug-related renal adverse events was 0.4% for micafungin and 0.5% for fluconazole. Similarly, the incidence of transaminitis or hepatic dysfunction did not differ between micafungin and fluconazole. Isolated cases of significant hemolysis have been reported in patients treated with micafungin. In a study of micafungin among stem cell transplant recipients, the only adverse events noted in >2% of patients were nausea (2.6%), diarrhea (3.1%) and hyperbilirubinemia (2.4%).

Micafungin is pregnancy category C and is found in the milk of lactating, drug-treated rats. No cases of micafungin overdosage have been reported. Repeated daily doses of up to 8mg/kg (max 896mg) in adult patients have been administered in clinical trials with no reported dose-limiting toxicity.

5.1.6. Drug-drug interactions

Micafungin is metabolized to M-1 (catechol form) by arylsulfatase, with further metabolism to M-2 (methoxy form) by catechol-O-methyltransferase. Hydroxylation by CYP enzymes is not a major pathway for micafungin metabolism *in vivo* and micafungin is neither a substrate nor inhibitor of P-glycoprotein *in vitro*. Fecal excretion is the major route of elimination. No dose adjustment of micafungin is required based on gender or race.



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Eleven drug-drug interaction studies were conducted in healthy controls to evaluate the potential for micafungin to interact with other medications [22, 24]. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed. Intravenous doses of micafungin 100 mg were unchanged during co-administration in healthy subjects.

5.1.7. Dosage and administration of micafungin

All patients will receive micafungin 100mg intravenously daily (see Section 9). Each dose should be infused over 1 hour to minimize infusion-related histamine reactions.

5.1.8. Dose adjustments

No dose adjustments will be made during the course of the trial without an IRB-approved, protocol deviation.

5.2. POSACONAZOLE

5.2.1. Overview

Posaconazole (NOXAFIL® Schering Corporation, Kenilworth, NJ) is a triazole antifungal with a broad spectrum of antifungal activity including emerging fungi such as the zygomycetes.

Like the other triazole antifungals, posaconazole inhibits the fungal enzyme lanosterol 14-alpha-demethylase (3–5). A reduction in this enzyme causes a decrease in fungal ergosterol synthesis, which is vital for the formation of fungal cell walls. The cell wall abnormalities result in either cell death or blunted cell growth.

Posaconazole has shown in vitro fungistatic and fungicidal activity against *Candida* species (2–5, 16–21). Posaconazole has shown potent in vitro activity against *Aspergillus* species (3–5, 22, 23). A global surveillance program evaluated the in vitro activity of the triazole antifungals and AmB against *Aspergillus* species and other filamentous fungi. This surveillance program found that both posaconazole and voriconazole inhibited 94% of all *Aspergillus* isolates tested. Another study found that posaconazole, voriconazole, and caspofungin inhibited 98%, 95%, and 98% of *Aspergillus* isolates tested, respectively. Posaconazole, voriconazole, and caspofungin are more potent than AmB against *A. fumigatus*.

5.2.2. Pharmacokinetics

Posaconazole is available as a suspension for oral administration. The pharmacokinetic properties of posaconazole are listed on table 1.

Table 1. Pharmacokinetic properties of triazole antifungals*

Property	Posaconazole	Voriconazole	Fluconazole	itraconazole
Bioavailability	Variable	>95%	>90%	50%–75%
Protein binding	>90%	58%	11%	99%
Volume of distribution	1774 L	4.6 L/kg	0.7–0.8 L/kg	11 L/kg
Time to maximum concentration	4–5 hours	1–2 hours	2–4 hours	4–5 hours
Metabolism	Hepatic: glucuronidation to inactive metabolites	Hepatic: CYP2C19, 2C9, 3A4	Hepatic: 11% metabolized	Hepatic: CYP3A4
Elimination half-life	25–35 hours	6–24 hours (variable)	22–31 hours	35–64 hours
Elimination route	<1% excreted unchanged in urine; 66% excreted unchanged in feces	Hepatic; <2% excreted unchanged in urine	80% excreted unchanged in urine	Hepatic; <1% excreted unchanged in urine



Absorption

Posaconazole is absorbed with a median T_{max} of ~3 to 5 hours. Dose proportional increases in plasma exposure (AUC) to posaconazole were observed following single oral doses from 50 mg to 800 mg and following multiple-dose administration from 50 mg BID to 400 mg BID. No further increases in exposure were observed when the dose was increased from 400 mg BID to 600 mg BID in febrile neutropenic patients or those with refractory invasive fungal infections. Steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration.

Following single-dose administration of 200 mg, the mean AUC and C_{max} of posaconazole are approximately 3 times higher when administered with a nonfat meal and approximately 4 times higher when administered with a high-fat meal (~50 gm fat) relative to the fasted state. Following single-dose administration of 400 mg, the mean AUC and C_{max} of posaconazole are approximately 3 times higher when administered with a liquid nutritional supplement (14 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.

Courtney and colleagues conducted a randomized, open-label, crossover, single-dose study in 20 adult men to evaluate the effect of food on the bioavailability of two formulations of posaconazole [25].

Subjects were given posaconazole 200 mg as suspension with a high-fat breakfast, as suspension with a nonfat breakfast, or as tablets with a high-fat breakfast after a 10-hour fast. Drug exposure was greater, as shown by an increase in the area under the curve (AUC) of 37%, when posaconazole was given in suspension rather than tablet form. Mean AUC and maximum concentrations (C_{max}) were four times greater when posaconazole was administered with a high-fat meal than when it was administered after a fast. Drug exposure was 2.6 times greater when posaconazole was given with a nonfat meal than when it was given after a fast. The authors concluded that posaconazole suspension administered with food is the optimal regimen to ensure maximal systemic exposure.

Sansone-Parsons and colleagues conducted a randomized, open-label, crossover study in 24 adults to determine the effect of a nutritional supplement on the pharmacokinetics of posaconazole [26]. Study participants received a single dose of posaconazole 400 mg oral suspension either along with 8 ounces of a nutritional supplement (Boost Plus) or after fasting overnight. The C_{max} and AUC values were higher in subjects who received posaconazole concomitantly with the nutritional supplement. The time to achieve C_{max} and the half-life were not different between groups. The authors concluded that the bioavailability of posaconazole is increased when given with a nutritional supplement.

Based on these studies, it is recommended that posaconazole be administered with food or a nutritional supplement whenever possible [22, 27-29]. If a patient cannot be fed, posaconazole should be divided into multiple daily doses (every 6 hours), and the use of alternative antifungal agents should be considered.

Ezzet and colleagues conducted a randomized, open-label, crossover study in 18 healthy men to determine the bioavailability of posaconazole when given without food [30]. Subjects were given the following doses of posaconazole suspension after fasting for 12 hours: 800 mg once a day (regimen A), 400 mg every 12 hours (regimen B), or 200 mg every 6 hours (regimen C). Subjects continued to fast for 48 hours after the dose was given. The study found that the bioavailability of posaconazole oral suspension increased by 98% when the dose was divided every 12 hours and increased by 220% when the dose was divided every 6 hours in fasting subjects. This was roughly equivalent to



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posaconazole exposure after a nonfat meal. The authors concluded that divided daily dose administration (either every 12 or 6 hours) increases exposure to posaconazole under fasting conditions.

Distribution

Posaconazole has an apparent volume of distribution of 1774 L, suggesting extensive extravascular distribution and penetration into the body tissues.

Posaconazole is highly protein bound (>98%), predominantly to albumin.

Metabolism

Posaconazole primarily circulates as the parent compound in plasma. Of the circulating metabolites, the majority are glucuronide conjugates formed via UDP glucuronidation (phase 2 enzymes). Posaconazole does not have any major circulating oxidative (CYP450 mediated) metabolites. The excreted metabolites in urine and feces account for ~17% of the administered radiolabeled dose.

5.2.3. Indications and usage

Posaconazole (NOXAFIL[®]) is approved by the Food and Drug Administration for use as prophylaxis against invasive *Aspergillus* and *Candida* infections in immunocompromised patients including patients undergoing hematopoietic stem cell transplantation who have graft-versus-host disease and patients with hematological malignancies who are receiving chemotherapy. Posaconazole is also approved for the treatment of oropharyngeal candidiasis including candidiasis Refractory to itraconazole and/or fluconazole [29].

Dose and duration of therapy for each indication are summarized below:

Indication	Dose and duration
Prophylaxis of Invasive Fungal Infections	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.
Oropharyngeal Candidiasis	Loading dose of 100 mg (2.5 mL) twice a day on the first day, then 100 mg (2.5 mL) once a day for 13 days.
Oropharyngeal Candidiasis Refractory to itraconazole and/or fluconazole	400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response.

5.2.4. Formulation and labeling

Posaconazole is supplied as a 40-mg/mL oral suspension in 4-ounce amber bottles (3). Each dose of posaconazole should be given with a full meal or liquid nutritional supplement to enhance absorption. If a patient cannot tolerate feedings, alternative antifungals should be considered.



5.2.5. Adverse events

Raad and associates collected the overall long-term safety data of posaconazole in 428 patients with IFIs and 66 patients with fever and neutropenia [31-32]. Overall, treatment-related adverse effects were reported in 38% of patients. The most common adverse drug effects reported were nausea (8%) and vomiting (6%). Treatment-related prolongation of the corrected QT interval (QTc) occurred in 1% of patients, and 2% of patients had elevated hepatic enzymes. Overall, the long-term safety of posaconazole of six months or longer revealed a favorable adverse-effect profile in seriously ill immunocompromised patients.

In clinical reports, the tolerability of posaconazole was acceptable and comparable to other triazoles. [11] Common adverse events included fever, nausea, vomiting, diarrhea, abdominal pain, dry mouth, headache, and fatigue. Some of the less common but more notable events reported with posaconazole administration included hypokalemia, rash, anemia, thrombo -cytopenia, and QTc prolongation.

In clinical trials, there were infrequent cases of hepatic reactions (e.g., mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis). Rarely, more severe hepatic reactions including cholestasis or hepatic failure including fatalities were reported in patients with serious underlying medical conditions (e.g., hematologic malignancies) during treatment with posaconazole. Liver function tests should be monitored at the start of and during the course of therapy.

5.2.6. Drug interactions

Posaconazole has been shown to interact with several medications, including drugs that suppress the immune system, and these reactions may be serious [29].

Co-administration with sirolimus or ergot alkaloids is contraindicated. Co-administration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine, or quinidine, is also contraindicated since this may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes.

Serious and rare fatal toxicity from cyclosporine has occurred when taken in combination with Posaconazole and therefore reduction of the dose of drugs like cyclosporine or tacrolimus and frequent monitoring of drug levels of these medications are necessary when taking them in combination with Posaconazole

5.2.7. Dosage and administration

All patients will receive posaconazole 400mg twice daily. Each dose will be administered with a carbonated beverage or high fat nutritional supplement as tolerated to maximize absorption.

5.2.8. Dose adjustments

No dose adjustments will be made during the course of the trial without an IRB-approved, protocol modification.



6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Subjects of greater than or equal to 18 years of age of either sex and of any race.
2. Disease definition:
 - a. Anticipated or documented prolonged neutropenia ($ANC < 500/mm^3$ [$0.5 \times 10^9/L$]) at baseline or likely to develop within 3 to 5 days and lasting for at least 7 days due to:
 - i. Intensive induction chemotherapy for new diagnosis of acute myelogenous leukemia, acute lymphocytic leukemia or myelodysplastic syndrome receiving standard anthracycline based chemotherapy
 - ii. Re-induction of acute myelogenous or lymphocytic leukemia after primary relapse
 - iii. Myelodysplastic syndromes requiring induction (myelosuppressive) chemotherapy
3. Female subjects of childbearing potential must have a negative serum pregnancy test as per MSKCC guidelines.
4. Able to swallow oral medications

6.2 Subject Exclusion Criteria

1. Subjects with history of presumed or proven invasive fungal infection within 30 days of randomization.
2. Subjects who are taking the following:
 - a. Drugs known to interact with posaconazole and that may lead 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);
 - b. Drugs known to lower the serum concentration/efficacy of posaconazole: cimetidine, rifampin, carbamazepine, phenytoin, rifabutin, barbiturates, and isoniazid at entry or within 24 hours before entry;
 - c. Subjects who are planned to receive $>2mg$ flat dose of vinca alkaloids.
3. Subjects with a history of hypersensitivity or idiosyncratic reactions to azole agents.
4. Subjects with renal insufficiency (estimated creatinine clearance less than 20 mL/minute at baseline or likely to require dialysis during the study).
5. Subjects having an electrocardiogram with a prolonged QTc interval by manual reading: QTc greater than 490 msec.



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6. Subjects with moderate or severe liver dysfunction at baseline, defined as aspartate aminotransferase, alanine aminotransferase, 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.
7. Subjects who are undergoing re-induction chemotherapy and have participated in this study during their first induction chemotherapy.
8. Subjects who will be receiving dasatinib.

7.0 RECRUITMENT PLAN

7.1. Recruitment

Candidates for the study will be identified at the outpatient Leukemia Clinic during the evaluation visit prior to admission or upon admission for induction Chemotherapy. The RSA and the PI or co-PI will attend the weekly Leukemia scheduling meeting and keep track of upcoming admissions. Patients may sign consent for the study during their outpatient visit or upon admission to the hospital for induction chemotherapy. An estimated 7-10 patients per month are admitted to undergo induction or re-induction chemotherapy. We estimate to accrue 2-3 patients per month. We estimate to complete the study in 4 years.

8.0 PRETREATMENT EVALUATION

Baseline Study Procedures

The assessments noted below are usually conducted as part of the patient routine care prior to induction chemotherapy.

- History, physical examination, weight, height, vital signs performed within 7 days prior to randomization.
- For women of childbearing potential: serum pregnancy test as per MSKCC guidelines.
- Blood tests within 7 days from randomization
 - Hematology: complete blood count with manual differential and platelet count
 - Serum chemistry: creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, chloride, calcium, magnesium, and albumin
 - Fungal markers testing (including serum Galactomannan, BD glucan and 3 ml of whole blood to be stored for nucleic acid based assays).
- Prior CT scan of the chest (at the discretion of the investigator).
- Baseline EKG prior to chemotherapy as per MSKCC guidelines.

A flowchart of study procedures and assessments is provided on Section 10.



9.0 TREATMENT/INTERVENTION PLAN

9.1 Treatment Plan

After signing informed consent patients will be randomized to micafungin or posaconazole. The randomization will be performed by the Office of Clinical Research Protocol Participant Registration through the Clinical Research Database.

Micafungin will start one day after completing induction chemotherapy and will be administered at approximately the same time each day of treatment. Micafungin will be administered as per MSKCC guidelines.

Posaconazole will start one day after completing induction chemotherapy and will be administered at approximately the same times each day of treatment. Ten ml of Posaconazole solution (40mg/mL) will be administered orally twice daily with fatty snack or a nutritional supplement or a carbonated beverage (such as ginger ale).

The study drug will continue for maximum of 4 weeks or until an absolute neutrophil count of $>500/\text{mm}^3$ for 2 consecutive days, systemic antifungal therapy (AmBisome) for >3 consecutive days, toxicity requiring discontinuation, or death whichever occurs first.

If the patient develops clinically suspected or documented fungal infection the study drug will be discontinued and the patient will start antifungal therapy with AmBisome as per MSKCC guidelines. The evaluations to establish diagnosis of fungal infection are outlined in section 10.

9.2 Toxicity

The study drug will be discontinued if any of the following toxicities occur AND are thought by the PI to be related to the study drug.

- Hepatic toxicity: ALT or AST exceeding 5 times the upper limit of normal or 3x above baseline.
- Cutaneous toxicity: A skin rash can occasionally occur. This ordinarily will not constitute grounds for discontinuation of study drug unless there is skin necrosis or ulceration or generalized exfoliative dermatitis.
- Cardiac toxicity: If a significant arrhythmia or prolongation of QT occurs, study medication must be held, and the subject must undergo further assessment by a cardiologist to evaluate the significance of the findings. If the PI and cardiologist conclude that it is not related to the study drug, study drug can be resumed. Otherwise, the patient will be withdrawn from study treatment. Routine EKG monitoring is not part of the standard of care for patients on posaconazole. EKGs will be obtained at the discretion of the treating physician when clinically indicated or when the patient requires additional medications known to cause QT prolongation alone or given concomitantly with posaconazole (for example quinolones or macrolides).



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- Renal insufficiency: The patient experiences serious renal impairment ($GFR < 25$) or requires hemodialysis
- For any other Grade III or IV toxicity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 which is not typically expected post induction chemotherapy and may be possibly related to study drug.

If the PI thinks that toxicity is unlikely due to the study drug it is permissible to have up to 3 days interruption of study drug interruption while the cause of toxicity is being investigated. During study drug interruption patient will receive AmBisome 3mg/kg IV daily. If the same toxicity recurs after the patient resumes the study drug the primary end point of clinical failure is met and the study drug will be discontinued.

There will be no dose adjustment of study medications for toxicity.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Day 1 through Week 4

The following assessments will be performed bi-weekly on two non-consecutive days, preferably three days apart (e.g., Mondays and Thursdays). A flowchart of study procedures and assessments is provided in section 10.

1. Administration of antifungal medications
2. Vital signs: body temperature, blood pressure, body weight, and pulse rate. Interim history and directed physical exam. The physical exam should focus on organs systems that are clinically relevant in the setting of invasive fungal infections.
3. Adverse event recording
4. Blood tests
 - Hematology: complete blood count with differential and platelet count
 - Serum chemistry: creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, chloride, calcium, magnesium, and albumin
 - 10 ml of blood will be collected for fungal markers including galactomannan assay and BD glucan as part of routine care. Blood will be collected until patient is discharged or Week 6, whichever occurs first.
 - 10 ml of whole blood will collected in EDTA anticoagulated tube to be stored for future testing for fungal pathogens by nucleic acid based assays. De-identified specimens will be sent to Viracor Inc for fungal PCR. Due to the exploratory nature of the assays the results of the fungal PCR will not be made available for clinical decision making. Blood will be collected until patient is discharged or Week 6, whichever occurs first.
5. Weekly fungal surveillance cultures will be obtained specifically for the study: Stool and throat fungal cultures will be obtained weekly starting on day 1 prior to starting study drug.



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Additional stool and throat specimens will be obtained within 24 hours of discontinuation of study drug due to suspected or proven fungal infection. Fungal cultures will be processed at the clinical microbiology laboratory. Fungal isolates will be stored until completion of the study. We will assess changes in fungal colonization during study drug exposure. We will also study antifungal susceptibility patterns over time and correlate the fungal susceptibilities of isolates causing colonization with any isolates causing invasive infection. Surveillance cultures will be collected until discharge or Week 6, whichever comes first.

6. Patients with persistent fever (≥ 96 hours) on broad spectrum antibiotics and/or signs or symptoms suggestive of fungal infection will have CAT SCAN of the chest as part of the standards of care for the evaluation of neutropenic patients. CAT scans of the abdomen/pelvis, head or sinuses will be obtained if clinically indicated at the discretion of the treating physician
7. If the CAT SCAN of the chest is suggestive of an infectious process it is strongly encouraged the patient undergoes bronchoscopy with bronchoalveolar lavage unless there is a clinical contraindication documented by the treating physician.
8. BAL specimens will be sent for:
 - Bacterial and Fungal cultures
 - Cytology
 - Galactomannan
 - Nucleic acid based assays for fungal pathogens. Leftover BAL specimens will be sent to Viracor for fungal PCR and will also be tested for fungal DNA by the MSK Clinical Microbiology Laboratory using the Luminex platform.
9. Patients with persistent fever (>96 hours) on broad spectrum antibiotics and/or signs or symptoms suggestive of fungal infection will have fungal marker testing by serum galactomannan and BD glucan and 3-5 ml of whole blood collected in an EDTA anticoagulated tube and stored for future testing for fungal pathogens by nucleic acid base assay.
10. Patients randomized to posaconazole will have the posaconazole serum concentration measured on day 7, day 14 and day 28 if they remain on posaconazole or at discontinuation of posaconazole if this occurs earlier.

Week 5 - Week 12 (± 7 Days)

A chart review will be done on weeks 6, 8, 10 and 12.

We will record:

- Survival status
- Diagnostic or therapeutic procedures performed for diagnosis or treatment of fungal infection.
- Outcome of suspected or documented fungal infections including:
 - Systemic antifungals type dose and duration.



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- Radiologic assessments
- Microbiology assessment
- Pathology reports
- The investigator's overall assessment of fungal infections based on MSG/EORTC criteria listed in Appendix 1

One tube of blood (5ml) will be collected once during weeks 5-12 for research purposes.



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FLOW CHART OF STUDY PROCEDURES

	Screening ¹	Day 1	Week 1	Week2	Week 3	Week 4	Week 5	Week 6	Weeks 7-12
			Day 7 ±2 days	Day 14 ±2 days	Day 21 ±2 days	Day 28 ±3 days	Day 35 ±2 day	Day 42 ±2 day	±5 days
Informed consent	X								
History/physical	X								X
Vital signs	X	X	X	X	X	X			
Administer study drug		X	X	X	X	X			
Interim history and Directed Exam		X	X	X	X	X			
EKG	X								
Hematology ²	X	X	X	x	x	X	X	X	X
Chemistry ²	X	X	X	x	x	X	X	X	X
Fungal Markers ²		X	X	X	X	X	X	X	
Serum Pregnancy test	X								
CAT scan of chest ³	X		X	X	X	X			
Bronchoscopy ⁴									
Bronchoalveolar lavage testing ⁵									
Posaconazole concentration ⁶			X	X		X			
AE Assessment ⁷			X	X	X	X			X
Follow up ⁸									X
Surveillance fungal cultures ⁹		X	X	X	X	X	X	X	
Blood collection for SNPs									X



- ¹ Informed consent may be obtained up to 3 weeks prior to randomization. History/physical, EKG, hematology, chemistry and serum pregnancy test (as needed) may be obtained within 7 days prior to randomization
- ² Assessments will be performed biweekly during weeks 1-6 on two non-consecutive days preferably 3 days apart. 10 ml of serum will be collected for galactomannan and BD glucan testing. 3-5 ml of whole blood will be collected in an EDTA anticoagulated tube and stored for future testing by nucleic acid-based assays on a biweekly basis until Week 6 or discharge, whichever occurs first.
- ³ During weeks 1-4, the initial CAT scan of the chest will be performed will be performed for persistent fever (≥ 96 hours) on broad spectrum antibiotics or when clinically suspected fungal infection and thereafter as per standards of care at MSKCC.
- ⁴ It is strongly encouraged for patients with persistent fever for ≥ 96 hours or signs of fungal infection to undergo bronchoscopy and bronchoalveolar lavage (BAL) unless there is clinical contraindication. De-identified left over BAL specimens will be sent to Luminex to perform nucleic acid based assays for fungal pathogens.
- ⁵ BAL will be tested for routine bacterial and fungal cultures, viral cultures, AFB cultures and cytology, galactomannan concentration. Results from these tests will be available for clinical decision making. Left over BAL specimens will be tested for Aspergillus by an exploratory nucleic acid-based assay (NASBA). On the day of BAL, serum will be collected for galactomannan testing and 3ml of blood will be collected in an EDTA anticoagulated tube for future testing by NASBA.
- ⁶ For patients randomized to posaconazole.
- ⁷ Key adverse events will be recorded through 3 days after the last dose of study drug.
- ⁸ Follow up will be done through medical chart review. We will review medical assessments, laboratory, radiology and pathology results during week 5-12.
- ⁹ Throat and stool cultures will be obtained weekly specifically for the study. Fungal isolates will be stored until further testing. We will study changes in fungal colonization and fungal susceptibility profile overtime. This will be obtained for research purposes and will be collected on a weekly basis until Week 6 or discharge, whichever occurs first.
- ¹⁰ One tube (5 ml) of blood will be collected once during weeks 5-12 for research purposes. Blood will be stored for future testing of genetic polymorphisms of Dectin-1.

11.0 TOXICITIES/SIDE EFFECTS

Micafungin and posaconazole are currently FDA approved. Both drugs have been used in thousands of immunocompromised patients with very favorable safety profiles.



11.1. Micafungin

- Micafungin has been studied in over 3500 subjects in 41 clinical trials and is found to have a safety profile comparable to fluconazole.
- Clinically supported details regarding the safety profile of micafungin can be found at: <http://www.mycamine.com/about/intro.php>

Likely

- Vomiting
- Nausea
- Headache
- Diarrhea

These side effects disappear after stopping the medication

Less Likely

- Fever
- Abnormal liver function tests
- Phlebitis (redness, swelling and pain at the vein used to infuse mycamine)

These side effects disappear after stopping the medication

Rare but serious

- Anaphylaxis (A life-threatening allergic reaction that presents with difficulty breathing, low blood pressure and throat and face swelling)

11.2. Posaconazole

Likely

- Nausea
- Diarrhea
- Vomiting
- Rash
- Fever
- Abdominal Pain
- Headache
- Fatigue



These side effects disappear after stopping the medication

Less Likely

- Abnormal EKG (QT/QTc prolongation)
- Inflammation of the liver

Usually these side-effects disappear after stopping the medication

Rare but serious

- Liver failure
- Life-threatening arrhythmias(torsades de points)

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The principal outcome measure is “clinical success,” which is the absence of clinical failure. “Clinical failure” is defined as:

1. Systemic antifungal therapy with AmBisome for > 3 consecutive days due to any of the following:

- Suspected fungal infection defined as: fevers (temperature, $\geq 38^{\circ}\text{C}$ [$\geq 100.4^{\circ}\text{F}$]) persisting for >96 h during the neutropenic phase, despite broad-spectrum antibacterial therapy and exhaustive diagnostic evaluation has excluded other etiologies but has also failed to demonstrate a probable or proven invasive fungal infection
- Probable pulmonary aspergillosis
- Proven invasive or disseminated infection.
- For patients randomized to posaconazole clinically documented colitis precluding administration of oral medications and or nutritional supplements required for absorptions of posaconazole.
- Adverse event requiring discontinuation of study drug.

2. Death



13.0 CRITERIA FOR REMOVAL FROM STUDY

In accordance with the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and the US FDA Regulations, a patient has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The Investigator also has the right to withdraw patients from the study (see below). Should a patient (or a patient's legally authorized representative) decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

A complete final evaluation will be made at the time of the patient's withdrawal with an explanation of why the patient is withdrawing, and an attempt should be made to perform a follow-up evaluation.

Patients may be removed from study if one or more of the following events occur:

- Significant noncompliance on the part of the patient
- Refusal of the patient to continue treatment or observations
- Unacceptable toxicity
- Progressive disease that in the Investigator's opinion would interfere with the interpretation of results from the study
- Decision by the Investigator that termination is in the patient's best medical interest
- Unrelated medical illness or complication
- Lost to follow-up.

14.0 BIOSTATISTICS

This is a single center randomized open label trial to compare micafungin to posaconazole for prevention of fungal infection in high risk patients treated for acute leukemia or myelodysplastic syndrome at MSKCC. Target accrual is 114 patients (57 patients per treatment arm. We anticipate accrual of approximately 2-3 patients per month and hence accrual should be completed in 4 years.

The primary objectives of the trial are to compare the rates of clinical failure between the two treatment arms. Clinical failure is defined as any of the following: systemic antifungal therapy for >3 days, drug discontinuation due to an adverse event or death. We will compare time from start of prophylaxis to need for systemic therapy in the two arms using a log-rank.

On the basis of the prior multicenter, randomized prophylactic trial of posaconazole the rate of clinical failure for posaconazole is estimated at 40-50%. Patients who receive > 1 dose of study drug will be included in the intent to treat analyses. Randomized patients who receive ≤ 1 dose of study drug will be marked as non-evaluable and will be replaced.

With 57 patients per arm, the trial is powered to detect absolute differences of approximately 25% (e.g., 15% versus 40% in proportion of clinical failure in the two groups with approximately 80% power and a significance level of 5% using a two-tailed test. A stratified chi-square test will be used to compare the two groups (stage of disease ie newly diagnosed AML/ALL/MDS or AML in first relapse. Due to the low event rates for secondary endpoints such as proven infection, rate of discontinuation, and toxicity, rates will be estimated by treatment arm. Comparisons between arms will be performed if numbers permit. If many patients die before the landmark time a then a cumulative incidence function will be utilized to estimate the rates at 6 and 12 weeks. The number and proportion of clinically successful patients will be computed per treatment along with a 95% confidence interval. Overall survival will be estimated via Kaplan-Meier methodology. All patients will be followed for a minimum of 12 weeks and survival rates at 12 weeks will be compared between the two treatment arms using Fishers exact test.



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15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (<http://ppr/>). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

After eligibility is established and immediately after consent is obtained and a patient number is assigned patients will be registered and randomized using the Clinical Research Database (CRDB). Patients will be 1:1 randomized to the two arms. Randomization will be accomplished by the method of random permuted block and stratified by stage of disease ie newly diagnosed AML/MDS or AML in first relapse.

16.0 DATA MANAGEMENT ISSUES

This is a single institution trial and all patients will be treated at Memorial Sloan-Kettering Cancer Center. A Research Study Assistant (RSA) will be assigned to this study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data manager will also monitor laboratory compliance throughout the study. Laboratory data will be tabulated and summarized based on MSKCC normal ranges.

The data collected for this study will be entered into the MSKCC Clinical Research Data Base (CRDB).

16.1 Quality Assurance

Registration reports will be generated by the RSA on a regular basis to monitor patient accruals and completeness of the registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Memorial Sloan-Kettering Cancer Center (MSKCC) has established standard procedures for data safety monitoring of clinical research (see Data and Safety Monitoring Plans).



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16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) plans at MSKCC were approved by the National Cancer Institute (NCI) in September 2001. The plans address the new policies set forth by NCI in the document titled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at:

<http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:
<http://mskweb2.mskcc.org/irb/index.htm>.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (i.e. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Consent process: Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC IRB guidelines.

Benefits: It is known that posaconazole and micafungin are effective in preventing fungal infections in immunocompromised patients.

Protocol Amendments and Study Termination: All protocol amendments will be reviewed and approved by the Institutional Review Board of Memorial Hospital before implementation.

Incentives: No incentives will be offered to patient/subjects for participation in this study. Participation is voluntary.

Costs: Micafungin will be provided by Astellas and will be free of charge to the patients. Posaconazole will be billed to the patient. Patients and/or their health care plan will need to pay for all of the costs of treatments in this study. All evaluations to be done before initiation of treatment and during the treatment are part of our standard evaluation for patients with AML/MDS

Eligibility Exceptions: There will be no exceptions to the eligibility requirements for this protocol without the authorization of the Institutional Review Board of Memorial Hospital.

Adverse Reporting Requirements: Severe or unexpected adverse reactions will be reported to Genovefa Papanicolaou, MD., principal investigator at MSKCC and the MSKCC IRB.

Inclusion of Children in Research: . Posaconazole is not approved for children 13 years of age. The protocol does not include children.

Inclusion of women and minorities: Memorial Sloan-Kettering Cancer Center has filed form HHS 441 (re: Civil Rights), form HHS 641 (handicapped Individuals), and form 639-A (re: Sex Discrimination). In selecting patients for study in the projects proposed in this protocol, we have taken due notice of NIH/ADAMHA policies concerning inclusion of women and



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minorities in clinical research populations. We expect that the study population will be fully representative of the range of patients seen at Memorial Hospital without exclusion as to age, gender, or ethnic background.

Alternatives to the Planned Study: Alternative treatment options include receiving standard antifungal prophylaxis with posaconazole or participation in other investigational studies. If relevant, other investigational options will also be outlined.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's names or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors from MSKCC or the NCI etc.), and appropriate personnel may review patient records as required.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE



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- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
 - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. The report will be forwarded to the FDA by the Institutional SAE Manager through the IND Office.

17.2.1

Toxicities will be reported using NCI's Common Terminology Criteria for Adverse Events Version 4.0.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.



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19.0 REFERENCES

1. Chamilos, G., et al., *Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989-2003)*. Haematologica, 2006. 91(7): p. 986-9.
2. Pagano, L., et al., *The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study*. Haematologica, 2006. 91(8): p. 1068-75.
3. Cornely, O.A., *Aspergillus to Zygomycetes: causes, risk factors, prevention, and treatment of invasive fungal infections*. Infection, 2008. 36(4): p. 296-313.
4. Lin, S.J., J. Schranz, and S.M. Teutsch, *Aspergillosis case-fatality rate: systematic review of the literature*. Clin Infect Dis, 2001. 32(3): p. 358-66.
5. Winston, D.J., et al., *Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial*. Ann Intern Med, 2003. 138(9): p. 705-13.
6. Kanda, Y., et al., *Prophylactic action of oral fluconazole against fungal infection in neutropenic patients. A meta-analysis of 16 randomized, controlled trials*. Cancer, 2000. 89(7): p. 1611-25.
7. Morgenstern, G.R., et al., *A randomized controlled trial of itraconazole versus fluconazole for the prevention of fungal infections in patients with haematological malignancies*. U.K. Multicentre Antifungal Prophylaxis Study Group. Br J Haematol, 1999. 105(4): p. 901-11.
8. Glasmacher, A., et al., *Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients*. J Clin Oncol, 2003. 21(24): p. 4615-26.
9. Marr, K.A., et al., *Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants*. Blood, 2004. 103(4): p. 1527-33.
10. Mattiuzzi, G.N., et al., *Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies*. Antimicrob Agents Chemother, 2006. 50(1): p. 143-7.
11. Cornely, O.A., et al., *Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia*. N Engl J Med, 2007. 356(4): p. 348-59.
12. Petraitis, V., et al., *Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits*. Antimicrob Agents Chemother, 2002. 46(6): p. 1857-69.
13. Walsh, T.J., *Echinocandins--an advance in the primary treatment of invasive candidiasis*. N Engl J Med, 2002. 347(25): p. 2070-2.
14. van Burik, J.A., et al., *Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation*. Clin Infect Dis, 2004. 39(10): p. 1407-16.
15. Toubai, T., et al., *Efficacy and safety of micafungin in febrile neutropenic patients treated for hematological malignancies*. Intern Med, 2007. 46(1): p. 3-9.
16. Denning, D.W., et al., *Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis*. J Infect, 2006. 53(5): p. 337-49.
17. Cada, D.J., T. Levien, and D.E. Baker, *Micafungin sodium*. Hosp Pharm 2005. 40: p. 693-703.
18. Denning, D.W., *Echinocandin antifungal drugs*. Lancet, 2003. 362(9390): p. 1142-51.
19. Espinel-Ingroff, A., *In vitro antifungal activities of anidulafungin and micafungin, licensed*



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IRB#: 10-038 A(17)

- agents and the investigational triazole posaconazole as determined by NCCLS methods for 12,052 fungal isolates: review of the literature. *Rev Iberoam Micol*, 2003. 20(4): p. 121-36.
20. Wiederhold, N.P. and R.E. Lewis, *The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy*. *Expert Opin Investig Drugs*, 2003. 12(8): p. 1313-33.
21. Hiemenz, J., et al., *Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant*. *Antimicrob Agents Chemother*, 2005. 49(4): p. 1331-6.
22. <http://www.astellas.us/docs/mycamine.pdf>.
23. Seibel, N.L., et al., *Safety, tolerability, and pharmacokinetics of Micafungin (FK463) in febrile neutropenic pediatric patients*. *Antimicrob Agents Chemother*, 2005. 49(8): p. 3317-24.
24. Theuretzbacher, U., *Pharmacokinetics/pharmacodynamics of echinocandins*. *Eur J Clin Microbiol Infect Dis*, 2004. 23(11): p. 805-12.
25. Courtney, R., et al., *Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults*. *Br J Clin Pharmacol*, 2004. 57(2): p. 218-22.
26. Sansone-Parsons, A., et al., *Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers*. *Antimicrob Agents Chemother*, 2006. 50(5): p. 1881-3.
27. Herbrecht, R., *Posaconazole: a potent, extended-spectrum triazole anti-fungal for the treatment of serious fungal infections*. *Int J Clin Pract*, 2004. 58(6): p. 612-24.
28. Torres, H.A., et al., *Posaconazole: a broad-spectrum triazole antifungal*. *Lancet Infect Dis*, 2005. 5(12): p. 775-85.
29. *Noxafil (posaconazole) oral suspension [package insert]*. 2006, Schering Corp: Kenilworth, NJ.
30. Ezzet, F., et al., *Oral bioavailability of posaconazole in fasted healthy subjects: comparison between three regimens and basis for clinical dosage recommendations*. *Clin Pharmacokinet*, 2005. 44(2): p. 211-20.
31. Raad, II, et al., *Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections*. *Clin Infect Dis*, 2006. 42(12): p. 1726-34.
32. Raad, II, et al., *Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions*. *Clin Infect Dis*, 2006. 42(10): p. 1398-403.
33. Ascioglu, S., et al., *Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus*. *Clin Infect Dis*, 2002. 34(1): p. 7-14.

20.0 APPENDICES

Appendix 1. MSG/EORTC definitions of possible, probable and proven invasive fungal infections.