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Protocol Page

A Phase II study of isavuconazole prophylaxis in adult patients with AML/MDS and neutropenia
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Core Protocol Information

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A phase II study of isavuconazole prophylaxis in adult patients with AML and neutropenia

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1. BACKGROUND AND RATIONALE

1.1 Acute Myeloid Leukemia (AML)

In 2015, it is estimated that there will be 20,830 new cases of AML in the US and an estimated 10,460 deaths. Intensive induction chemotherapy followed by appropriate post-remission therapy (repeated cycles of consolidation chemotherapy or allogeneic hematopoietic cell transplantation, allo-HCT) remains the cornerstone of therapy for patients eligible for such an approach.[1] Although no new agents have been approved for the treatment of AML, treatment outcomes have steadily improved over the last several decades.[2] Much of the improvement can be attributed to improvements in supportive care to carry patients through the inevitable period of severe pancytopenia caused by effective treatment.[3] Nevertheless, a recent analysis of Surveillance, Epidemiology and End Results (SEER) data has reported an early mortality rate (EMR) of 26.7%, much higher than the 12.2% EMR reported in a retrospective analysis of five Southwest Oncology Group clinical trials.[4] Although about 60-85% of young adults (<60 years of age) with AML will achieve complete remission (CR) with current intensive induction chemotherapy regimens, only about 35-40% will be cured.[1] The outlook is considerably more bleak for elderly patients, of whom approximately 40% to 60% will achieve remission, but only 5-15% will be cured.[1] In large, multi-institutional trials, 30-day mortality in adults up to 60 years of age after anthracycline-cytarabine induction chemotherapy for AML has ranged from 5-10%,[5, 6] and a trial in older patients reported a 30-day mortality rate of 11-12%.[7] Both 30- and 60-day mortality have remained in the 5-10% range irrespective of the use of two- or three-drug induction regimens in trials enrolling mostly younger patients.[8, 9] However, in a recent phase III trial[10] in patients with secondary AML, the majority of whom were ≥60 years of age, the 30- and 60-day mortality rates were 13% and 21%, respectively, despite a daunorubicin dose of only 45 mg/m^2/d. In this context, it is important to note that the median age at diagnosis of AML is now 72 years.[11] The increased EMR in population-based studies of unselected patients compared to that in carefully controlled clinical trials is attributable to the selection of patients with few comorbidities for clinical trials and the greater expertise, number of therapeutic options and closer follow-up available at highly specialized centers where such trials are usually conducted.[4]

1.2 Invasive fungal infections (IFIs) in AML patients and the need for effective prophylaxis

Invasive fungal infections (IFIs) are common in patients with AML and represent a major cause of infectious morbidity and mortality,[12-15] particularly aspergillosis[16, 17] and fusariosis,[18] as well as other mold infections, e.g., mucormycosis.[19] Additionally, rates of IFIs are anti-leukemic regimen-related, being especially high for three-drug regimens incorporating high-dose cytarabine.[20] IFIs often lead to dose-reductions and delays in the administration of potentially life-saving chemotherapy.[21] Importantly, the epidemiology of IFIs in leukemia patients is a "moving target" that continues to evolve.[22, 23] For example, the selection pressure of fluconazole prophylaxis and the longer survival of patients in a persistently neutropenic state secondary to better control of bacterial and *Candida* infections have led to

the emergence of invasive mold infections, particularly invasive aspergillosis (IA).[22, 24] Meta-analyses and systematic reviews of randomized controlled trials (RCTs) have consistently shown that the use of anti-fungal prophylaxis, particularly with mold-active agents, reduces IFI risk, IFI-related mortality and all-cause mortality (in some studies).[25-27] For these reasons, current international practice guidelines recommend the use of an anti-mold agent, rather than fluconazole, for antifungal prophylaxis during remission induction therapy.[28] However, the extensive use of these agents over the last several years may have contributed to an increased incidence of infections with difficult-to-treat opportunistic molds such as fungi of the order Mucorales, *Fusarium* and *Scedosporium*, in the face of declining mortality from IA, emphasizing the dynamic nature of IFI epidemiology.[22]

1.3 Choice of prophylactic antifungal agent

The ideal prophylactic antifungal agent is one that is safe and well-tolerated with long-term use, effective against a wide spectrum of organisms, and manufactured in intravenous (IV) and oral forms with good bioavailability.[23] Multiple clinical trials using various formulations have established that amphotericin B (AMB) is too toxic and no more effective than fluconazole for antifungal prophylaxis during AML induction therapy,[29-31] and while aerosolized preparations are better tolerated, they are not standardized for delivery to the alveoli and not recommended in this setting.[23]

Fluconazole is available both IV and orally and has excellent activity against *Candida albicans*, but most candidiasis in the setting of AML is now caused by resistant non-*albicans* species, and the drug has no activity against molds.[22, 23] In placebo-controlled studies, fluconazole was shown to reduce IFI incidence and IFI-attributable mortality in both the AML induction and HCT settings.[32, 33] Itraconazole has a broader spectrum of activity than fluconazole that includes *Aspergillus*, but is more toxic.[23] Taken together, the findings of multiple meta-analyses show that itraconazole is more effective than fluconazole in reducing the incidence of IFIs, without affecting IFI-attributable or all-cause mortality, at the cost of more adverse events (AEs) leading to drug discontinuation.[25, 26, 34, 35]

The echinocandins (caspofungin, micafungin, anidulafungin) have activity against *Candida* and *Aspergillus,* but not *Fusarium* or Mucorales, are only administered IV and have minimal drug-drug interactions (DDIs).[22, 23] Caspofungin has been compared to IV itraconazole as well as to "standard policy" regimens in the acute leukemia induction setting, and no significant differences in efficacy or safety were found.[36, 37] Micafungin was compared to fluconazole in a double-blind RCT in 882 adult and pediatric HCT recipients, and found to be superior as antifungal prophylaxis during the neutropenic phase following HCT.[38]

Voriconazole, considered the "gold standard" for the treatment of IA,[39] is available both IV and orally and is active against a broad range of fungi including *Candida*, *Aspergillus*, *Scedosporium* and *Fusarium* species.[23] Voriconazole has substantial DDIs, and its AE profile includes visual hallucinations, transient photopsia, cutaneous solar hypersensitivity, and transaminitis.[22, 23]

Retrospective studies from the MD Anderson Cancer Center (MDACC) have suggested the superiority of voriconazole and posaconazole over echinocandin prophylaxis in AML patients[40, 41]. The efficacy and safety of voriconazole as secondary prophylaxis of IFIs in allo-HCT recipients was shown in the prospective VOSIFI study[42], and studies from MDACC[43] and the Mayo Clinic[44] have documented the same in primary prophylaxis of IFIs in neutropenic patients with AML or myelodysplastic syndrome (MDS). However, the Mayo Clinic study was retrospective,[44] and the MDACC study,[43] which randomized patients to either IV voriconazole or IV itraconazole, did not reach its target accrual and did not find any significant differences in efficacy or safety. Voriconazole was superior to itraconazole as antifungal prophylaxis after alloHCT in an RCT (n=255), but only based on the ability to give it for significantly longer durations, with less need for other systemic antifungals.[45] A double-blind, placebo-controlled, phase III RCT of oral voriconazole in AML patients undergoing induction chemotherapy was halted prematurely due to ethical reasons.[46] With long-term use of voriconazole, some late toxicities have been described: peripheral neuropathy (PN, 9%),[47] fluoride excess and periostitis,[48] and non-melanoma skin cancer[49] in solid organ transplant recipients.

Posaconazole is a very broad-spectrum triazole antifungal with fewer DDIs than voriconazole and the major advantage of also having activity against several species of the Mucorales.[22, 23] In a large, phase III, multi-center trial in patients with AML/MDS and neutropenia, posaconazole prevented IFIs more effectively than physicians' choice of either fluconazole or itraconazole, and improved overall survival (OS)[50]. In an international, randomized, double-blind trial in allo-HCT recipients with severe graft-versus host disease (GVHD), posaconazole and fluconazole were equally effective in preventing IFIs, but posaconazole was superior in preventing IA and reducing the rate of IFI-related deaths.[51] These trials, conducted using an oral suspension of posaconazole, led to its approval by the FDA, but concerns remained regarding its erratic bioavailability, particularly in hospitalized patients with diarrhea, with sub-therapeutic drug levels being linked to breakthrough IFIs in AML patients.[23] Subsequently, posaconazole tablets, administered at a dose of 300 mg once daily, were shown to achieve the desired exposure target,[52] and the improved bioavailability of these delayed-release posaconazole tablets has been demonstrated to translate into a significantly higher proportion of patients achieving therapeutic serum levels as compared to those receiving the oral suspension.[53, 54] Furthermore, switching from posaconazole suspension to tablets has been demonstrated to increase serum drug levels in leukemia patients without clinically relevant hepatotoxicity.[55] Although of considerable utility in the era of posaconazole suspension use, therapeutic drug monitoring (TDM)[56] is not currently recommended in the context of posaconazole tablets.[23] However, patients experiencing diarrhea and those of higher body weight may be more likely to have lower levels.[57] The risk of treatment-emergent PN in patients treated long-term with posaconazole has been reported to be 3%.[47]

1.4 Isavuconazole/Isavuconazonium (Cresemba®): rationale for prophylactic use

Isavuconazole is a new, broad-spectrum triazole antifungal that has been approved by the FDA for the treatment of invasive aspergillosis and mucormycosis.[58] The drug is available both orally and IV as an

inactive prodrug, isavuconazonium sulfate, which is quickly broken down to the active component, isavuconazole and an inactive cleavage product.[58] Similar to other azoles, isavuconazole inhibits fungal cell growth and replication by inhibiting the synthesis of ergosterol, an integral component of the fungal cell wall membrane, via inhibition of lanosterol 14-α-demethylase (CYP51), leading to an accumulation of toxic 14-α-methylsterols and a depletion of membrane-associated ergosterol.[59] The side arm of the active drug orients the molecule so that the triazole ring engages the heme moiety at the bottom of the binding pocket in the fungal CYP51 protein, and confers broad spectrum anti-fungal activity.[60]

The FDA approval of isavuconazole was based on 2 phase III trials: SECURE,[61, 62] a randomized, double-blind, non-inferiority trial that compared it to voriconazole for primary treatment of IA and other invasive mold infections, and VITAL,[63] an open-label, non-comparative trial that evaluated isavuconazole for the treatment of IA in patients with renal impairment, and IFIs caused by rare molds, including members of the order Mucorales. In the SECURE trial, isavuconazole was similar to voriconazole in terms of both all-cause mortality and response rate;[61, 62] a matched case control analysis comparing the outcomes of 21 patients with invasive mucormycosis in the VITAL trial with those of 33 historical patients treated with amphotericin B showed comparable efficacy.[64] In a subset analysis of patients participating in the SECURE and VITAL trials, isavuconazole appeared promising for the treatment of *Fusarium* and *Scedosporium* infections.[65] The recommended dosing regimen for both the oral and IV formulations is a loading dose of 600 mg of isavuconazole, given as 200 mg (372 mg of isavuconazonium) every 8 hours, for 2 days followed by 200 mg daily thereafter.[66] A small study (n=20) of isavuconazole prophylaxis has been performed in patients with AML who had undergone chemotherapy and had pre-existing or expected neutropenia.[67] Headache and rash were the most common adverse events, and 18 of 20 patients were classified as having had treatment success. Either 200 mg or 400 mg daily was recommended as the prophylactic dose.[67] In a randomized, double-blind phase II trial that evaluated 3 different dosing strategies (200 mg on day 1 and then 50 mg once daily, 400 mg on day 1 and then 400 mg once weekly and 400 mg on day 1 and then 100 mg once daily) of isavuconazole in comparison to fluconazole (200 mg on day 1 and then 100 mg once daily) in immunocompromised patients with *Candida* esophagitis, all 3 isavuconazole regimens were well-tolerated and associated with high clinical cure rates, similar to those with fluconazole.[68] ACTIVE is a phase III RCT comparing the safety and efficacy of IV and oral isavuconazole with caspofungin followed by voriconazole for the treatment of candidemia and other invasive *Candida* infections.[59, 66] Whether therapeutic drug monitoring (TDM) of isavuconazole levels will be necessary or useful is not known with certainty at this time.[59, 60]

Isavuconazole has several attractive attributes that represent advantages over both voriconazole and posaconazole.[58, 60] The IV formulation is water-soluble, thus eliminating the need for a cyclodextrin vehicle and any resultant nephrotoxicity; it does not cause visual disturbances, hallucinations and photosensitivity, which are common adverse effects (AEs) of voriconazole; it is only a weak inhibitor of P-glycoprotein (P-gp), unlike posaconazole, a strong inhibitor contraindicated, for example, with IDH inhibitors, a class of drugs with great promise in AML;[69] it shortens, rather than prolongs, the QTc

interval, thereby potentially making it safer to use than other azoles with a broad range of tyrosine kinase inhibitors[70, 71] and other medications frequently used in patients with AML (e.g., levofloxacin, ondansetron) that prolong the QTc interval. Indeed, for a variety of reasons mostly related to DDIs, patients with AML are not able to receive optimal prophylactic therapy with broad spectrum anti-mold triazoles (i.e., voriconazole or posaconazole) and are placed on suboptimal prophylactic regimens, e.g., with echinocandins.

Given the broad spectrum of anti-fungal activity,[59, 60] excellent safety and oral bioavailability of isavuconazole, the availability of an IV preparation without nephrotoxic excipients, its improved DDI profile compared to voriconazole and posaconazole, and the shortening, rather than lengthening, of the QTc interval seen with this agent,[58, 60] investigation of its utility in the prophylactic setting in neutropenic patients with AML and other hematologic malignancies and in HCT recipients appears warranted.[23, 67]

2. DRUG INFORMATION

2.1 Product description

Isavuconazonium sulfate is a water-soluble prodrug consisting of a tetrazolium salt linked to an aminocarboxy moiety.[60] The empirical formula is $C_{35}H_{35}F_2N_8O_5S.HSO_4$. The prodrug is rapidly ($t_{1/2}$ <1 min) and almost completely (>98%) converted by plasma esterases after IV administration to the active moiety isavuconazole and an inactive prodrug cleavage product.[59, 60] Following oral administration, isavuconazonium sulfate undergoes chemical hydrolysis in the gastrointestinal lumen to isavuconazole.[59]

2.2 Storage and handling

Isavuconazonium sulfate capsules should be stored at 20°C to 25°C (68°F to 77°F) in the original packaging to protect from moisture. Excursions are permitted from 15°C to 30°C (59°F to 86°F).

Unreconstituted vials of isavuconazonium sulfate for injection should be stored at 2° to 8°C (36° to 46°F) in a refrigerator. Each vial is a single-dose vial of unpreserved sterile lyophile. Following reconstitution of the lyophile with water for injection USP, the reconstituted solution should be used immediately, or stored below 25°C for a maximum of 1 hour prior to preparation of the patient infusion solution. The prepared infusion solution should be kept for not more than 6 hours at room temperature [20°C to 25°C (68°F to 77°F)] or 24 hours at 2° to 8°C (36° to 46°F) prior to use. Isavuconazonium sulfate for injection vials are for single-dose use only.

2.3 How supplied

Isavuconazonium sulfate capsules are available in aluminum blister packs. Capsules are packaged in aluminum blister packs, seven (7) capsules per sheet with desiccant. Each capsule contains 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole). Capsules are opaque and elongated, and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with “766” in black ink.

Each single-dose vial of isavuconazonium sulfate for injection contains 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole). Isavuconazonium sulfate for injection is supplied in a single-dose vial as a sterile lyophilized white to yellow powder. Individually packaged vials are available for intravenous administration.

2.4 Route of administration and pharmacokinetics[59, 60, 66]

Isavuconazonium sulfate can be administered both IV and orally, and is quickly ($t_{1/2}$ <1 min) and almost completely (>98%) hydrolyzed by plasma esterases after IV administration to isavuconazole and an inactive cleavage product. Isavuconazole is well-absorbed after oral administration, within 2-3 hours. Its high oral bioavailability (98%) allows 1:1 dosage conversion from the IV formulation. The prodrug and the inactive cleavage product are not detected in plasma in significant concentrations after oral administration. After IV administration, the prodrug is undetectable in plasma by 1.25 hours from the start of the 1-hour infusion, and exposure (based on AUCs) to the prodrug is <1% of that to isavuconazole. There is no clinically significant effect of food on the AUC, $t_{1/2}$ or plasma concentration of isavuconazole at 24 hours.

Overall, the pharmacokinetics of isavuconazole are characterized by slow elimination (mean plasma $t_{1/2}$130 hours), low plasma clearance (~10% of hepatic blood flow), extensive tissue distribution, high volume of distribution (V_d, ~450 L), and high plasma protein binding (>99%), predominantly to serum albumin. Asians may have ~40% lower total clearance than Caucasians, and the peripheral V_d increases with body mass index and is greater in patients than in healthy volunteers. AUCs in elderly females may be 38% and 47% greater than in elderly males and younger females, respectively. However, no dose adjustments based on age, gender or race are recommended. Multiple-dose pharmacokinetic studies of oral and IV isavuconazole show dose-proportional increases in C_{max} and AUC, indicating linear kinetics.

Isovuconazole is mainly metabolized by CYP3A4, CYP3A5 and uridine diphosphate-glucoronosyltransferase (UGT). Renal excretion of isavuconazole itself is <1% of the dose administered, and the drug does not accumulate in patients with renal dysfunction. No dose adjustments are required, even in patients with end stage renal disease (ESRD). The high plasma protein binding precludes removal by hemodialysis. Penetration into cerebrospinal fluid (CSF) is likely to be low. The systemic clearance of isavuconazole is significantly decreased (40-48%) in patients with mild to moderate hepatic impairment (Child-Pugh classes A and B), with roughly a 64-84% increase in the AUC. However, no dose adjustment is recommended in these patients. Isavuconazonium sulfate has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

2.5 Availability

Isavuconazonium sulfate for this study will be provided by Astellas Pharma US, Inc.

2.6 Agent destruction and return

Unused/expired drug will be disposed of onsite according to institutional guidelines.

2.7 Contraindications

- Isavuconazonium sulfate is contraindicated in persons with known hypersensitivity to isavuconazole.

- Coadministration of strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (400 mg every 12 hours), with isavuconazonium sulfate is contraindicated because strong CYP3A4 inhibitors can significantly increase the plasma concentration of isavuconazole .

- Coadministration of strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates with isavuconazonium sulfate is contraindicated because strong CYP3A4 inducers can significantly decrease the plasma concentration of isavuconazole.

- Isavuconazonole shortens the QTc interval in a concentration-related manner, and is, therefore, contraindicated in patients with familial short QT syndrome.

2.8 Drug interactions[59, 60]

Isavuconazole is a sensitive substrate of CYP3A4 and co-administration with strong CYP3A4 inhibitors, e.g., ketoconazole or strong CYP3A4 inducers, e.g., rifampin, carbamazepine, St. John's wort or long-acting barbiturates is contraindicated. Caution is advised when isavuconazonium sulfate is coadministered with lopinavir/ritonavir.

Isavuconazole is a mild to moderate inhibitor of CYP3A4, and increases the AUCs of tacrolimus and sirolimus. TDM of cyclosporine, sirolimus, and tacrolimus levels is recommended during concomitant therapy with isavuconazonium sulfate.

A comprehensive listing of CYP3A4 inducers and inhibitors can be found here:
http://medicine.iupui.edu/clinpharm/ddis/

Isavuconazole is a mild inducer of CYP2B6, and reduces the systemic exposure of bupropion (dose increase of bupropion may be necessary but not above the maximum recommended dose); thus, co-administration of narrow therapeutic index CYP2B6 substrates such as efavirenz or cyclophosphamide should be cautious.

Isavuconazole is a mild inhibitor of P-gp, breast cancer resistance protein (BCRP), the human organic cation transporters 1 and 2 (OCT1/2), and human multi-drug and toxin extrusion (MATE1). It also has mild indirect inhibitory effects on substrates of UGT, such as mycophenolic acid. Co-administration with mycophenolate mofetil should be cautious and may require monitoring for mycophenolic acid toxicity. Co-administration of isavuconazole with drugs that are P-gp substrates and have a narrow

therapeutic window, e.g., digoxin, colchicine, dabigatran, may require dose adjustment, and monitoring of digoxin levels is recommended.

Co-administration with medications that alter gastric pH does not appear to affect the pharmacokinetics of isavuconazole.

No dose adjustments are recommended for warfarin, methadone, metformin, caffeine, repaglinide, omeprazole, methotrexate (although a 29% increase in levels of the metabolite 7-hydroxy-methotrexate is observed), dextromethorphan, midazolam (but dose reduction of midazolam should be considered as a 2.05-fold increase in AUC occurs), prednisone, atorvastatin (caution is advised due to a potential increase in atorvastatin exposure), or oral contraceptives containing ethinyl estradiol and norethindrone.

2.9 Warnings and Precautions

2.9.1 Hepatic adverse drug reactions

Hepatic adverse drug reactions (e.g., elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin) have been reported in clinical trials. The elevations in liver-related laboratory tests were generally reversible and did not require discontinuation of isavuconazonium sulfate. Cases of more severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with azole antifungal agents, including isavuconazonium sulfate.

Liver function tests should be performed at the start and during the course of isavuconazonium sulfate therapy. Patients who develop abnormal liver-related laboratory tests during isavuconazonium sulfate therapy should be monitored for the development of more severe hepatic injury. Isavuconazonium sulfate should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to the drug**.**

2.9.2 Infusion-related reactions

Infusion-related reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during IV administration of isavuconazonium sulfate. The infusion should be discontinued if these reactions occur.

2.9.3 Hypersensitivity reactions

Serious hypersensitivity and severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Isavuconazonium sulfate should be discontinued if a patient develops a severe cutaneous adverse reaction. There is no information regarding cross-sensitivity between isavuconazonium sulfate and other azole antifungal agents. Caution should be used when prescribing isavuconazonium sulfate to patients with hypersensitivity to other azoles.

2.9.4 Embryo-fetal toxicity

Isavuconazonium sulfate may cause fetal harm when administered to a pregnant woman and should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the fetus. Perinatal mortality was significantly increased in the offspring of pregnant rats dosed orally with isavuconazonium sulfate at 90 mg/kg/day (less than half the maintenance human dose based on area under the curve (AUC) comparisons) during pregnancy through the weaning period.

Isavuconazonium chloride administration was associated with dose-related increases in the incidences of rudimentary cervical ribs in rats and rabbits at 30 and 45 mg/kg, respectively, doses equivalent to about one fifth and one tenth of the clinical exposures based on AUC comparisons. In rats, dose-related increases in the incidences of zygomatic arch fusion and supernumerary ribs/rudimentary supernumerary ribs were also noted at 30 mg/kg and above, equivalent to one fifth the clinical dose based on AUC comparisons.

2.9.5 Drug particulates

Following dilution, isavuconazonium sulfate IV formulation may form precipitate from the insoluble isavuconazole. The drug, should, therefore, be administered through an in-line filter.

2.10 Adverse events

Selected Treatment-Emergent Adverse Reactions with Rates of 5% or Greater in Isavuconazonium Sulfate-treated Patients in the SECURE Trial

System Organ Class Preferred Term	Trial 1	
	CRESEMBA (N=257) n (%)	Voriconazole (N=259) n (%)
Gastrointestinal disorders		
Nausea	71 (27.6)	78 (30.1)
Vomiting	64 (24.9)	73 (28.2)
Diarrhea	61 (23.7)	60 (23.2)
Abdominal pain	43 (16.7)	59 (22.8)
Constipation	36 (14.0)	54 (20.8)
Dyspepsia	16 (6.2)	14 (5.4)
General disorders and administration site conditions		
Edema peripheral	39 (15.2)	46 (17.8)
Fatigue	27 (10.5)	18 (6.9)
Chest pain	23 (8.9)	16 (6.2)
Injection site reaction	16 (6.2)	4 (1.5)
Hepatobiliary disorders		
Elevated liver laboratory tests[a]	44 (17.1)	63 (24.3)
Metabolism and nutrition disorders		
Hypokalemia	49 (19.1)	58 (22.4)
Decreased appetite	22 (8.6)	28 (10.8)
Hypomagnesemia	14 (5.4)	27 (10.4)
Musculoskeletal and connective tissue disorders		
Back pain	26 (10.1)	19 (7.3)
Nervous system disorders		

Headache	43 (16.7)	
Psychiatric disorders		
Insomnia	27 (10.5)	25 (9.7)
Delirium[b]	22 (8.6)	30 (11.6)
Anxiety	21 (8.2)	18 (6.9)
Renal and urinary disorders		
Renal failure	26 (10.1)	21 (8.1)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	44 (17.1)	35 (13.5)
Acute respiratory failure	19 (7.4)	22 (8.5)
Skin and subcutaneous tissue disorders		
Rash	22 (8.6)	36 (13.9)
Pruritus	21 (8.2)	15 (5.8)
Vascular disorders		
Hypotension	21 (8.2)	28 (10.8)

[a] Elevated liver laboratory tests include reactions of increased alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, blood bilirubin, and gamma-glutamyltransferase.
[b] Delirium includes adverse reactions of agitation, confusional state, delirium, disorientation, and mental status changes.

The following adverse reactions occurred in less than 5% of all CRESEMBA-treated patients in Trial 1 or 2. The list does not include reactions presented in Table 2. This listing includes adverse reactions where a causal relationship to isavuconazole cannot be ruled out or those which may help the physician in managing the risks to the patients.

Blood and lymphatic system disorders: agranulocytosis, leukopenia, pancytopenia

Cardiac disorders: atrial fibrillation, atrial flutter, bradycardia, reduced QT interval on electrocardiogram, palpitations, supraventricular extrasystoles, supraventricular tachycardia, ventricular extrasystoles, cardiac arrest

Ear and labyrinth disorders: tinnitus, vertigo

Eye disorders: optic neuropathy

Gastrointestinal disorders: abdominal distension, gastritis, gingivitis, stomatitis

General disorders and administration site conditions: catheter thrombosis, malaise,

chills

Hepatobiliary disorders: cholecystitis, cholelithiasis, hepatitis, hepatomegaly, hepatic

failure

Immune system disorders: hypersensitivity

Injury, poisoning and procedural complications: fall

Metabolism and nutrition disorders: hypoalbuminemia, hypoglycemia, hyponatremia

Musculoskeletal and connective tissue disorders: myositis, bone pain, neck pain

Nervous system disorders: convulsion, dysgeusia, encephalopathy, hypoesthesia, migraine, peripheral neuropathy, paraesthesia, somnolence, stupor, syncope, tremor

Psychiatric disorders: confusion, hallucination, depression

Renal and urinary disorders: hematuria, proteinuria

Respiratory, thoracic and mediastinal disorders: bronchospasm, tachypnea

Skin and subcutaneous tissue disorders: alopecia, dermatitis, exfoliative dermatitis, erythema, petechiae, urticaria

Vascular disorders: thrombophlebitis

Laboratory effects
In the SECURE trial, elevated liver transaminases (alanine aminotransferase (ALT) or aspartate aminotransferase (AST)) >3 x the upper limit of normal (ULN) were reported at the end of study treatment in 4.4% of patients who received isavuconazonium sulfate. Elevations of liver transaminases >10 x ULN developed in 1.2% of patients who received isavuconazonium sulfate.

3. STUDY DESIGN

This is a single-arm, open-label, non-randomized, primary prophylaxis study with a target accrual of 100 patients.

4 OBJECTIVES AND ENDPOINTS

4.1 OBJECTIVES

4.1.1 Primary

4.1.1.1 To assess whether prophylaxis with isavuconazole effectively prevents the occurrence of proven or probable IFIs in patients with newly diagnosed AML/MDS receiving successive cycles of intensive chemotherapy or other therapies for up to 100 days from prophylaxis initiation.

4.1.2 Secondary

4.1.2.1 To evaluate the incidence of IA within 100 days of beginning isavuconazole prophylaxis in newly diagnosed patients with AML/MDS receiving intensive chemotherapy or other therapies.
4.1.2.2 To evaluate the incidence of other IFIs within 100 days of beginning isavuconazole prophylaxis in newly diagnosed patients with AML/MDS receiving intensive chemotherapy or other therapies.
4.1.2.3 To evaluate the composite outcome of treatment success vs. failure in this patient population (Definition of treatment failure: occurrence of proven or probable IFI, receipt of any other systemic antifungal agent for ≥4 days for suspected IFI, occurrence of an AE possibly or probably related to the study drug resulting in discontinuation of treatment, or withdrawal from the study with no additional follow-up).
4.1.2.4 To measure the overall survival (OS) of study participants.
4.1.2.5 To measure the IFI-free survival of study participants.
4.1.2.6 To document the time to death from any cause in the study population.
4.1.2.7 To document the time to death related to IFI in the study population.
4.1.2.8 To document the time to diagnosis of proven or probable IFI in the study population.
4.1.2.9 To document the time to initiation of empiric anti-fungal therapy in the study population.
4.1.2.10 To characterize the safety, tolerability and AE profile of isavuconazole in the prophylactic setting.

4.1.3 Exploratory

4.1.3.1 To assess the potential role, if any, of TDM of isavuconazole levels in the prophylactic setting in patients with newly diagnosed AML/MDS receiving cytotoxic chemotherapy or other therapies.
4.1.3.2 To determine the *in vitro* susceptibility of agents causing "breakthrough" IFIs to antifungal agents.

4.2 ENDPOINTS

4.2.1 Primary

4.2.1.1 Incidence of proven or probable IFI (by EORTC/MSG criteria)[72] during the first 100 days from initiation of isavuconazole prophylaxis.

4.2.2 Secondary

4.2.2.1 Incidence of IA within 100 days of isavuconazole prophylaxis initiation.
4.2.2.2 Incidence of other IFIs within 100 days of isavuconazole prophylaxis initiation.
4.2.2.3 Rates of treatment success vs. failure (defined above).
4.2.2.4 Overall survival.
4.2.2.5 Survival without proven or probable IFI.
4.2.2.6 Time to death from any cause.
4.2.2.7 Time to death related to IFI.
4.2.2.8 Time to diagnosis of proven or probable IFI.
4.2.2.9 Time to first use of empiric antifungal therapy.
4.2.2.10 AEs throughout the duration of isavuconazole prophylaxis until 30 days after the last dose of study drug.

4.2.3 Exploratory

4.2.3.1 Plasma isavuconazole (trough) levels on day 8 and day 15 using a validated assay.[73, 74]
4.2.3.2 Antimicrobial susceptibility testing of fungal isolates from proven "breakthrough" IFIs.

5 ELIGIBILITY CRITERIA

5.1 INCLUSION CRITERIA (all criteria must be met)

5.1.1 Patients with either newly diagnosed AML or MDS who have either begun (within 4 days of starting study drug) or are planned to begin specific treatment for their AML/MDS. Hydroxyurea and cytarabine used for cytoreduction while awaiting initiation of definitive therapy are not considered "specific"treatment. Patients who are participating in other therapeutic clinical trials for their AML/MDS may participate in this trial.
5.1.2 Patients must have or be anticipated to have neutropenia (absolute neutrophil count (ANC) <0.5 x 10^9/L)[75] for ≥7 days as a result of treatment of their AML/MDS.
5.1.3 Age ≥18 years.
5.1.4 Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
5.1.5 Patients must have reasonable liver function, i.e., total bilirubin ≤3 x ULN AND AST/ALT ≤5 x ULN.
5.1.6 Patients must be able to take oral medications, although a brief period of IV therapy (<4 days) is permitted at trial entry.
5.1.7 Patients must be willing and able to provide written informed consent for the trial.
5.1.8 Women of childbearing potential (WOCBP) must practice 2 effective methods of birth control during the course of the study. Male patients who are partners of WOCBP should also practice an effective method of contraception. Effective methods of birth control include diaphragm or condoms with spermicidal foam or jelly, birth control pills (BCPs), injections or patches, intra-uterine devices (IUDs) and surgical sterilization.

- Postmenopausal women must be amenorrheic for ≥12 months to be considered of non-childbearing potential.

- Women and men must continue birth control for the duration of the trial and ≥3 months after the last dose of study drug.
- All WOCBP MUST have a negative pregnancy test prior to first receiving study medication.

5.2 EXCLUSION CRITERIA

5.2.1 Proven, probable or possible IFI (by EORTC/MSG criteria,[72] see sections 9.1 and 9.2) within the previous 30 days.
5.2.2 Use of any systemic antifungal therapy for >72 hours during the week prior to study drug initiation.
5.2.3 History of hypersensitivity or idiosyncratic reactions to azoles.
5.2.4 Patients with familial short QT syndrome or with QTc interval ≤300 ms.
5.2.5 Patients on strong CYP3A4 inducers or inhibitors that cannot be discontinued.
5.2.6 Women who are pregnant or nursing, or intend to be/do so during the course of the study.
5.2.7 Patients with severe hepatic impairment (Child-Pugh class C).
5.2.8 Patients with known or suspected Gilbert's syndrome at the time of study enrollment.
5.2.9 Patients with known gastrointestinal conditions that could potentially interfere with absorption of orally administered medications.
5.2.10 Any condition that, in the opinion of the investigator, may interfere with the objectives of the study, e.g., any condition requiring the use of prohibited drugs or unstable medical conditions other than AML/MDS, such as a cardiac or neurologic disorder expected to be unstable or progressive during the course of the study (e.g., seizures or demyelinating syndromes, acute myocardial infarction within 3 months of study entry, myocardial ischemia or unstable congestive heart failure, unstable arrhythmias).

6 TREATMENT PLAN

6.1 General

All patients should be registered with the Data Management Office PDMS/CORE system.

Isavuconazonium sulfate will be administered orally in this study. However, IV administration for <4 days will be permitted if required at study entry. During the course of the study, if required (e.g., due to mucositis), switching between the IV and oral formulations of isavuconazonium sulfate is acceptable without dose changes or the need for any loading doses as bioequivalence has been demonstrated. However, every effort should be made to minimize the duration of IV administration.

Dosing will be identical for oral and IV administration of isavuconazonium sulfate. Isavuconazonium sulfate will be administered at a dose of 372 mg (i.e., 2 capsules, or 200 mg of isavuconazole) orally every 8 hours for 6 doses (48 hours), and 372 mg (i.e., 2 capsules, or 200 mg of isavuconazole) orally once daily thereafter. Maintenance doses should be started 12 to 24 hours after the last loading dose.

If IV administration is required at therapy initiation, 372 mg (1 reconstituted vial, or 200 mg of isavuconazole) will be administered IV every 8 hours for 6 doses, followed by 372 mg (1 reconstituted vial, or 200 mg of isavuconazole) IV once daily. Maintenance doses should be started 12 to 24 hours after the last loading dose.

If a switch from oral to IV therapy is needed at a later time point, 1 reconstituted vial IV will be substituted for 2 capsules orally once daily. Treatment should be switched back to the oral route as soon as the patient is able to take oral medications.

Capsules should be swallowed whole. They should not be chewed, crushed, dissolved, or opened. Isavuconazonium sulfate can be taken without regard to food.

- **Reconstitution Instructions for the Injection Formulation**

Aseptic technique must be strictly observed in all handling. Isavuconazonium sulfate is water soluble, preservative-free, sterile, and nonpyrogenic.

- Reconstitute one vial of isavuconazonium sulfate by adding 5 mL water for injection, USP to the vial.
- Gently shake to dissolve the powder completely.
- Visually inspect the reconstituted solution for particulate matter and discoloration. Reconstituted isavuconazonium sulfate should be clear and free of visible particulate.
- The reconstituted solution may be stored below 25°C for maximum 1 hour prior to preparation of the patient infusion solution.

- **Dilution and Preparation Instructions for the Injection Formulation**

- Remove 5 mL of the reconstituted solution from the vial and add it to an infusion bag containing 250 mL (approximately 1.5 mg isavuconazonium sulfate per mL) of compatible diluent. The diluted solution may show visible translucent to white particulates of isavuconazole (which will be removed by in-line filtration).
- Use gentle mixing or roll bag to minimize the formation of particulates. Avoid unnecessary vibration or vigorous shaking of the solution. Do not use a pneumatic transport system.
- Apply in-line filter with a microporous membrane pore size of 0.2 to 1.2 micron and in-line filter reminder sticker to the infusion bag.
- Infuse over a minimum of 1 hour to minimize the risk of infusion-related reactions. Do not administer as an IV bolus. Do not infuse isavuconazonium sulfate with other medications.
- The intravenous administration should be completed within 6 hours of dilution at room temperature. If this is not possible, immediately refrigerate (2° to 8°C / 36° to 46°F) the infusion solution after dilution and complete the infusion within 24 hours. Do not freeze the infusion solution.

- **Compatibility for the Injection Formulation**

Isavuconazonium sulfate for injection should only be administered with the following diluents:

- 0.9% sodium chloride injection, USP
- 5% dextrose injection, USP

6.2 Duration of prophylaxis

Study drug treatment will be administered daily continuously until, whichever occurs first:

- recovery from neutropenia (ANC $\geq 0.5 \times 10^9$/L) and attainment of complete remission (CR), with or without complete count recovery[28] or
- occurrence of a proven or probable IFI as defined by EORTC/MSG criteria,[72] or
- 12 weeks have elapsed from the start of therapy, or
- development of unacceptable toxicity, or
- patient's withdrawal from the study (patient or investigator decision), or

- patient's death

Isavuconazonium sulfate will be provided at no cost to the patients participating in this study.

6.3 Therapeutic drug monitoring

Isavuconazole plasma concentrations will be determined immediately before dosing on days 8 and 15 using a validated liquid chromatography-mass spectroscopy assay as previously described.[73, 74] These studies will be performed in the laboratory of Dr. Nathan Wiederhold at the University of Texas Health Sciences Center in San Antonio. 0.5 ml of plasma will be required for the assay. Blood will be collected in EDTA tubes. Plasma will be separated from the blood and frozen. Samples will be shipped in batches on dry ice.

6.4 *In vitro* susceptibility testing of fungal isolates

This will be performed in the laboratory of Dr. D. P. Kontoyiannis according to the methods of the Clinical and Laboratory Standards Institute for all IFIs that occur during the study for which a specimen is available for fungal culture.

6.5 Long-term follow-up

The Long-Term Follow-Up schedule begins at the end of treatment assessment and continues until death. All patients who receive at least one dose of study drug will be followed for survival every 6-12 months by telephone call to patient, family, local physician, surface or electronic mail. All patient follow up will continue under DR09-0223. A separate informed consent for that study will be required. Patients may be removed from this current protocol and followed up on the DR09-0223 after completing all protocol related assessments.

7 PRE-TREATMENT EVALUATION (all procedures must be completed within the week preceding study treatment initiation)

7.1 Complete history and physical examination including demographics, concurrent medications, ECOG performance status, vital signs, height and weight.
7.2 Informed consent.
7.3 Baseline serum or urine pregnancy test.
7.4 Baseline complete blood count (CBC) and differential.
7.5 Baseline comprehensive metabolic panel (CMP, defined below in study calendar).
7.6 Baseline electrocardiogram (ECG).
7.7 Baseline chest x-ray (computed tomography (CT) of chest (± sinuses) if patient is febrile and/or presents with signs/symptoms of respiratory infection (lungs or sinus)).
7.8 Baseline assessment of bone marrow iron stores (to be done on bone marrow obtained assessment of status of AML/MDS, separate bone marrow examination not required for study). Failure to perform this will not be considered a protocol deviation or violation.

8 EVALUATION DURING STUDY

8.1 Complete history and physical examination including ECOG performance status, vital signs, and weight at study drug initiation and every 3 weeks (±1 week) thereafter during the study.
8.2 CBC and differential at least 1-2 times per week (differential not required if total WBCs ≤0.5 x 10^9/L).
8.3 CMP (defined below in study calendar) at least weekly.
8.4 EKG on day 10.
8.5 Blood cultures if patient develops fever (oral temperature ≥ 100.4 ºF or 38 ºC sustained over a 1-hour period or a single oral temperature measurement of ≥ 101 ºF or 38.3 ºC).[75]
8.6 Chest x-ray (CXR) if patient develops neutropenic (ANC <500/mm^3) fever[75] or any sign or symptom of pulmonary infection (lungs or sinus).
8.7 CT scan of the chest (± sinus) within 3 (±1) days of development of neutropenic fever or any sign or symptom of respiratory infection. If positive for infection, CT chest (±sinus) needs to be repeated 2 weeks after institution of therapeutic antimicrobials and then as per physician discretion until resolution of the infection.
8.8 Iron staining of bone marrow at the time of response assessment for AML/MDS.[28] Failure to perform this will not be considered a protocol deviation or violation.
8.9 Plasma isavuconazole levels on day 8 and day 15 just prior to dosing.
8.10 Antimicrobial susceptibility testing of fungal isolates from any IFIs that may develop during the course of the study.
8.11 Patients that come off therapy will continue follow-up for toxicity (clinic visit or telephone interview) for 30 days (+/- 5 days) after the end of therapy. At the end-of-study visit, patients will have a physical examination, including recording of vital signs, weight and assessment of ECOG performance status, a CBC, CMP, and AE evaluation.
8.12 All study participants will be given a study drug diary to keep a log of each dose of study drug taken, the time the dose was taken, and any missed doses along with the reason for missing the dose, as well as doses that may be vomited up.

Concomitant medications

a) All patients may also receive standard antibacterial and antiviral prophylaxis.

b) No concomitant antifungal therapy is allowed while patients are receiving study drug.

c) Co-administration of strong CYP3A4 inducers or inhibitors is contraindicated.
d) Concomitant medications will be entered in the medical record, not the case report form.

STUDY CALENDAR

	Pre-Study*	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study[f]
Isavuconazonium sulfate		A	A	A	A	A	A	A	A	A	A	A	A	
Informed consent	X													
Demographics	X													
Medical history[c]	X	X			X			X			X			
Concurrent meds	X	X----------X												
Physical exam[c]	X	X			X			X			X			X

Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X			X			X			X			X
Performance status	X	X			X			X			X			X
CBC w/diff, plts (at least 1-2 times per week during study)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP[a] at least weekly	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG (baseline and day 10)	X		X											
Adverse event evaluation		X----------X												X
Chest x-ray	X	If any sign or symptom of pulmonary infection or neutropenic (ANC < 500/mm^3) fever develops.												
CT scan of chest (±sinuses)	X[b]	Within 3 (±1) days of development of neutropenic (ANC <500/mm^3) fever or any sign or symptom of respiratory infection (lungs or sinus).												
Blood cultures		If patient develops fever (single oral temp ≥101ºF (38.3ºC) or oral temp ≥100.4ºF (38ºC) sustained x 1 hour).												
Iron staining of bone marrow	X	Whenever bone marrow is sampled for assessment of disease status of AML/MDS.												
ß-HCG	X[d]													
Isavuconazole levels [e]			X	X										
Antimicrobial susceptibility testing of fungal isolates		Any time a breakthrough fungal infection occurs and a sample is available for fungal culture.												

*Within 1 week prior to study treatment initiation.
A: *Isavuconazonium sulfate*: 372 mg (200 mg of isavuconazole) daily.
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, ~~SGOT [AST],~~ SGPT [ALT], sodium.
b: Only if patient is febrile and/or presents with signs/symptoms of respiratory infection (lungs or sinus).
c: ±1 week.
d: Serum or urine pregnancy test (women of childbearing potential).
e: On days 8 and15 (before the day's dose).
f: Off-study evaluation (clinic visit or telephone interview).
g: Differential not required if total WBCs ≤ 0.5 x 10^9/L.

9 ASSESSMENT OF EFFICACY

9.1 EORTC/MSG criteria for proven IFIs

Fulfillment of any of these criteria represents a proven IFI.

Analysis and specimen	Molds[a]	Yeasts[a]
Microscopic analysis: sterile material	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells—for example, *Cryptococcus* species indicated by encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae[c]
Culture		
Sterile material	Recovery of a mold or "black yeast" by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine	Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 h ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process
Blood	Blood culture that yields a mold[d] (e.g., *Fusarium* species) in the context of a compatible infectious disease process	Blood culture that yields yeast (e.g., *Cryptococcus* or *Candida* species) or yeast-like fungi (e.g., *Trichosporon* species)
Serological analysis: CSF	Not applicable	Cryptococcal antigen in CSF indicates disseminated cryptococcosis

[a] If culture is available, append the identification at the genus or species level from the culture results.
[b] Tissue and cells submitted for histopathologic or cytopathologic studies should be stained by Grocott-Gomorri methenamine silver stain or by periodic acid Schiff stain, to facilitate inspection of fungal structures. Whenever possible, wet mounts of specimens from foci related to invasive fungal disease should be stained with a fluorescent dye (e.g., calcofluor or blankophor).
[c] *Candida, Trichosporon,* and yeast-like *Geotrichum* species and *Blastoschizomyces capitatus* may also form pseudohyphae or true hyphae.
[d] Recovery of *Aspergillus* species from blood cultures invariably represents contamination.

9.2 EORTC/MSG criteria for probable and possible IFIs

At least one host factor, one clinical feature and one form of mycological evidence are required for a diagnosis of "probable" IFI, as defined in the table below.

A "possible" IFI is defined by the presence of appropriate host factors and sufficient clinical evidence consistent with IFI but without any mycological support.

- Host factors[a]
  - Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease
  - Receipt of an allogeneic stem cell transplant
  - Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks
  - Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
  - Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)
- Clinical criteria[b]
  - Lower respiratory tract fungal disease[c]
    - The presence of 1 of the following 3 signs on CT:
      - Dense, well-circumscribed lesions(s) with or without a halo sign
      - Air-crescent sign
      - Cavity
  - Tracheobronchitis
    - Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
  - Sinonasal infection
    - Imaging showing sinusitis plus at least 1 of the following 3 signs:
      - Acute localized pain (including pain radiating to the eye)
      - Nasal ulcer with black eschar
      - Extension from the paranasal sinus across bony barriers, including into the orbit
  - CNS infection
    - 1 of the following 2 signs:
      - Focal lesions on imaging
      - Meningeal enhancement on MRI or CT
  - Disseminated candidiasis[d]
    - At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:
      - Small, target-like abscesses (bull's-eye lesions) in liver or spleen
      - Progressive retinal exudates on ophthalmologic examination
- Mycological criteria
  - Direct test (cytology, direct microscopy, or culture)
    - Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:
      - Presence of fungal elements indicating a mold
      - Recovery by culture of a mold (e.g., *Aspergillus, Fusarium,* Zygomycetes, or *Scedosporium* species)
  - Indirect tests (detection of antigen or cell-wall constituents)[e]
    - Aspergillosis
      - Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF
    - Invasive fungal disease other than cryptococcosis and zygomycoses
      - β-D-glucan detected in serum

NOTE. Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.

[a] Host factors are not synonymous with risk factors and are characteristics by which individuals predisposed to invasive fungal diseases can be recognized. They are intended primarily to apply to patients given treatment for malignant disease and to recipients of allogeneic hematopoietic stem cell and solid-organ transplants. These host factors are also applicable to patients who receive corticosteroids and other T cell suppressants as well as to patients with primary immunodeficiencies.

[b] Must be consistent with the mycological findings, if any, and must be temporally related to current episode.

[c] Every reasonable attempt should be made to exclude an alternative etiology.

[d] The presence of signs and symptoms consistent with sepsis syndrome indicates acute disseminated disease, whereas their absence denotes chronic disseminated disease.

[e] These tests are primarily applicable to aspergillosis and candidiasis and are not useful in diagnosing infections due to *Cryptococcus* species or Zygomycetes (e.g., *Rhizopus, Mucor,* or *Absidia* species). Detection of nucleic acid is not included, because there are as yet no validated or standardized methods.

10 CRITERIA FOR REMOVAL FROM THE STUDY

Patients will be removed from the study if:

- 12 weeks have elapsed from the start of therapy, or
- The ANC has recovered to ≥0.5 x 10^9/l and CR with or without complete count recovery has been documented (per ELN criteria),[28] or
- A proven or probable IFI has occurred (as defined by the EORTC/MSG),[72] or
- Unacceptable drug toxicity develops, or
- The patient or investigator decide to withdraw the patient from the study, or
- Patient dies while on study.

11 STATISTICAL CONSIDERATIONS

This is an open label, phase II clinical trial to evaluate the efficacy of isavuconazole prophylaxis in adult patients with newly diagnosed AML/MDS and neutropenia. A total of 100 patients will be accrued from M.D. Anderson Cancer Center (MDACC), at a rate of 5 patients per month. The primary endpoint is the incidence of proven or probable invasive fungal infections (IFI) for up to 100 days from prophylaxis initiation. Occurrence of IFIs will be assessed during the period of prophylaxis (see section 6.2) and up to 100 days from prophylaxis initiation.

The method of Thall, Simon and Estey[76] will be used for futility and toxicity monitoring in this study.

A 10% frequency of IFIs is observed in general in AML during remission induction. The current standard of care is posaconazole prophylaxis in preventing IFI. Assuming that isavuconazole is as effective as posaconazole, subjects receiving isavuconazole would be expected to have a 5% rate of IFIs. We assume a priori for IFI rate, p (IFI) ~ beta (0.1, 1.9). The following futility stopping rule will be applied in cohort sizes of 10, starting from the 10^{th} patient: the trial will be stopped if Pr(p(IFI)> 0.05 | data) > 0.87. That is, we will stop the trial for new patient enrollment if at any time during the study we determine that there is a more than 87% chance that the IFI rate is more than 5%. Stopping boundaries corresponding to the IFI monitoring rule are shown in Table 1 below. The operating characteristics for the monitoring are summarized in Table 2. Multc Lean Desktop (version 2.1) was used to generate the IFI stopping boundaries and the OC table. We will submit a futility/toxicity summary to the IND Office Medical Monitor, after the first ten patients have completed study therapy, or administration is discontinued, whichever comes first; and every ten patients thereafter.

Table 1. IFI stopping boundaries in cohort sizes of 10 .

Number of patients	No. of patients with IFIs that will lead to the trial being stopped
10	2-10
20	3-20
30	4-30
40-50	5-50
60	6-60

70-80	7-80
90	8-90

Table 2. Operating characteristics for IFI monitoring in cohort sizes of 10 (max sample size = 100).

True IFI rate	Prob(stop the trial early)	Average sample size
0.01	0.005	99.6
0.02	0.02	98.1
0.03	0.06	95.3
0.04	0.13	90.9
0.05	0.23	84.9
0.06	0.35	77.7
0.07	0.48	69.8
0.08	0.60	61.8
0.09	0.71	54.2
0.1	0.80	47.3
0.15	0.98	25.5

Toxicity will be monitored in all patients. Denote the probability of toxicity by p (Tox), where toxicity is defined as any Grade ≥3 clinically relevant non-hematologic toxicity, grade ≥4 hematologic toxicity lasting ≥6 weeks with a hypocellular bone marrow and <5% blasts or a serious adverse event (SAE) that is definitely, probably or possibly related to the study drug (AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0). We assume a priori for toxicity rate, p (tox) ~ beta (0.6, 1.4). The following toxicity stopping rule will be applied in cohort sizes of 10, starting from the 10^{th} patient: the trial will be stopped if Pr(p(tox)> 0.3 | data) > 0.9. That is, we will stop the trial for new patient enrollment if at any time during the study we determine that there is a more than 90% chance that the toxicity rate is more than 30%. Stopping boundaries corresponding to the toxicity monitoring rule are shown in Table 3 below. The operating characteristics for the monitoring are summarized in Table 4. Again, Multc Lean Desktop (version 2.1) was used to generate the toxicity stopping boundaries and the OC table.

Table 3. Toxicity stopping boundaries in cohort sizes of 10 .

Number of patients	No. of patients with toxicity that will lead to the trial being stopped
10	6-10
20	9-20
30	13-30
40	16-40
50	20-50
60	23-60
70	27-70
80	30-80
90	33-90

Table 4. Operating characteristics for toxicity monitoring in cohort sizes of 10 (max sample size = 100).

True toxicity rate	Prob(stop the trial early)	Average sample size
0.1	0.0002	99.9
0.2	0.02	98.6
0.3	0.26	83.1
0.4	0.86	43.5
0.6	1.0	14.4

Analysis Plan

The primary endpoint is the incidence of proven or probable invasive fungal infections (IFI). The IFI rate will be estimated along with the exact 95% confidence interval.

Secondary endpoints include incidence of IA, overall survival, and time to diagnosis of IFI, etc. Descriptive statistics will be used to summarize all secondary endpoints. The incidence rates of binary secondary endpoints will be estimated, along with the exact 95% confidence intervals. The probabilities of time-to-event outcomes (such as time to death) will be estimated using the method of Kaplan and Meier. Log-rank tests will be used to compare the time-to-event outcomes among subgroups of patients.

Subjects who entered the study and did not take any study drug will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency. The proportion of patients with AEs will be estimated among all patients.

12 REPORTING REQUIREMENTS

These guidelines will be followed for the recording and reporting of adverse events and SAEs.

1. Baseline events will be recorded in the medical history section of the case report form (CRF) and will include the terminology event name, grade and start date of the event.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent form (ICF) is signed.
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course of protocol defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably or definitely related to the study drugs(s).
    b. All serious adverse events regardless of attribution to the study drug(s).
    c. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g., marrow hypocellularity on day 42 or later (≥6 weeks) from start of therapy without evidence of leukemia (<5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
5. SAEs will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia Department-specific adverse event recording and reporting guidelines.

Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this

definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered SAEs. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- SAEs will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. SAEs must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any SAEs that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- SAEs will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that SAEs are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

These reports will also be submitted to Astellas safety by email at: Safety-US@us.astellas.com

Reporting of External SAEs

- The MDACC institutional policy for reporting of external SAEs will be followed.

13 CONFIDENTIALITY PLAN

All data will be entered in PDMS/CORE.

14 REFERENCES

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