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**CHILDREN'S ONCOLOGY GROUP**

**ACCL1131**

# A Phase III Open-Label Trial of Caspofungin vs. Azole Prophylaxis for Patients at High-Risk for Invasive Fungal Infections (IFI) Following Allogeneic Hematopoietic Cell Transplantation (HCT)

**A Phase III Study**

**A Groupwide Phase III Study**



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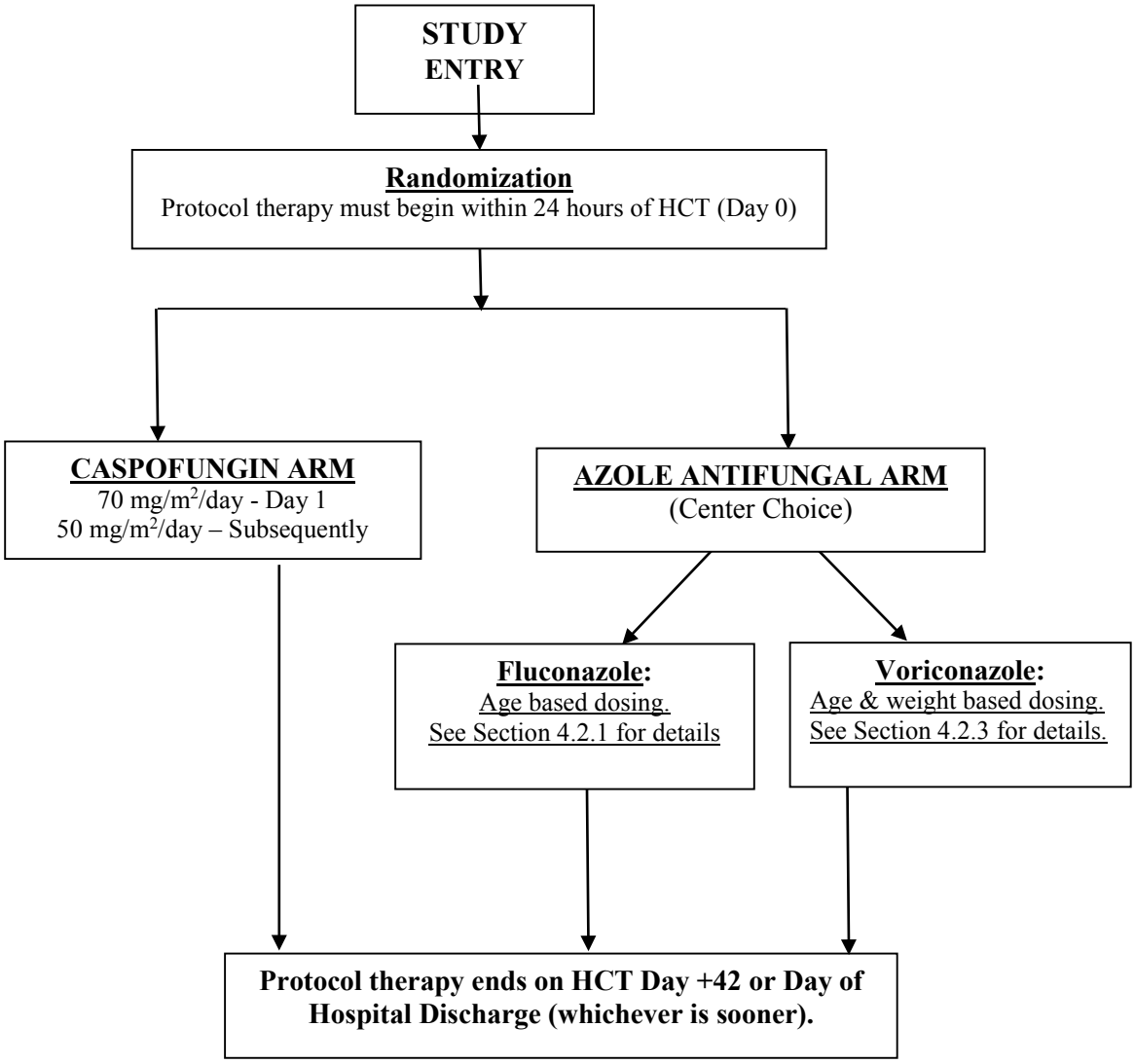
## ABSTRACT

Invasive fungal infections (IFI) are a significant cause of morbidity and mortality in patients undergoing allogeneic hematopoietic cell transplant (HCT). Over 50% of infectious-related deaths in this population are attributable to IFI. These dismal numbers are despite empiric therapy and treatment with the best available agents. The failure of these strategies to impact morbidity and mortality from IFI makes a strong case for the exploration of preventive strategies. This study will utilize a 2-arm, open-label randomized design to evaluate the efficacy of prophylaxis with caspofungin in comparison with an azole in children undergoing allogeneic HCT from an unrelated or mismatched related donor. The study agent will begin following at the time of transplant and continue through Day +42 or hospital discharge. This study also seeks to evaluate the usefulness of the Fungitell beta-D glucan Assay in early diagnosis of IFI. ACCL1131 will also explore the relationship between proven or probable IFI and single nucleotide polymorphisms (SNP) of genes involved in immunity.

**EXPERIMENTAL DESIGN SCHEMA**



# 1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

## 1.1 Primary Objective

1.1.1
To determine if caspofungin is associated with a lower incidence of proven/probable IFI during the first 42 days following allogeneic HCT at high-risk for IFI compared with azole (fluconazole or voriconazole) prophylaxis.

## 1.2 Exploratory Objectives

Clinical

1.2.1
To determine if caspofungin is associated with a lower incidence of proven/probable IFI during the first 100 days following high-risk allogeneic HCT compared with azole (fluconazole or voriconazole) prophylaxis.

1.2.2
To determine if caspofungin is associated with a lower incidence of proven/probable IFI during the first 42 and 100 days following high-risk allogeneic HCT compared with fluconazole prophylaxis.

1.2.3
To determine if caspofungin is associated with a lower incidence of proven/probable IFI during the first 42 and 100 days following high-risk allogeneic HCT compared with voriconazole prophylaxis.

1.2.4
To determine if caspofungin is associated with a superior fungal-free survival (FFS) (time to death or proven/probable IFI) at 42 and 100 days following high-risk allogeneic HCT compared with azole prophylaxis.

1.2.5
To describe the effect that caspofungin and azoles have on the incidence and severity of acute graft-versus-host disease (GVHD).

Biological

1.2.6
To define the test characteristics of weekly Fungitell Assay testing for identifying IFI in pediatric HSCT recipients receiving antifungal prophylaxis during the post-transplant neutropenic period.

1.2.7
To create a DNA specimen bank in anticipation of the development of biology correlative studies exploring the relationship between IFI and single nucleotide polymorphisms (SNPs) of genes involved in immunity.

## 2.0 BACKGROUND

### 2.1 Rationale for Selected Approach and Trial Design

Almost all centers use anti-fungal prophylaxis for allogeneic HCT recipients, but no standard class of agents has emerged. A formal survey of the 80 COG HCT Centers shows that the majority of centers utilize fluconazole, although some centers have adopted voriconazole or an echinocandin, despite a paucity of data to support this practice (details below). Fluconazole is the trial-proven gold standard due to good tolerability and reasonable coverage of many *Candida* spp.[1,2] However the emergence of fluconazole-resistant *Candida*, plus the risk of *Aspergillus* spp. (not covered by fluconazole) in high-risk patients, makes the identification of a superior agent a priority. While voriconazole does have excellent anti-*Aspergillus* activity, it has failed to show superiority to fluconazole post HCT,[3] possibly due to erratic drug levels,[4-6] a problem especially apparent in young children.[7-9] In addition, voriconazole has multiple drug interactions with post-HCT immunosuppression medications.[6,10-12] The echinocandins have significant activity against almost all *Candida* spp., the most common organisms encountered in the first month post-HCT, and there appears to be little concern for emerging resistance.[13] In addition, echinocandins have some anti-*Aspergillus* activity, an excellent safety profile, few drug interactions, and an IV formulation (important for children with post-HCT mucositis and an inability to tolerate or absorb oral medications). The one randomized trial of an echinocandin for post-HCT prophylaxis showed promise at decreasing the need for empiric anti-fungal agents, but enrolled few pediatric patients and many low-risk patients, making it difficult to definitely determine the utility of echinocandins in high-risk pediatric HCT patients.[14]

The recently published ASBMT Supportive Care Guidelines recommend fluconazole for standard-risk patients and consideration of micafungin for adult patients at high risk for mold infection, *but no alternative agent is recommended for pediatric patients, because no data exists for this population*.[15] In addition, micafungin is not FDA-approved for use in children, has no accepted dose for children less than 2 years of age, and carries an EMEA black-box warning in Europe about animal studies showing a risk of developing liver tumors after prolonged administration.[16] Therefore, this study is designed to definitively determine if caspofungin, an FDA-approved agent for children over 3 months of age, is effective at preventing IFI infections. Given the safety of caspofungin, its excellent anti-*Candida* properties, and potential ability to suppress *Aspergillus*, we hypothesize that caspofungin will be superior to standard azole prophylaxis at preventing IFI post-HCT in patients at high risk for developing IFI. As IFI represent a significant source of post-HCT morbidity and mortality, reduction of IFIs should translate to improved post-HCT survival.

The study has been designed as an open-label comparison of an echinocandin (caspofungin) vs. an azole (local center determination of fluconazole or voriconazole). This open-label randomized trial will test the effectiveness of our intervention in a setting that will mirror usual clinical practice and thus, this more pragmatic design can better inform decision-making.[17,18] Because of this approach, the lack of blinding is not a weakness. There are other major feasibility issues with the use of these agents that favor the open-label approach. In an allogeneic HCT population, echinocandins and azoles (esp. voriconazole) have significant and dramatic differences relative to their interactions with concomitant medications. This is most important and relevant for the calcineurin inhibitors (CIs; cyclosporine and tacrolimus) and sirolimus. Caspofungin has no apparent effect on the levels of CIs.[10] On the other hand, fluconazole is an inhibitor of several CYP enzymes and therefore causes an approximate 16-21% increase in the levels of CIs.[11] Furthermore, voriconazole is a major inhibitor of CYP2C9, which causes significant interactions with these crucial transplant medications. The FDA label reports that concomitant use of voriconazole can cause a 1.7 to 3-fold increase in cyclosporine or tacrolimus levels, and recommends that the dosing of cyclosporine be decreased by 50% and the dosing of tacrolimus be decreased by 66% of the normal dose. A recent study demonstrated in a cohort of 27 adult BMT patients receiving voriconazole, 100% of patients required multiple tacrolimus dose reductions to achieve a safe target level.[6] Furthermore, the use of voriconazole with sirolimus is officially contraindicated, and when its use has been reported, investigators have recommended dropping the levels of sirolimus to 90% of original dosing at the time of initiation of voriconazole.[12] Given these drug-drug interactions, it is not safe and likely not possible

to conduct the trial in a truly blinded fashion. One potential limitation of an open label trial is the potential for observer bias in outcome determination. In this study, the primary outcome will be determined through a blinded review committee. This will minimize the possibility of observer bias, and has been successfully utilized in other anti-fungal prophylaxis trials in which a double-blind design was not feasible.[19,20] Similarly, in non-transplant patients, multiple highly influential trials of extended-spectrum azoles have utilized a non-blinded approach.[21-23] Furthermore, open-label trials have another inherent advantage to double-blinded trials, which is that treating physicians may be uncomfortable not knowing what medications their patients are receiving. This can potentially lead to both decreased trial participation and to unanticipated confounders. This can be seen in the trial by Wingard *et al.* in which 7.8% of the fluconazole arm and 11.5% of the voriconazole arm received simultaneous off-study use of other mold-active agents.[3] We would not expect this type of confounding behavior in an open-label trial.

There are no data to support the concept that certain underlying conditions may confer a lower risk for IFI due to the presence of a relatively intact immune system prior to transplant. A recent publication by Hol *et al.* demonstrated that in 209 pediatric patients undergoing allogeneic HSCT, there was no difference in IFI rate based on the underlying condition ($p = 0.967$).[24] This suggests that it is the transplant process itself, with the accompanying disruption in both innate and adaptive immunity, which is the primary risk factor for development of an IFI. Most reports do not distinguish the rates of IFI between various donor types. One series of retrospective data (primarily in adults) showed that the risk of IFI at 1 year in alternate donors was ~2% higher than seen in matched-siblings.[50] However, in the most recent pediatric-specific paper by Hol *et al.*, there was a non-significant difference in IFI rate between MSD (9.3%) vs. MUD (10.5%) vs. UCB (14.3%) (p = 0.3). Given the similar IFI risk across donor sources, all allogeneic donor types will be considered eligible for enrollment on this trial. There will be no limitations to trial enrollment based on race or gender as there is no data to support differences in the incidence or outcomes of IFIs due to race or gender.

### 2.2 Trial Importance

The profound immunosuppression that occurs while undergoing HCT places patients at high risk for infectious complications.[25] Although bacteria represent the most common infection following HCT, IFI account for a significant amount of post-transplant mortality. The 1-year incidence of IFI in the pediatric HCT population has been reported to be as high as 13-20%, with 58-83% mortality.[26-29] The most commonly identified invasive fungal organisms following HCT are *Candida* spp. and *Aspergillus* spp. *Candida spp*. are most commonly encountered during the neutropenic period in the first several weeks following HCT, while *Aspergillus* spp. have a bimodal distribution, with a first peak at a median of 16 days and the second at a median of 96 days post-allogeneic HCT.[25,30] Different centers have reported slightly different incidences of developing an IFI early post HCT, ranging from 8.7% (first 28 days)[26], to 4.1% (first 30 days)[27], to 6.5% (first 40 days, *Aspergillus* only).[28] Patients that are considered to be high-risk for developing an IFI following allogeneic HCT are those who undergo transplant from either an unrelated donor (including umbilical cord blood) or a partially-matched related donor, for treatment of a malignancy, bone marrow failure syndrome, or congenital immunodeficiency.[15,28,29] Guidelines have been developed by the European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) to standardize the definitions of proven, probable, and possible IFI.[31]

Based upon the above data, most centers employ an anti-fungal strategy that includes prophylaxis for allogeneic HCT recipients. However, no standard class of agent has emerged. Furthermore, given the different spectrum of organisms in the acute neutropenic phase and the later post-engraftment phase, it is very possible that the optimal agent may differ depending on time following stem cell infusion. This proposal is focused on the acute neutropenic phase.

A positive study outcome will result in less IFI in patients undergoing alternative donor allogeneic HCT. Because IFI represents a major source of morbidity and mortality, this would improve overall outcomes and

subsequently allow expanded access of patients to alternative donor HCT, a potentially curative approach for children with high-risk leukemia.

In addition, the diagnosis of IFI is often difficult because of the lack of specific clinical symptoms in high-risk patients and the invasiveness of standard diagnostic tests; therefore much attention has been focused on developing noninvasive tests for diagnosing IFI. Serum beta-D glucan (found in all fungi except *Crytpococcus spp.* and Zygomycetes) can be detected using an approved diagnostic serum assay (the Fungitell Assay) and has been found to have high specificity and high positive predictive values for the detection of IFI in adults.[32] However, data on the performance of this assay in children are limited. A positive result of this aspect of the trial will allow earlier treatment of IFI in the future, and early treatment has been associated with superior resolution rates. In addition to early detection of fungal infections, there also is interest in identifying patients particularly susceptible to IFIs so that they can receive early targeted interventions. There is considerable evidence that there is a genetic component to the susceptibility and outcome of infection in both normal and immunocompromised populations. A recent study suggests an association between the donor *TLR4* haplotype S4 and the risk of invasive aspergillosis (IA) among recipients of HCTs from unrelated donors.[33] Another study reports that polymorphisms in the chemokine ligand 10 are associated with developing IA after allogeneic HCT.[34] Other studies have demonstrated that polymorphisms in plasminogen or dectin-1 may also contribute to the development of IA post-HCT.[35,36]

One of the biologic aim of the trial will be to create a DNA specimen bank to be used in future attempts to identify, in a homogenously treated cohort, those patients at the genetic level that have the highest risk for the development of an IFI, which in the future may allow for enhanced prophylaxis efforts in these patients, while allowing less stringent prophylaxis (with less toxicity) for patients at low genetic risk for IFI development.

## 2.3 Selection of Study Medication

### 2.3.1 Prophylactic Fluconazole is Superior to Placebo in Allogeneic HCT Patients

Based on two pivotal trials, the most common agent used for primary prophylaxis for IFI in children is fluconazole, despite the fact that fluconazole has no activity against *Aspergillus* spp. The first trial was performed by Goodman *et al.*, who conducted a double-blind, randomized, multicenter trial in which patients greater than 12 years of age receiving autologous or allogeneic HCTs were randomly assigned to receive prophylactic fluconazole (400 mg daily) versus placebo from the start of the conditioning regimen until one of the following: the absolute neutrophil count (ANC) recovered >1000/µL, toxicity was suspected, or a systemic fungal infection was suspected or proven.[1] Systemic fungal infections occurred in 15.8% patients who received placebo as compared with 2.8% who received fluconazole ($P < .001$). There was no significant difference in overall mortality between the groups.

Slavin *et al.* also performed a randomized, double-blind, placebo-controlled trial and assessed the efficacy and toxicity of 400 mg/day fluconazole in preventing fungal infections during the first 75 days after autologous or allogeneic marrow transplantation in patients greater than 12 years of age.[2] During prophylaxis, systemic fungal infections occurred in 7% of 152 fluconazole-treated patients compared with 18% of 148 placebo-treated patients ($P = .004$). The probability of survival was improved in fluconazole recipients, in whom 20% expired up to Day 110 after transplantation compared with 35% mortality in placebo recipients ($P = .004$). Fluconazole also appeared to protect from severe GVHD of the gut, possibly from decreased intestinal antigenic stimulation.[29]

The dosing of fluconazole used on prior prophylaxis trials that have included patients under the age of 12 years have been either 6 mg/kg/day[3] or 8 mg/kg/day.[14] The pediatric fluconazole dose which is equivalent to the dose recommended for adults in the source guideline (400 mg/day) ranges from 6-12 mg/kg/day depending on patient age and weight.[37-41] This is based on pharmacokinetic studies in children showing that children less than 15 years of age have a higher volume of distribution and faster elimination rate compared to

adults.[37,38,40] From a safety standpoint, fluconazole is believed to be safe and well tolerated in doses up to 12 mg/kg/day.[39] This dose range is higher than the ASBMT recommendation of 3-6 mg/kg/day.[15] However, we feel that the higher dose is justified given the available information outlined above and the adequate safety data. The dose of 12 mg/kg/day also unifies our approach with that of COG ACCL0933.

2.3.2 Prophylaxis with Amphotericin or Extended Spectrum Azoles in Allogeneic HCT Patients

Because fluconazole does not possess anti-*Aspergillus* activity, several trials have compared it to mold-active agents. Wolff *et al.* randomized patients undergoing allogeneic or autologous marrow or peripheral stem cell transplantation to receive fluconazole (400 mg/day PO or IV) or amphotericin B (0.2 mg/kg/day IV) beginning 1 day prior to stem cell transplantation and continuing until recovery of ANC > 500/µl.[42] Amphotericin B was significantly more toxic than fluconazole. Proven fungal infections occurred in 9.1% and 14.3% of related allogeneic marrow recipients receiving fluconazole or amphotericin B, respectively. Given the lack of significant benefit and the higher adverse event rate, low-dose amphotericin B has failed to supplant fluconazole as standard-of-care prophylaxis.

Extended-spectrum azoles such as itraconazole do possess anti-*Aspergillus* activity. Marr *et al.* performed a randomized trial of 304 patients receiving allogeneic stem cell transplant to receive either fluconazole (400 mg/day) or itraconazole (oral solution 2.5 mg/kg 3 times daily, or 200 mg IV daily) for 180 days after transplantation, or until 4 weeks after discontinuation of GVHD therapy.[19] More patients in the itraconazole arm developed hepatotoxicity, and more patients were discontinued from itraconazole because of toxicities or gastrointestinal intolerance (36% vs. 16%, $P < .001$). Fewer patients in the itraconazole arm developed IFI while on study drug (fluconazole 15% vs. itraconazole 7%, $P = .03$); however there was no difference in overall or fungal-free survival. Because of its poor tolerability, itraconazole prophylaxis has generally been abandoned.

A multi-center, randomized, double-blind trial was performed in 600 patients to compare fluconazole (400 mg daily in adults) versus voriconazole (200 mg twice daily in adults) for the prevention of IFIs in standard risk allogeneic HCT patients receiving full-intensity conditioning regimens.[3] The cumulative rates of proven, probable and presumptive IFI were similar in the two arms: 11.2% for fluconazole and 7.3% for voriconazole at 6 months ($P = .12$) and 13.7% and 12.7% at 12 months ($P = .59$), respectively. Event-free and overall survival rates also were similar in both arms at 6 and 12 months. Rates of expected or unexpected severe adverse events and rates of premature study drug withdrawal were similar in both arms. Therefore, there did not appear to be a significant benefit of voriconazole compared with fluconazole as primary prophylaxis against IFI following HCT, although its use has been adopted by many centers. Possible reasons cited by others as to why voriconazole did not appear to be superior to fluconazole include: 1) that a significant fraction of patients treated with standard dosing of voriconazole may have had sub-therapeutic levels[5]; and 2) that voriconazole is possibly an inferior anti-Candida drug than fluconazole, with primarily fungistatic effects.[43]

There is currently no accepted dosing schema for voriconazole in children less than 2 years of age, where clearance is expected to be even higher than in children between 2 and 12 years of age.[8] Because of this, centers that choose to utilize voriconazole as their comparator arm will not be able to enroll patients between the ages of 3 months to 2 years. The dosing of older children will be based on the most recent pharmacokinetic data available.[44]

2.3.3 Echinocandins as Prophylaxis in Allogeneic HCT

Echinocandins are a novel class of antifungal agents that target β-(1,3)-D-glucan synthase and interrupt biosynthesis of the glucan polymers that make up fungal cell walls. Because mammalian cells do not possess cell walls, echinocandin administration to human patients has resulted in minimal toxicity. Echinocandins possess fungicidal activity against *Candida* spp. (including *Candida krusei* and *Candida glabrata*, which possess significant degrees of fluconazole resistance) and *Pneumocystis jirovecii,* as well as fungistatic activity against *Aspergillus* spp. The echinocandins may be superior to fluconazole[45] or amphotericin B[46] for treatment

of invasive candidiasis which, when combined with their anti-*Aspergillus* activity and excellent safety profile, makes them an attractive class of agent to use in the early post-HCT period.

Van Burik *et al.* conducted a randomized, double-blind, multi-institutional Phase III trial involving 882 adult and pediatric patients undergoing autologous or allogeneic HCT, and compared 50 mg of micafungin (1 mg/kg for patients weighing < 50 kg) versus 400 mg of fluconazole (8 mg/kg for patients weighing < 50 kg) administered once per day.[14] Success was defined as the absence of suspected, proven, or probable IFI through the end of therapy and as the absence of proven or probable IFI through the end of the 4-week period after treatment. Micafungin was extremely well-tolerated (discontinuation of study drug because of an adverse event: 4.2% in micafungin arm versus 7.2% in fluconazole arm). The overall efficacy of micafungin was superior to that of fluconazole as antifungal prophylaxis during the neutropenic phase after HCT (80.0% in the micafungin arm vs. 73.5% in the fluconazole arm; $P$ = .03). This trial was the first antifungal agent to demonstrate superior efficacy and tolerability compared to fluconazole. However, the number of pediatric subjects enrolled was small (n = 84). Also, micafungin was most effective at preventing the need for empiric antifungal therapy, which is a less clinically important endpoint, and did not reduce the incidence of proven or probable IFI. The lack of impact on IFIs may have been because the incidence of breakthrough IFIs in both groups was very low, likely due to the inclusion of low-risk patients (46% autologous HCT recipients) and very few patients undergoing umbilical cord blood transplant (n = 30), a population of significant interest to pediatric transplant physicians. A retrospective evaluation of 123 adult allogeneic HCT recipients who received caspofungin 35-50 mg/day for up to 100 days after transplantation as primary antifungal prophylaxis demonstrated that 7.3% developed breakthrough IFI in the first 100 days post-HCT. No caspofungin-related adverse events were reported.[47] The major disadvantages to echinocandin use are cost and that it is only available in parental form. Thus, it is more difficult to administer once the patient has recovered from the neutropenic period and is ready for discharge from inpatient hospitalization.

2.3.4 Summary of the Two Azole Control Design

On January 26, 2011 (4 months after initial publication of the voriconazole trial by Wingard *et al.*[3]), we initiated a survey of the 80 COG Transplant Centers in North America and Australia/New Zealand in order to determine local standard-of-care anti-fungal prophylaxis for patients undergoing alternative donor (unrelated or mismatched related) HCT. The response rate was 80%, similar to the 83% seen in a survey of COG centers regarding anti-infective prophylaxis in patients with AML.[48] We found that for patients undergoing unrelated donor HCT (including umbilical cord blood), 56% of centers continue to use fluconazole, while 28% of centers have adopted voriconazole, 11% of centers utilize an echinocandin, and 5% administer a lipid formulation of amphotericin B. The data were very similar for patients undergoing mismatch related donor HCT (57%, 27%, 8%, and 8%, respectively). These results indicate that the profound lack of data for this patient population has led to a clinical situation where there is no clear universal agent of choice. Despite the fact that some centers have already adopted an echinocandin as the prophylaxis of choice, fully 89% of respondents indicated that they would be willing to participate in a trial of an echinocandin vs. an azole (center choice of fluconazole or voriconazole), as we have proposed for this trial. Even if all of the non-responding centers refused to participate, this would still be 71% of COG Transplant Centers. Finally, centers willing to participate were asked which azole they would choose as the comparator, and interestingly the pediatric HCT community was split almost evenly between fluconazole (54%) and voriconazole (46%), further justifying our two-azole design.

Therefore, our study is designed so that the local institutions will be allowed to choose what their standard-of-care anti-fungal prophylactic azole is for the study population in question. This practical study design reflects the real-world situation in which different agents have been adopted by individual centers on the basis of insufficient data. Furthermore, this design mirrors the Phase III trial in which posaconazole was compared to either fluconazole or itraconazole (two agents with different spectrums of activity) in non-transplant patients with neutropenia.[22] In other words, that highly influential study used a similar strategy of comparing posaconazole against agents with and without mold activity in order to optimize acceptability of the trial.

For patients undergoing allogeneic HCT, fluconazole's spectrum of activity is limited primarily to *Candida* spp. It has been demonstrated in two pivotal trials to be superior to placebo, but no patients under the age of 12 years were included in either trial.[1,2] Therefore, while fluconazole has been adopted as the "gold standard" for prophylaxis, for young children this is not based on any data. Voriconazole has the attractive feature of possessing activity against *Aspergillus* spp., as well as certain fluconazole-resistant strains of *Candida*, however, with the small trade-off that it is potentially less effective than fluconazole against fluconazole-susceptible strains of *Candida*, where it is fungistatic, rather than fungicidal.[43] More importantly, the pharmacokinetics of voriconazole are not simple. In adults and children over the age of 12 years (the subjects of most trials to date), voriconazole has non-linear properties with relatively well-established dosing regimens. Even in adults however, recent studies have called into question the "standard" dosing, and have proposed dosing based on serum drug levels due to ~25% of patients found to have extremely low voriconazole levels.[4,5,49] Part of this variability may be due to polymorphisms of the gene encoding for CYP2C19, which can result in an increase or decrease in voriconazole metabolism.[5] In children, the situation is even more problematic due to linear kinetics. In children between the ages of 2 and 12 years, the optimal dose may be 7 mg/kg twice daily,[7,9] while in children < 2 years of age, it may be as high as 8.5 mg/kg/dose twice daily.[8] However, none of these opinions regarding dosing and drug level monitoring have been universally-accepted, leading to a potential wide range of different treatment strategies and outcomes. Nevertheless, because of the advantage of voriconazole against *Aspergillus* spp., its use has been adopted for primary prophylaxis at many institutions, despite a paucity of data to support this practice.

In the only head-to-head prospective trial of fluconazole vs. voriconazole, although there was a trend towards less IFI in the voriconazole arm, the difference was not statistically significant ($P = .12$).[3] Furthermore, while patients over two years of age were eligible for this trial, in reality the number of pediatric patients enrolled was very small (n = 51), and in fact, no patient under the age of 9 years was given fluconazole. Therefore, the best trial to date has not been able to demonstrate that there is a difference between using fluconazole or voriconazole for IFI prophylaxis, despite the theoretical reasons why they might be different. Consequently, this is the rationale for the comparator being either fluconazole or voriconazole. Also, no trial to date has proven what the optimal agent is for children, especially those less than 12 years of age.

Because of this lack of convincing data to support one azole over the other, when designing this trial, it was felt that forcing the local institutions to adopt one agent as their standard-of-care would likely lead to a significant degree of non-participation. This potential conflict was confirmed during informal polling of leading pediatric transplant physicians both on the COG Stem Cell Transplant Steering Committee and at the open sessions of the last several COG National Meetings. In contrast, the study design that we have proposed clearly has widespread support in the pediatric HCT community (89% of respondents indicating that they wished to participate in the trial). As noted above, this potential issue has been dealt with before in other trials, such as the non-blinded randomized comparison of posaconazole to the institutional choice of fluconazole or itraconazole, which led to its wide acceptance by the community.[22]

# 3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

## 3.1 Study Enrollment

### 3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

### 3.1.2 IRB Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206),
Emailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

### 3.1.3 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the RDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

### 3.1.4 Timing

Patients must be enrolled before protocol-directed antifungal prophylaxis begins. The date protocol-directed antifungal prophylaxis is projected to start must be no later than **five (5)** calendar days after the date of study enrollment.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.5 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study. To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

3.1.6 Randomization

Randomization will take place at the time a patient is entered On Study via RDE. Patients will be assigned to either antifungal prophylaxis with caspofungin or antifungal prophylaxis with an azole (fluconazole or voriconazole). Randomization will be stratified by:

- Center choice of azole: fluconazole vs. voriconazole.
- Age: ≥ 12 years vs. < 12 years
- Type of transplant: Umbilical cord blood (UCB) donor vs. Non-UCB donor with ex vivo T-cell-depletion vs. Non-UCB donor with standard pharmacologic GVHD prophylaxis.

## 3.2 Patient Eligibility Criteria

**Important note**: **The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.**

**All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. See Section 7.1 for required studies to be obtained prior to starting protocol therapy.**

INCLUSION CRITERIA

3.2.1 Age

For centers that will use fluconazole as the antifungal comparator:
Age ≥ 3 months and < 21 years.

For centers that will use voriconazole as the antifungal comparator:
Age ≥ 2 years and < 21 years.

3.2.2 Diagnosis

- The patient must be undergoing allogeneic HCT from any donor (including matched related) with any stem cell source for any underlying condition.

3.2.3 Performance Level

Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.
See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

3.2.4 Organ Function Requirements

3.2.4.1 Adequate Renal Function Defined As:

– Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 $m^2$ **or**

– A serum creatinine based on age/gender as follows:

| Age | Maximum Serum Creatinine (mg/dL) | |
|---|---|---|
| | Male | Female |
| 1 month to < 6 months | 0.4 | 0.4 |
| 6 months to < 1 year | 0.5 | 0.5 |
| 1 to < 2 years | 0.6 | 0.6 |
| 2 to < 6 years | 0.8 | 0.8 |
| 6 to < 10 years | 1 | 1 |
| 10 to < 13 years | 1.2 | 1.2 |
| 13 to < 16 years | 1.5 | 1.4 |
| ≥ 16 years | 1.7 | 1.4 |

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR[50] utilizing child length and stature data published by the CDC.

3.2.4.2 Adequate Liver Function Defined As:

- Total bilirubin < 2.5 mg/dL unless the increase in bilirubin is attributable to Gilbert's Syndrome, and

- SGOT (AST) or SGPT (ALT) < 5X upper limit of normal (ULN) for age.

EXCLUSION CRITERIA

3.2.5 Within 90 days of enrollment:

- Patients with a proven or probable invasive mold infection are not eligible.
- Patients with an incompletely treated invasive yeast infection are not eligible.

Patients with an elevated galactomannan level (≥ 0.5 Index) within 30 days prior to time of enrollment (if performed) must have a full evaluation for invasive aspergillosis (including a negative chest CT scan) during that time period to be eligible for enrollment.

3.2.6 Patients receiving treatment for an IFI are not eligible.

3.2.7 Patients with a history of echinocandin or azole hypersensitivity are not eligible.

3.2.8 Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.

3.2.9 Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation.

3.2.10 Lactating females are not eligible unless they have agreed not to breastfeed their infants.

REGULATORY

3.2. 11 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2. 12 All institutional, FDA, and NCI requirements for human studies must be met.

## 4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

### 4.1 Overview of Treatment Plan

This is a randomized open-label clinical trial designed to assess the efficacy of caspofungin for preventing IFI (including IA) compared to antifungal prophylaxis with an azole (fluconazole or voriconazole), the standard therapies used in most COG institutions as prophylaxis in patients undergoing HCT.

At the time of enrollment, the enrolling center will declare whether the comparator arm will be fluconazole or voriconazole based upon that institution's standard of care and the choice of comparator should remain constant for the duration of the study.

Patients who consent to participate in ACCL1131 will be randomly assigned to antifungal prophylaxis with either an azole or caspofungin. Treatment with any antifungal prophylaxis initiated prior to enrollment must be terminated prior to starting protocol-directed antifungal therapy. Protocol prophylaxis will be started within 24 hours of transplant (Day 0). Administration of antifungal prophylaxis will continue until (a) HCT Day +42; OR (b) Day of Hospital Discharge; OR (c) Patient meets any off-protocol criteria (Section 8.1). Following discontinuation of study medications, institutions may revert to local standard of care for post-engraftment antifungal prophylaxis.

If other systemic antifungal therapy is initiated for empiric therapy or treatment of suspected infection, then protocol prophylaxis should be held and assigned prophylaxis should resume when other systemic antifungal therapy is discontinued if this occurs prior to Day +42, Day of Hospital Discharge, or at the time a patient is taken off-protocol therapy (see Section 8.1).

Fluconazole and voriconazole may be administered either intravenously (IV) or orally. Caspofungin is only available as an IV formulation.

#### 4.1.1 Randomization

At the time of enrollment, patients will be randomly assigned to one of two treatment regimens:

i) Azole Arm: This group will receive fluconazole or voriconazole, and represents the **standard arm**.

ii) Caspofungin Arm: This group will receive caspofungin and represents the **experimental arm**.

Randomization will be stratified into groups based on:

i) Center choice of azole: 1) fluconazole vs. 2) voriconazole.
ii) Age: 1) ≥12 years vs. 2) < 12 years
iii) Type of transplant: 1) Umbilical cord blood (UCB) donor vs. 2) Non-UCB donor with ex vivo T-cell-depletion vs. 3) Non-UCB donor with standard pharmacologic GVHD prophylaxis.

4.1.2 Empirical Antifungal Therapy

The persistence of fever for 3 to 5 days despite broad spectrum antibiotic therapy warrants the investigation for IFIs and initiation of empiric antifungal therapy.[51] Amphotericin B (lipid products) is a reasonable option based on its broad spectrum of activity as empiric antifungal therapy in all treatment arms. The type, dose, and duration of non-assigned antifungal agent usage will be tracked. Assigned antifungal prophylaxis should be held during administration of these other systemic antifungal agents.

4.1.3 Concomitant Therapy Restrictions

4.1.3.1 Fluconazole

Some azoles, including fluconazole, have been associated with prolongation of the QT interval by electrocardiogram. Drugs known to prolong the QT interval should be used with caution or avoided with fluconazole. The administration of terfenadine with high dose fluconazole (≥ 400 mg adult dose) and cisapride with any dose of fluconazole is contraindicated. A list of drugs that prolong the QT interval can be found at http://www.azcert.org.

Clinically or potentially significant drug interactions with fluconazole and the following agents have been observed: oral hypoglycemics (tolbutamide, glyburide, glipizide), coumarin-type anticoagulants (e.g., warfarin), phenytoin, cyclosporine, rifampin, theophylline, rifabutin, tacrolimus, short-acting benzodiazepines (more pronounced with oral fluconazole), and oral contraceptives. Since rifampin enhances the metabolism of concurrently administered fluconazole and the dose of fluconazole may need to be increased, the use of rifampin in this study should be avoided. Careful monitoring is required when fluconazole is administered with the other drugs. Careful monitoring of calcineurin inhibitor levels is highly recommended on this protocol.

Co-administration of oral fluconazole with combination contraceptives has resulted in an overall mean increase in ethinyl estradiol and levonorgestrel levels. However, in some patients, levels of ethinyl estradiol and levonorgestrel decreased by up to 47% and 33%, respectively. While there is evidence that fluconazole can inhibit the metabolism of ethinyl estradiol and levonorgestrel, there is no evidence that fluconazole can induce the metabolism of these drugs. The clinical significance of the above effects is currently undetermined and may simply be a product of inter-individual variation in metabolism.

Fluconazole inhibits several cytochrome P450 (CYP450) isoenzymes and may increase the serum level of drugs metabolized by CYP450 especially at high doses (> 200 mg adult dose). For a list of drugs metabolized by the CYP450 system see http://medicine.iupui.edu/flockhart.

4.1.3.2 Voriconazole

Some azoles, including voriconazole, have been associated with prolongation of the QT interval by electrocardiogram. Drugs known to prolong the QT interval should be used with caution or avoided with voriconazole. The administration of terfenadine and cisapride with any dose of voriconazole is contraindicated. A list of drugs that prolong the QT interval can be found at http://www.azcert.org.

Clinically or potentially significant drug interactions with voriconazole and the following agents have been observed: oral hypoglycemics (tolbutamide, glyburide, glipizide), coumarin-type anticoagulants (e.g., warfarin), phenytoin, cyclosporine, rifampin, theophylline, tacrolimus, short-acting benzodiazepines, and oral contraceptives. Since rifabutin enhances the metabolism of concurrently administered voriconazole and the dose of voriconazole may need to be increased, the use of rifabutin in this study should be avoided. Careful monitoring is required when voriconazole is administered with the other drugs. Currently, the co-administration of voriconazole and sirolimus is contraindicated due to significant elevation in sirolimus levels. It is also to be expected that the co-administration of voriconazole and a calcineurin inhibitor

(cyclosporine or tacrolimus) will result in a 1.7 to 3 fold increase in cyclosporine or tacrolimus levels. The FDA label recommends that the dosing of cyclosporine be decreased by 50%, and the dosing of tacrolimus be decreased by 66%, of the normal dose when given with voriconazole. Careful monitoring of calcineurin inhibitor levels is highly recommended on this protocol.

Voriconazole inhibits several cytochrome P450 (CYP450) isoenzymes and may increase the serum level of drugs metabolized by CYP450. For a list of drugs metabolized by the CYP450 system see http://medicine.iupui.edu/flockhart.

4.1.3.3 Caspofungin

Co-administration of caspofungin with certain inducers of drug clearance and/or mixed inducer/inhibitors (e.g., efavirenz, nevirapine, phenytoin, rifampin, dexamethasone, and carbamazepine) may result in clinically important reductions in plasma caspofungin concentrations. Therefore, the use of these interacting drugs should be avoided if possible.

Cyclosporine increases the caspofungin area under the concentration curve (AUC) which may result in a transient elevation of ALT/SGPT and AST/SGOT. Liver function tests should be closely monitored in patients receiving caspofungin and cyclosporine. Patients who develop abnormal liver function tests should be monitored and the risk/benefit of continuing concomitant therapy should be evaluated. The manufacturer of caspofungin recommends that concomitant use with cyclosporine should only occur in those patients for whom the potential benefit outweighs the potential risk. Centers comfortable with the use of tacrolimus for GVHD prophylaxis may consider utilizing this agent in place of cyclosporine.

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp

## 4.2 Administration Schedule: AZOLE ARM

### 4.2.1 FLUCONAZOLE COMPARATOR

Patients randomized to this regimen will start prophylaxis within 24 hours of transplant (Day 0). Continue prophylaxis until the occurrence of any of the following, whichever is sooner:

- Day +42
  *OR*
- Day of Hospital Discharge
  *OR*
- Patient meets any of the off protocol therapy criteria (Section 8.1)

If other systemic antifungal therapy is initiated for empiric therapy or treatment of suspected infection, then fluconazole prophylaxis should be held, and fluconazole should resume when other systemic antifungal therapy is discontinued if this occurs prior to Day +42, Day of Hospital Discharge, or patient off protocol.

Following completion of study prophylaxis, institutions may revert to local standard of care for post-engraftment anti-fungal prophylaxis.

**FLUCONAZOLE**: **by slow IV infusion over 1-2 hours* (or longer) OR by mouth.**

Age ≥ 3 months to 17.99 years: Dose: 12 mg/kg/day once daily (maximum dose: 400 mg/day)
Age ≥ 18 years to 20.99 years: Dose: 6 mg/kg/day once daily (maximum dose: 400 mg/day)

*For IV: The rate of infusion should not exceed 200 mg/hour.

Rounding:
*Tablets*: Round the dose to the closest 50 mg.
*Suspension*: Round the volume to the closest tenth of an mL. Round 0.05 mL up (e.g., round 3.15 mL to 3.2 mL).

Oral fluconazole can be taken at any time during the day with or without food. It should be administered at approximately the same time each day. If vomiting occurs within 30 minutes of taking the dose, the dose may be repeated once. If a dose is missed, it should be taken immediately and only if there are at least 12 hours until the next scheduled dose.

**SEE SECTION 5.0 FOR DOSE MODIFICATIONS FOR TOXICITIES.** For COG Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp

The therapy delivery map (TDM) for fluconazole prophylaxis is on the next page.

| 4.2.2 **Fluconazole Treatment Arm**. Patients randomized to fluconazole arm. | _____ Patient name or initials _____ DOB |
|---|---|

Prophylaxis with fluconazole begins within 24 hours of transplant (Day 0). Extensive administration details are in Section 4.2.1. This TDM is on One (1) page.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| FLUCONAZOLE | Slow IV infusion over 1-2 hours* (or longer) OR by mouth. | ≥ 3 months – 17.99 years: 12 mg/kg/day (IV or enteral dose) **Maximum dose: 400 mg/day**<br><br>18 – 20.99 years: 6 mg/kg/day (IV or enteral dose) **Maximum dose: 400 mg/day** | Once daily | Start within 24 hours of transplant (Day 0).<br><br>*For IV**:** The infusion rate should not exceed 200 mg/hour<br><br>See Section 4.2.1 for oral drug administration. | a. History, PE (ht, wt, BSA), albumin<br>b. CBC, diff, plts, creatinine, AST, ALT, bilirubin<br>c. GVHD Scoring<br>d. IFI Checklist<br>*If patient consents:*<br>e. beta-D glucan testing (see Section 13)<br>f. SNP (see Section 14)<br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |

**Enter Date of Transplant Here_____ Ht____cm Wt___kg BSA___m²**

| Date Due | Date Given | Day | FLUCONAZOLE _____mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|
| | | **Enter calculated dose above and actual dose administered below** | | | |
| | | 1 *[HCT Day 0 or +1]^* | _____mg | a, b, e, f | |
| | | … | | | |
| | | 4 | | b | |
| | | … | | | |
| | | 8 | | a, b, e | |
| | | … | | | |
| | | 11 | | b | |
| | | … | | | |
| | | 15 | | a, b, c, e | |
| | | … | | | |
| | | 18 | | b | |
| | | … | | | |
| | | 22 | | a, b, c, e | |
| | | … | | | |
| | | 25 | | b | |
| | | … | | | |
| | | 29 | | a, b, c, e | |
| | | … | | | |
| | | 32 | | b | |
| | | … | | | |
| | | 36 | | a, b, c, e | |
| | | … | | | |
| | | 39 | | b | |
| | | … | | | |
| | | 43* [HCT Day +42] | Or End Date: _____ | a, b, c, d, e | |

*Continue prophylaxis until criteria in Section 4.2.1 are met (may be less than 43 days).
^Following completion of study prophylaxis, institutions may revert to local standard of care for post-engraftment antifungal prophylaxis.
^Because study medication may be started within 24 hours of HCT, some patients may actually begin on HCT Day -1, such that they would potentially receive up to 44 days of study medication.

**SEE SECTION 5.0 FOR DOSE MODIFICATIONS FOR TOXICITIES** and the COG website posted materials for Supportive Care Guidelines https://members.childrensoncologygroup.org/prot/reference_materials.asp

### 4.2.3 VORICONAZOLE COMPARATOR

Patients randomized to this regimen will start prophylaxis within 24 hours of transplant (Day 0). Continue prophylaxis until the occurrence of any of the following, whichever is sooner:

- Day +42
  *OR*
- Day of Hospital Discharge
  *OR*
- Patient meets any of the off protocol therapy criteria (Section 8.1)

If other systemic antifungal therapy is initiated for empiric therapy or treatment of suspected infection, then voriconazole prophylaxis should be held and voriconazole should resume when other systemic antifungal therapy is discontinued if this occurs prior to Day +42, Day of Hospital Discharge, or patient off protocol.

Following completion of study prophylaxis, institutions may revert to local standard of care for post-engraftment anti-fungal prophylaxis.

**VORICONAZOLE**: **by slow IV infusion over 1-2 hours* (or longer) OR by mouth:**

| Age | Weight | Loading dose*<br>IV q12h x 2 doses | Maintenance dose<br>IV or PO q12h |
|---|---|---|---|
| 2 – 11.99 years | all | IV: 9 mg/kg | IV: 8 mg/kg<br>or<br>PO: 9 mg/kg<br>(max: 350 mg/dose) |
| 12 – 13.99 years | < 50 kg | IV: 9 mg/kg | IV: 8 mg/kg<br>or<br>PO: 9 mg/kg<br>(max: 350 mg/dose) |
| 12 – 13.99 years | ≥ 50 kg | IV: 6 mg/kg | IV: 4 mg/kg<br>or<br>PO: 200 mg |
| ≥ 14 years | All | IV: 6 mg/kg | IV: 4 mg/kg<br>or<br>PO: 200 mg |

***All loading doses should be given IV q12h x 2 doses followed by either IV or PO maintenance dosing q12h.***

Centers that currently modify voriconazole prophylaxis dosing based on trough concentrations may continue this practice, and therefore may end up either exceeding the study recommended maximum dose listed above (if the trough is low) or be lower than the study recommended starting dose based on weight (if the trough is high). The actual dose administered and the reason for an adjustment to the study recommended dose will be recorded.

*For IV: The rate of infusion should not exceed 3 mg/kg/hour

Oral voriconazole is available as 50 and 200 mg tablets and as an oral suspension at a concentration of 40 mg/mL.

Rounding:
*Tablets*: Round the dose to the closest 50 mg.
*Suspension*: Round the volume to the closest tenth of a mL. Round 0.05 mL up (e.g., round 3.15 mL to 3.2 mL).

Oral voriconazole is best taken 1 hour before or 1 hour after a meal. It should be administered at approximately the same times each day. If vomiting occurs within 30 minutes of taking the dose, the dose may be repeated once. If a dose is missed, it should be taken immediately and only if there are at least 12 hours until the next scheduled dose.

**SEE SECTION 5.0 FOR DOSE MODIFICATIONS FOR TOXICITIES.** For COG Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp

The therapy delivery map (TDM) for voriconazole prophylaxis is on the next page.

| 4.2.4 **Voriconazole Treatment Arm**. Patients randomized to voriconazole arm. | _____ Patient name or initials _____ DOB |
|---|---|

Prophylaxis with voriconazole begins within 24 hours of transplant (Day 0). Extensive administration details are in Section 4.2.3. This TDM is on One (1) page.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| VORICONAZOLE | Slow IV infusion over 1-2 hours[#] (or longer) OR by mouth. | 2 - 11.99 years (all weights):<br>LD IV: 9 mg/kg/dose<br>MD IV: 8 mg/kg/dose **or**<br>PO: 9 mg/kg/dose<br>(max: 350 mg/dose)<br><br>12 – 13.99 years < 50 kg:<br>LD IV: 9 mg/kg/dose<br>MD IV: 8 mg/kg/dose **or**<br>PO: 9 mg/kg/dose<br>(max: 350 mg/dose)<br><br>12 – 13.99 years ≥ 50 kg:<br>LD IV: 6 mg/kg/dose<br>MD IV: 4 mg/kg/dose **or**<br>PO: 200 mg/dose<br><br>≥ 14 years (all weights):<br>LD IV: 6 mg/kg/dose<br>MD IV: 4 mg/kg/dose **or**<br>PO: 200 mg/dose | **Twice daily**<br>Day 1<br>Day 2 (and subsequently)<br><br>Day 1<br>Day 2 (and subsequently)<br><br>Day 1<br>Day 2 (and subsequently)<br><br>Day 1<br>Day 2 (and subsequently) | Start within 24 hours of transplant (Day 0).<br><br>[#]For IV**:** The infusion rate should not exceed 3 mg/kg/hour | a. History, PE (ht, wt, BSA), albumin<br>b. CBC, diff, plts, creatinine, AST, ALT, bilirubin<br>c. GVHD Scoring<br>d. IFI Checklist<br>*If patient consents:*<br>e. beta-D glucan testing (see Section 13)<br>f. SNP (see Section 14)<br><br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |

**Enter Date of Transplant Here_____ Ht____cm Wt____kg BSA____m²**

| Date Due | Date Given | Day | VORICONAZOLE<br>Day 1:_____mg;<br>Day 2 and Subsequently: _____mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|
| | | **Enter calculated dose above & actual dose administered below** | | | |
| | | 1 *[HCT Day 0 or +1]^* | **LD: _____mg _____mg** | a, b, e, f | |
| | | 2 | **MD: _____mg _____mg** | | |
| | | ... | | | |
| | | 4 | | b | |
| | | ... | | | |
| | | 8 | | a, b, e | |
| | | ... | | | |
| | | 11 | | b | |
| | | ... | | | |
| | | 15 | | a, b, c, e | |
| | | ... | | | |
| | | 18 | | b | |
| | | ... | | | |
| | | 22 | | a, b, c, e | |
| | | ... | | | |
| | | 25 | | b | |
| | | ... | | | |
| | | 29 | | a, b, c, e | |
| | | ... | | | |
| | | 32 | | b | |
| | | ... | | | |
| | | 36 | | a, b, c, e | |
| | | ... | | | |
| | | 39 | | b | |
| | | ... | | | |
| | | 43*[HCT Day +42] | Or End Date: _____ | a, b, c, d, e | |

*Continue prophylaxis until criteria in Section 4.2.1 are met (may be less than 43 days).
^ Following completion of study prophylaxis, institutions may revert to local standard of care for post-engraftment antifungal prophylaxis. ^Because study medication may be started within 24 hours of HCT, some patients may actually begin on HCT Day -1, such that they would potentially receive up to 44 days of study medication.

**SEE SECTION 5.0 FOR DOSE MODIFICATIONS FOR TOXICITIES** and the COG website posted materials for Supportive Care Guidelines
https://members.childrensoncologygroup.org/prot/reference_materials.asp

### 4.3 Administration Schedule: CASPOFUNGIN ARM

Patients randomized to this regimen will start prophylaxis within 24 hours of transplant (Day 0). Continue prophylaxis until the occurrence of any of the following, whichever is sooner:

- Day +42
  *OR*
- Day of Hospital Discharge
  *OR*
- Patient meets any of the off protocol therapy criteria (Section 8.1)

If other systemic antifungal therapy is initiated for empiric therapy or treatment of suspected infection, then caspofungin prophylaxis should be held and caspofungin should resume when other systemic antifungal therapy is discontinued if this occurs prior to Day +42, Day of Hospital Discharge, or patient off protocol.

Following completion of study prophylaxis, institutions may revert to local standard of care for post-engraftment anti-fungal prophylaxis.

**CASPOFUNGIN: by slow IV infusion over no less than 1 hour.**

Loading dose (LD): 70 mg/m$^2$/day***(Maximum dose: 70 mg/day)** First day of therapy.
Maintenance dose (MD): 50 mg/m$^2$/day***(Maximum dose: 50 mg/day)** – Subsequent days

*Use the Mosteller Formula for BSA calculation.

**SEE SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES.**

The therapy delivery map (TDM) for caspofungin prophylaxis is on the next page.

| 4.3.1 **Caspofungin Treatment Arm**<br>Patients randomized to caspofungin arm. | _____ Patient name or initials _____ DOB |
|---|---|

Prophylaxis with caspofungin begins within 24 hours of transplant (Day 0). Extensive administration details are in Section 4.3. This TDM is on One (1) page.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| CASPOFUNGIN | IV over 1 hour | 70 mg/m$^2$/day<br>50 mg/m$^2$/day | 1<br>2 (and subsequently) | Start within 24 hours of transplant (Day 0).<br><br>**LD: Maximum dose: 70 mg/day**<br><br>**MD: Maximum dose: 50 mg/day** | a. History, PE (ht, wt, BSA), albumin<br>b. CBC, diff, plts, creatinine, AST, ALT, bilirubin<br>c. GVHD Scoring<br>d. IFI Checklist (see Section 10.2)<br><br>*If patient consents::*<br>e. beta-D glucan testing (see Section 13)<br>f. SNP (see Section 14)<br><br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |

**Enter Date of Transplant Here:_____ Ht_____cm Wt____kg BSA____m$^2$**

| Date Due | Date Given | Day | CASPOFUNGIN<br>Day 1:_____mg;<br>Day 2 and Subsequently: _____mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|
| | | **Enter calculated dose above and actual dose administered below** | | | |
| | | 1<br>*[HCT Day 0 or +1]^* | LD: _____mg | a, b, e,f | |
| | | 2 | MD: _____mg | | |
| | | ... | | | |
| | | 4 | | b | |
| | | ... | | | |
| | | 8 | | a, b, e | |
| | | ... | | | |
| | | 11 | | b | |
| | | ... | | | |
| | | 15 | | a, b, c, e | |
| | | ... | | | |
| | | 18 | | b | |
| | | ... | | | |
| | | 22 | | a, b, c, e | |
| | | ... | | | |
| | | 25 | | b | |
| | | ... | | | |
| | | 29 | | a, b, c, e | |
| | | ... | | | |
| | | 32 | | b | |
| | | ... | | | |
| | | 36 | | a, b, c, e | |
| | | ... | | | |
| | | 39 | | b | |
| | | ... | | | |
| | | 43* [HCT Day +42] | Or End Date: _____ | a, b, c, d, e | |

*Continue prophylaxis until criteria in Section 4.2.1 are met (may be less than 43 days).^ Following completion of study prophylaxis, institutions may revert to local standard of care for post-engraftment antifungal prophylaxis.
^Because study medication may be started within 24 hours of HCT, some patients may actually begin on HCT Day -1, such that they would potentially receive up to 44 days of study medication.

**SEE SECTION 5.0 FOR DOSE MODIFICATIONS FOR TOXICITIES** and the COG website posted materials for Supportive Care Guidelines https://members.childrensoncologygroup.org/prot/reference_materials.asp

## 5.0 DOSE MODIFICATIONS FOR TOXICITIES

### 5.1 Impaired Renal Function

When estimating renal function for adjusting drug doses, use the Schwartz formula for patients < 18 years of age and the Cockcroft and Gault equation for patients ≥ 18 years of age.

**Fluconazole:**

| **Creatinine clearance** (mL/min/1.73m$^2$) | **Percent of dose** | **Dose in mg/kg (max dose)** | |
|---|---|---|---|
| | | **≥ 3 months to 17.99 years:** | **≥ 18 years to 20.99 years:** |
| > 50 | 100% | 12 mg/kg (max 400 mg) | 6 mg/kg (max 400 mg) |
| ≤ 50 (no dialysis) | 50% | 6 mg/kg (max 200 mg) | 3 mg/kg (max 200 mg) |
| Hemodialysis | 100% after each dialysis | 12 mg/kg (max 400 mg after each dialysis) | 6 mg/kg (max 400 mg after each dialysis) |

**Voriconazole:**

| **Creatinine clearance** (mL/min/1.73m$^2$) | **Percent of dose** | **Dose in mg/kg (max dose)** |
|---|---|---|
| > 50 | PO & IV: 100% | Per Section 4.2.3 |
| ≤ 50 (no dialysis) | PO: 100%<br>IV: Switch patient to oral voriconazole* | Per Section 4.2.3 |
| Hemodialysis | PO: 100% after each dialysis<br>Avoid IV dosage form* | Per Section 4.2.3 |

*Parenteral formulation of voriconazole contains the excipient sulfobutyl ether beta-cyclodextrin sodium which accumulates in patients with renal impairment, and can worsen renal impairment. If a patient with renal failure cannot take the oral formulation of voriconazole, then voriconazole should be held until either the renal failure or inability to tolerate oral medications improves, at which point it may be restarted.

**Caspofungin:**
Adjustment of the dose is not needed in the setting of impaired renal function. Caspofungin is not dialyzable and supplementation is not required following hemodialysis**.**

### 5.2 Impaired Liver Function

**Fluconazole:**
Fluconazole should be held in patients who develop signs and symptoms consistent with liver disease or elevations in hepatic function tests as defined by an ALT or AST > 5 x ULN or serum total bilirubin > 2 x ULN. Once the ALT and AST are < 2.5 x ULN for age and the serum total bilirubin is < 1.5 x ULN for age, the fluconazole can be re-started at the calculated dose (no dose adjustment). More frequent monitoring (2-3 times per week) of ALT, AST, and total bilirubin should be considered upon resumption of fluconazole. If the ALT, AST, or total bilirubin again become elevated past these criteria (ALT or AST > 5 x ULN or serum total bilirubin > 2 x ULN), then fluconazole should be discontinued (the patient will be removed from protocol therapy).

**Voriconazole:**
Voriconazole should be held in patients who develop signs and symptoms consistent with liver disease or elevations in hepatic function tests as defined by an ALT or AST > 5 x ULN or serum total bilirubin > 2 x ULN. Once the ALT and AST are < 2.5 x ULN for age and the serum total bilirubin is < 1.5 x ULN

for age, the voriconazole can be re-started at the calculated dose (no dose adjustment). More frequent monitoring (2-3 times per week) of ALT, AST, and total bilirubin should be considered upon resumption of voriconazole. If the ALT, AST, or total bilirubin again become elevated past these criteria (ALT or AST > 5 x ULN or serum total bilirubin > 2 x ULN), then voriconazole should be discontinued (the patient will be removed from protocol therapy).

**Caspofungin:**

For all patients:

| Child – Pugh score[52] | Percent of dose | Dose in mg/m$^2$ (max dose) |
|---|---|---|
| Mild (5-6) | 100% | Loading dose: 70 mg/m$^2$/dose (max 70 mg)<br>Maintenance dose: 50 mg/m$^2$/dose (max 50 mg) |
| Moderate (7-9) | Loading dose: 100%<br>Maintenance dose: 70% | Loading dose: 70 mg/m$^2$/dose (max 70 mg)<br>Maintenance dose: 35 mg/m$^2$/dose (max 35 mg) |
| Severe (> 9) | Hold | Hold |

To calculate the Child-Pugh Score:

| Factor | 1 Point | 2 Points | 3 Points |
|---|---|---|---|
| Total Bilirubin (mg/dL) | < 2.0 | 2.0-3.0 | > 3.0 |
| Albumin (g/dL) | > 3.5 | 2.8-3.5 | < 2.8 |
| INR | < 1.7 | 1.7-2.2 | > 2.2 |
| Ascites | No Ascites | Ascites, controlled | Ascites, poorly controlled |
| Encephalopathy | No Encephalopathy | Encephalopathy, controlled | Encephalopathy, poorly controlled |

Caspofungin may be restarted or increased if liver function (and Child-Pugh score) improves.

### 5.3 Other Toxicities

Fluconazole, voriconazole, and caspofungin can be held (for up to a seven day window) in patients who develop any toxicity that the local investigator believes may be related to the drug. If the protocol agent is ultimately deemed to not be responsible for the toxicity, the agent can be re-started at the calculated dose. If the toxicity returns, then the agent should be discontinued (the patient will be removed from protocol therapy). Other systemic antifungal prophylactic agents should not be utilized during this potential toxicity window.

## 6.0 DRUG INFORMATION

**Please see Appendix IV for drug interactions associated with the drugs used in this study**. See the consent document for toxicities. All other information is available on the COG website in the commercial agent monographs manual titled "Drug Information for Commercial Agents used by the Children's Oncology Group." This manual is provided under Standard Sections for Protocols at: https://members.childrensoncologygroup.org/prot/reference_materials.asp.

### 6.1 CASPOFUNGIN (caspofungin acetate, Cancidas®) (01/25/13)

**Source and Pharmacology:**
Caspofungin acetate, a semisynthetic lipopeptide synthesized from a fermentation product of *Glarea lozoyensis*, is an echinocandin antifungal agent. It inhibits the synthesis of beta (1, 3)-D-glucan, an essential component of filamentous fungal cell wall that is not present in mammalian cells. Caspofungin has been shown to be active both *in vitro* and in clinical infections against most strains of the following organisms: *Aspergillus (A) fumigatus, A flavus, A terreus, Candida (C) albicans, C glabrata, C guilliermondii, C krusei, C parapsilosis, C tropicalis*. Following an intravenous infusion, the plasma concentration of caspofungin declines in a polyphasic manner. A short alpha-phase that occurs immediately post-infusion is followed by a beta-phase (half-life of 9 to 11 hours) and an additional, longer half-life phase, gamma-phase (half-life of 40-50 hours). Caspofungin is extensively (about 97%) protein bound to albumin and is cleared mainly by distribution (rather than excretion or biotransformation). Caspofungin is slowly metabolized in the liver via hydrolysis and *N*-acetylation. Following a single intravenous dose, 35% of the parent drug and metabolites was excreted in feces and 41% was excreted in the urine. After multiple doses of caspofungin 50 mg/day were given intravenously to adults, the total body clearance was 10.6 ± 3.8 mL/min. When a dose of 50 mg/m$^2$/day was given intravenously to children and adolescents, the total body clearance was 12.6 ± 5.5 mL/min in adolescents (12 to 17 years of age), 6.4 ± 2.6 mL/min in children 2 to 11 years and 3.2 ± 0.4 mL/min in children 3 to 23 months.

Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for, and does not inhibit or induce, cytochrome P-450 isoenzymes *in vitro*. However, co-administration of caspofungin with certain inducers of drug clearance and/or mixed inducer/inhibitors (e.g., efavirenz, nevirapine, phenytoin, rifampin, dexamethasone, and carbamazepine) may result in clinically important reductions in plasma caspofungin concentrations. Cyclosporine increases caspofungin area under the curve (AUC) which results in a transient elevation of alanine transaminase (ALT) and aspartate transaminase (AST) and co-administration with tacrolimus may decrease tacrolimus AUC.

**Toxicity:**

| | **Common** Happens to 21-100 subjects out of every 100 | **Occasional** Happens to 5-20 subjects out of every 100 | **Rare** Happens to < 5 subjects out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | Pyrexia, chills, diarrhea, rash, infusion reaction (systemic) | Peripheral edema, phlebitis, nausea, vomiting, abdominal pain, cough, erythema, headache, hypotension | Anaphylaxis, respiratory failure, infusion site pain/pruritus/swelling, urticaria, arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, myocardial infarction, tachycardia, abdominal distension, upper abdominal pain, constipation, dyspepsia, asthenia, fatigue, anorexia, dizziness, somnolence, tremor, flushing, hypertension |
| **Prompt:** Within 2-3 weeks, prior to next course | Hypokalemia | Increase liver function tests (ALT/AST/Alkaline phosphatase), increase bilirubin, pneumonia | Anemia, coagulopathy, febrile neutropenia, neutropenia, thrombocytopenia, mucosal inflammation, petechiae, hepatic failure, hepatomegaly, hepatotoxicity, hepatic necrosis, jaundice, bacteremia, sepsis, urinary tract infection hypomagnesemia, hypercalcemia, hyperglycemia, arthralgia, back pain, pain in extremity, convulsion, anxiety, confusional state, depression, insomnia, hematuria, renal failure, dyspnea, epistaxis, hypoxia, tachypnea, pancreatitis, erythema multiforme, Stevens-Johnson, skin exfoliation |
| **Unknown Frequency and Timing:** | U.S. Food and Drug Administration's Pregnancy Category: Category C. It is not known if caspofungin crosses the placenta in humans. There are no adequate and well-controlled studies with the use of caspofungin in pregnant women.<br>In animal studies, caspofungin acetate has been shown to be embryotoxic. Abnormalities in rats, treated with caspofungin doses comparable to the human dose, included incomplete ossification of the skull and torso and increased incidence of cervical rib. In rabbits, incomplete ossifications of the talus/calcaneus were noted. In rats and rabbits caspofungin crossed the placenta and was evident in fetal plasma. | | |

**Formulation and Stability:**

Caspofungin is available as a lyophilized white to off-white powder/cake as a single-use vial in two vial sizes (50 mg and 70 mg). Only the 50 mg vials will be provided for use in this study. Each vials contains an intentional overfill. The 50 mg vials contain 54.6 mg. The 50 mg vials also contain 39 mg of sucrose and 26 mg of mannitol. The pH is adjusted during manufacturing with glacial acetic acid and sodium hydroxide. The lyophilized powder vials should be stored refrigerated at 2° to 8°C (36 to 46°F).

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.

**Preparation instructions in this monograph apply only to the Merck USA product as supplied for this study.**

Prior to reconstitution, equilibrate the refrigerated vial to room temperature. Aseptically add 10.8 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol to the vial. **Use diluents <u>without</u> benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.**

The concentration of the reconstituted solution depends on the vial size and is listed in the table below:

| CANCIDAS vial* | Total Drug Content (including overfill) | Reconstitution Volume to be added* | Resulting Concentration following Reconstitution** |
|---|---|---|---|
| 50 mg | 54.6 mg | 10.8 mL | 5 mg/mL |

**Preparation instructions apply only to the Merck USA product as provided in this study.*
*****Note different concentrations following reconstitution of the product in the vial.***

The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained. Visually inspect the reconstituted solution for particulate matter or discoloration during reconstitution and prior to infusion. Do not use hazy, precipitated, or discolored solutions. The reconstituted solution may be stored for up to 1 hour at ≤ 25°C (≤ 77°F). Since caspofungin vials are for single use only; the remaining solution should be discarded.

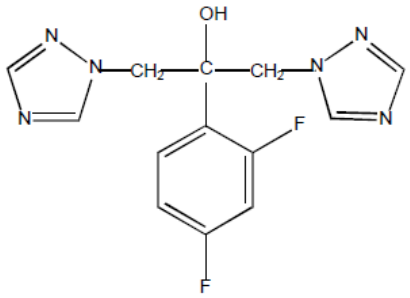
Dilute the appropriate volume of reconstituted caspofungin in 0.9%, 0.45% or 0.225% Sodium Chloride Injection or Lactated Ringers Injection. The final concentration should not exceed 0.5 mg/mL. The stability of the diluted solution for administration is 24 hours if stored at ≤ 25°C (≤ 77°F) or 48 hours if stored refrigerated at 2 to 8°C (36 to 46°F). Since the infusion solution contains no preservatives and as with all parenteral drug products, aseptic technique must be used during the preparation of the infusion bag. Institution guidelines should be followed to determine the expiration time of the infusion solution. The expiration time should not exceed 24 hours at ≤ 25°C (≤ 77°F) and 48 hours refrigerated.

Caspofungin is administered by slow intravenous infusion over no less than 1 hour. Do not mix or co-infuse caspofungin with other medications, as there are no data available on the compatibility of caspofungin with other intravenous medications. DO NOT USE DILUENTS CONTAINING DEXTROSE since caspofungin is not stable in diluents containing dextrose. The infusion line should be flushed with 0.9% sodium chloride before and after drug administration.

**Supplier:** Caspofungin will be supplied by the manufacturer Merck & Company, Inc., USA. The University of Pennsylvania School of Medicine will distribute the study medication to the study sites through their Investigational Drug Service Pharmacy. Drug ordering and drug destruction information can be found on the study website. Drug receiving and accountability records should be maintained and performed according to local institutional procedures. **Commercial supplies of caspofungin may be utilized in place of the study-supplied drug.**

## 6.2 FLUCONAZOLE (Diflucan®) (08/12/11)

**Source and Pharmacology:**
Fluconazole is a triazole antifungal agent. It is structurally related to imidazole-derivative azole antifungal agents (e.g., clotrimazole, ketoconazole, miconazole) however, imidazoles have 2 nitrogens in the azole ring (imidazole ring) and fluconazole and other triazoles (e.g., itraconazole, terconazole) have 3 nitrogens in the ring (triazole ring). In addition, fluconazole contains a second triazole which makes it a bistriazole derivative and a halogenated phenyl ring. Replacement of the imidazole ring with a triazole ring apparently results in increased antifungal activity and an expanded antifungal spectrum of activity. Presence of the two triazole rings may contribute to fluconazole's resistance to first-pass metabolism and the drug's low lipophilicity and protein binding. Presence of a halogenated phenyl ring increases antifungal activity and contributes to the aqueous solubility which make fluconazole suitable for IV formulation.




Fluconazole is a highly selective inhibitor of the fungal cytochrome P-450 dependent lanosterol 14-alpha-demethylase. This enzyme converts lanosterol to ergosterol. The subsequent loss of normal sterols correlates with the accumulation of 14 alpha-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole. Mammalian cell demethylation is much less sensitive to fluconazole inhibition.

Fluconazole is active against many fungi, including yeasts and dermatophytes. Fluconazole has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections: *Candida (C) albicans, C. glabrata* (Many strains are intermediately susceptible), *C parapsilosis, C tropicalis,* and *Cryptococcus neoformans*. *Candida krusei* is considered to be resistant to fluconazole. Resistance to fluconazole may arise from a modification in the quality or quantity of the target enzyme (lanosterol 14-α-demethylase), reduced access to the drug target by efflux of fluconazole out of the cell, or some combination of these mechanisms.

The pharmacokinetics of fluconazole are similar following IV or oral administration. In healthy adults receiving 50- or 100-mg doses of fluconazole given once daily by IV infusion over 30 minutes, serum concentrations of the drug 1 hour after dosing on the sixth or seventh day of therapy ranged from 2.14-2.81 or 3.86-4.96 mcg/mL, respectively. In a multiple-dose study in children 5-15 years of age, IV administration of 2-, 4-, or 8-mg/kg doses of fluconazole resulted in mean peak plasma concentrations of 5.5, 11.4, or 14.1 mcg/mL, respectively. Fluconazole is widely distributed into body tissues and fluids following oral or IV administration. In adult humans with normal renal function, concentrations of the drug in urine and skin may be 10 times higher than concurrent plasma concentrations. Concentrations in saliva, sputum, nails, blister fluid, blister skin, and vaginal tissue are approximately equal to concurrent plasma concentrations. Fluconazole, unlike some azole-derivative antifungal agents (e.g., itraconazole, ketoconazole), distributes readily into the CSF following oral or IV administration. Another difference from other azole-derivative antifungals (e.g., itraconazole, ketoconazole, miconazole), is that fluconazole is only 11-12% bound to plasma proteins while the other azole derivatives are highly protein bound.

The plasma elimination half-life of fluconazole in adults with normal renal function is approximately 30 hours (range: 20-50 hours). The mean plasma half-life of fluconazole in children 5 to 15 years of age after multiple IV doses is at the range of 15-18 hours. In healthy adults, fluconazole is eliminated mainly by renal excretion with approximately 80% excreted in the urine as unchanged drug. Small amounts of the drug are excreted in feces. Metabolism accounts for only 11% of total drug excreted. The renal clearance rate in adults is 0.27 to 0.63 mL/min/kg and in children age 5 to 15 years it is 0.4 to 0.66 mL/min/kg.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole should be administered with caution to patients with this potentially proarrhythmic condition. Clinically or potentially significant drug interactions between fluconazole and the following agents/classes have been observed: oral hypoglycemics (tolbutamide, glyburide, glipizide), coumarin-type anticoagulants (e.g., warfarin), phenytoin, cyclosporine, rifampin, theophylline, terfenadine, cisapride, astemizole, rifabutin, tacrolimus, short-acting benzodiazepines (more pronounced with oral fluconazole). Co-administration of oral fluconazole with combination contraceptives has resulted in an overall mean increase in ethinyl estradiol and levonorgestrel levels. However, in some patients, levels of ethinyl estradiol and levonorgestrel decreased by up to 47% and 33%, respectively. The clinical significance of the above effects is currently undetermined and may simply be a product of interindividual variation in metabolism.

**Toxicity:**

| | **Common**<br>Happens to 21-100 subjects out of every 100 | **Occasional**<br>Happens to 5-20 subjects out of every 100 | **Rare**<br>Happens to < 5 subjects out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | | Nausea, vomiting, diarrhea, abdominal pain, rash, pruritus | Anaphylaxis, allergic reaction, dyspnea, bloating, dyspepsia, taste perversion, QT prolongation, torsade de pointes, headache, dizziness, seizure. |
| **Prompt:**<br>Within 2-3 weeks, prior to next course | | Elevated ALT/AST | Stevens-Johnson syndrome and toxic epidermal necrolysis, hypokalemia, hypercholesterolemia, hypertriglyceridemia, leucopenia including neutropenia and agranulocytosis, eosinophilia, thrombocytopenia[L], hepatitis, cholestasis, fulminant liver failure |
| **Delayed:**<br>Any time later during therapy, excluding the above conditions | | | Alopecia with prolonged used |
| **Unknown Frequency and Timing:** | Pregnancy Category C. There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800 mg/day) of fluconazole. The relationship between fluconazole use and these events is unclear. Fluconazole should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus. | | |

*(L) Toxicity may also occur later.*

**Formulation and Stability:**
Fluconazole injection is an iso-osmotic, sterile, nonpyrogenic solution of fluconazole in a sodium chloride or dextrose diluent. Each mL contains 2 mg of fluconazole and 9 mg of sodium chloride or 56 mg of dextrose. The pH ranges from 4.0 to 8.0 in the sodium chloride diluent and from 3.5 to 6.5 in the dextrose diluent. Injection volumes of 100 mL and 200 mL are packaged in glass or in polyvinylchloride (PVC) bags. Specific storage requirements may vary among manufacturers. In general, fluconazole injection in glass bottles or PVC bags should be stored between 5-30°C (41-86°F) or between 5-25°C (41-77°F), respectively. Brief exposure to 40°C (104°F) does not adversely affect the product in the PVC container. Fluconazole solution should be protected from freezing. The overwrap moisture barrier should not be removed from the PVC bags until ready for use. The solution should not be used if it is cloudy or precipitated.

Fluconazole is available as 50, 100, 150, or 200 mg tablets that may contain lactose. Fluconazole for oral suspension contains 350 mg or 1400 mg of fluconazole powder in bottles which may contain sucrose and sodium benzoate. The tablets and dry powder of fluconazole for oral suspension should be stored between 68-77°F (20-25°C).

CANADIAN SITES:
Fluconazole injection is only available as 200 mg/100 mL. Oral fluconazole is available as 50 and 100 mg tablets. Fluconazole powder for oral suspension is only available as 350 mg of powder per bottle. Other product specifications are similar.

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.

Injection:
Fluconazole injection is provided as a 2 mg/mL solution in NS or $D_5W$ that is ready to infuse without further dilution. To prepare the infusion, the calculated dose volume in NS or $D_5W$ is transferred to an evacuated PVC infusion bag or to an evacuated glass bottle. Since fluconazole solution contains no preservatives, and as with all parenteral drug products, aseptic technique must be used during the preparation of the dose. Institution guidelines should be followed for determining the expiration time of the infusion solution.

Oral:
To mix the oral suspension tap bottle until all the powder flows freely. To reconstitute, add 24 mL distilled water or Purified Water (USP) to the fluconazole 350 mg or 1400 mg powder in bottle and shake vigorously to suspend the powder. The concentration of the reconstituted suspension is 10 mg/mL for the 350 mg bottle and 40 mg/mL for the 1400 mg bottle with a total volume of 35 mL of suspension per bottle. The reconstituted suspension should be stored between 86°F (30°C) and 41°F (5°C). Protect from freezing. Discard unused portion 2 weeks after reconstitution. Patients should be instructed to shake the oral suspension well before using. Oral fluconazole should be administered with or without food at approximately the same time each day and can be taken at any time during the day.

**Supplier:** Commercially available from various manufacturers. See package insert for further information.

## 6.3 VORICONIZOLE (Vfend®) (06/24/11)

**Source and Pharmacology:**
Voriconazole is a triazole antifungal derived from fluconazole with the aim of enhanced potency and spectrum of activity. Voriconazole has been studied in a variety of fungal infections and has demonstrated efficacy in those caused by *Aspergillus* sp, *Candida* sp, *Cryptococcus neoformans*, and *Fusarium* sp.; conversely, voriconazole has demonstrated poor *in vitro* activity against Zygomycetes and *Sporothrix schenckii*. Voriconazole inhibits ergosterol synthesis by interacting with 14-alpha demethylase, a cytochrome P450 enzyme necessary for the conversion of lanosterol to ergosterol. Inhibition of ergosterol synthesis results in increased cellular permeability and subsequent leakage of intracellular contents. Several other antifungal mechanisms have been proposed in certain yeast and filamentous fungi.

The oral bioavailability of voriconazole is around 96%; peak plasma levels occur 1 to 2 hours after an oral dose. Steady-state concentrations are achieved within 24 hours after an oral loading dose; in the absence of a loading dose, 6 days of accumulation are required to reach steady state. The absorption of voriconazole is not affected by increases in gastric pH, however, the mean Cmax and AUC are reduced by 34% and 24%, respectively, following a high fat meal. Voriconazole is widely distributed, with a volume of distribution of 4.6 L/kg. Approximately 58% of a dose of voriconazole is bound to plasma proteins. Voriconazole concentrations in human CSF are between 40% and 70% of the concentrations in the plasma.

Voriconazole displays nonlinear pharmacokinetics due to saturation of its metabolism in adult patients. It is metabolized by and is an inhibitor of cytochrome P450 enzymes 2C19, 2C9 and 3A4. Significant interpatient variability exists as a result of polymorphisms in the CYP2C19 isoenzyme, resulting in varying rates of metabolism. Genetic polymorphisms in CYP2C19 may result in approximately 4-fold higher voriconazole exposure in poor metabolizers vs. extensive metabolizers. Approximately 85% of a single dose appears in the urine with < 2% as unchanged drug. The elimination half-life has been reported as 6 hours; in patients receiving prolonged therapy it may take up to 6 days to recover 90% of the drug in the urine and feces.

Children < 12 years of age have a larger volume of distribution and a faster clearance of voriconazole than adolescents and adults. A pharmacokinetic analysis in 35 children age 2 to 12 years revealed that a maintenance dose of 4 mg/kg every 12 hours resulted in a similar steady state concentration compared to adults receiving 3 mg/kg every 12 hours. Unlike adult patients, voriconazole elimination was found to follow a linear model throughout the dosage range studied. The median (5th and 95th percentiles) terminal half-life was 7.5 (3.5 and 21.4) hours. Population pharmacokinetic modeling was performed in a retrospective evaluation of 108 voriconazole serum concentrations from 40 hospitalized pediatric patients. The mean oral bioavailability in the study was 75% in children < 12 years and 81% in patients ≥ 12 years. Simulations of fixed oral doses (200 mg twice daily) demonstrated a consistent increase in concentration by 520 ng/mL for a 1 mg/kg increase in dose; this is consistent with Michaelis-Menten kinetics. The authors concluded that 7 mg/kg IV every 12 hours is likely to achieve an appropriate voriconazole trough concentration in the majority of pediatric patients up to 12 years of age.

**Toxicity:**

| | **Common** Happens to 21-100 subjects out of every 100 | **Occasional** Happens to 5-20 subjects out of every 100 | **Rare** Happens to < 5 subjects out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | Visual changes (e.g., photophobia, color changes, increased or decreased visual acuity, or blurred vision) | Auditory or visual hallucinations, fever, nausea, rash | Anaphylactoid reactions, flushing, sweating, tachycardia, chest tightness, dyspnea, faintness, pruritis, chills, headache, hypokalemia, vomiting, QT interval prolongation, ventricular arrhythmias, torsade de pointes, cardiac arrest, sudden death |
| **Prompt:** Within 2-3 weeks, prior to next course | | | Increased serum creatinine, acute kidney failure, increased AST, increased ALT, increased alkaline phosphatase, cholestatic jaundice, clinical hepatitis, cholestasis, fulminant hepatic failure (including death), optic neuritis, papilledema, pancreatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, photosensitivity<br><br>Other less common adverse events have been reported; refer to the package insert for additional details. |
| **Unknown Frequency and Timing:** | U.S. Food and Drug Administration's Pregnancy Category: Category D.<br>Voriconazole can cause fetal harm when administered to a pregnant woman. Voriconazole was teratogenic in rats at doses 0.3 times the adult recommended dose and embryotoxic in rabbits at 6 times the recommended adult dose. Reduced fetal weight, skeletal abnormalities, and embryomortality were also reported in animal models. Additionally, plasma estradiol levels were reduced in pregnant rats at all dose levels of voriconazole. | | |

**Formulation and Stability:**

Injection

Voriconazole for injection is available in a single use vial as a sterile lyophilized powder without preservatives equivalent to 200 mg voriconazole and 3200 mg sulfobutyl ether beta-cyclodextrin sodium (SBECD). The powder for injection should be stored at 15°C to 30°C (59°F to 86°F). Reconstituted solutions are stable for up to 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F).

Tablets

Voriconazole 50 mg tablets are white, film-coated, and round; voriconazole 200 mg tablets are white, film-coated, and capsule shaped. Both tablet types are debossed with “Pfizer” on one side and either “VOR50” or “VOR200” on the reverse, for the 50 mg and 200 mg tablets, respectively. Tablets should be stored at 15°C to 30°C (59°F to 86°F).

Powder for Oral Suspension

Voriconazole for Oral Suspension is supplied in 100 mL high density polyethylene (HDPE) bottles with an accompanying 5 mL oral dispenser and press-in bottle adaptor. Each bottle contains 45 g of powder for oral suspension. Following reconstitution, the bottle contains 40 mg voriconazole per mL in a usable volume of 70 mL and approximately 5 mL of overfill. The powder for oral suspension should be stored at 2°C to 8°C (36°F to 46°F). Once reconstituted, the oral suspension should be stored at 15°C to 30°C (59°F to 86°F).

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.

Powder for injection
Aseptically reconstitute one 200 mg vial with 19 mL of sterile water for injection; the use of an automated syringe is not recommended. The resulting product is a clear, particle-free solution in a concentration of 10 mg/mL (20 mL total volume). This product should be further diluted with NS, LR, $D_5$WLR, $D_5W^1/_2$NS, $D_5$W, $D_5$W with KCl 20 mEq, $^1/_2$NS, or $D_5$WNS to a final concentration of 0.5 to 5 mg/mL prior to administration. Do not dilute with 4.2% sodium bicarbonate infusion; slight degradation of voriconazole can occur.

Voriconazole powder for injection does not contain preservatives. The manufacturer recommends using the reconstituted solution immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C (36°F to 46°F). Any unused solution should be discarded. The final voriconazole solution should be infused over 1 to 2 hours at a rate not to exceed 3 mg/kg/hr.

Powder for oral suspension
A 40 mg/mL suspension is made by adding 46 mL of water to the powder in bottle. Shake well for approximately 60 seconds. Place the push-in bottle adaptor in place prior to dispensing to the patient. Prior to each dose, the bottle containing suspension should be shaken well for at least 10 seconds. Each dose should be withdrawn from the vial using the provided oral dose dispenser. Do not refrigerate or freeze. Discard any unused suspension 14 days after reconstitution.

**Supplier:** Commercially available product.

## 7.0 REQUIRED OBSERVATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

### 7.1 Required and Optional Clinical, Laboratory and Disease Evaluations

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. These studies should be obtained even if the patient has been removed from protocol therapy, unless they are off study (see Section 8.0).

| STUDIES TO BE OBTAINED | Baseline | Day 0 to Day 42 (or Discharge) | Day 100^ End of ACCL1131 Monitoring |
|---|---|---|---|
| **REQUIRED** | | | |
| CBC, differential, platelets | X | Twice Weekly | X |
| Performance Status | X | | X |
| Creatinine, AST, ALT, bilirubin | X | Twice Weekly | X |
| Albumin | X | Weekly | X |
| IFI checklist | | X* | X* |
| GVHD Scoring | | Weekly(after Day 14) | X |
| **OPTIONAL (IF PATIENT CONSENTS)** | | | |
| Beta-D Glucan Assays | | Weekly[@] | |
| Sample for SNP Genotyping | X[#] | | X[#] |

^Day 100-114

*Submit relevant IFI checklist documents via the Document Imaging System: (626) 447-2204 as of Day 42 and Day 100. See Section 10.2 for further details.

[@] See Section 13 for details. It is suggested that specimens be obtained on Thursdays but other days are acceptable if more convenient. During the prophylaxis period, documentation of exposure or lack of exposure to each of the following will be performed: amoxicillin-clavulanate and intravenous immunoglobulin.

[#] See Section 14 for details. End of study sample may be collected on Day +100 +/-7 days.

**This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.**

7.1.1 History, Demographic and Clinical Information

Demographic and clinical information collected at baseline will include age, sex, performance status, Down syndrome, ethnicity, height, weight, and episodes of fully-treated proven/probable yeast infection in the 3 months prior and receipt of systemic antifungal therapy within 7 days prior to enrollment. Other information collected will include type of malignancy or underlying diagnosis, relapse status, donor type, degree of donor match, stem cell source, conditioning regimen and graft-versus-host disease (GVHD) prophylaxis.

### 7.2 Optional Studies

7.2.1 (1→3) Beta-D Glucan Assays

If patient consent is obtained, Fungitell beta-D-glucan Assay will be performed during the period of neutropenia in order to identify IFI. 5 mL of whole blood will be collected in a gold top serum-separator tube once weekly. See Section 13 for sample collection, processing and shipping details.

7.2.2 SNP Analysis

If patient consent is obtained, specimens will be collected and banked for genotyping. SNP analysis will be conducted in order to determine genes mediating immune function. Peripheral blood (5 mL) will be collected in a purple top tube at study entry and at end of study (Day +100 +/-7 days), optimally when the patient has an ANC > 1000/µL. Patients with weights less than 20 kg may have only 3 mL collected. See Section 14 for sample collection and shipping details.

### 7.3 Follow-up

See COG Late Effects Guidelines for recommended post treatment follow-up
http://www.childrensoncologygroup.org/disc/LE/default.htm

## 8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

### 8.1 Criteria for Removal from Protocol Therapy

a) Development of proven or probable IFI including IA according to the institutional diagnosis.
b) Refusal of further protocol therapy by patient/parent/guardian.
c) Completion of planned therapy (Day 42 or Day of Discharge).
d) Physician determines it is in patient's best interest.
e) Repeat eligibility studies are outside the parameters required for eligibility (if applicable, see Section 3.2 – only for patients that have not yet started protocol therapy).
f) Intolerable toxicities as outlined in Section 5.2 and Section 5.3.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data (including IFI checklist) will be required unless consent was withdrawn.

### 8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Withdrawal of consent for any further data submission.
d) Completion of Day 100 evaluation.

# 9.0 STATISTICAL CONSIDERATIONS

## 9.1 Statistical Design

This is a randomized open-label trial of anti-fungal prophylaxis for patients at high risk for IFI following allogeneic hematopoietic cell transplantation. Eligible patients are those undergoing an allogeneic HCT from an unrelated donor or mismatched family donor. Patients will be randomized at the time of enrollment to receive caspofungin or an azole comparator (fluconazole or voriconazole). Each participating institution will choose the comparator based upon institution standard of care and the choice of comparator should remain constant for the duration of the study. Randomization will be stratified by: 1) the comparator of choice: fluconazole or voriconazole; 2) Age: ≥12 years vs. < 12 years; 3) Type of transplant: Umbilical cord blood (UCB) donor vs. Non-UCB donor with ex vivo T-cell-depletion vs. Non-UCB donor with standard pharmacologic GVHD prophylaxis. Protocol-specified anti-fungal prophylaxis will start with 24 hours of Day 0 and continue until Day +42, day of discharge, or withdrawal from study for any reason. The primary aim of the study is to evaluate whether the caspofungin arm has a lower incidence of proven/probable IFI than the azole arm during the first 42 days following allogeneic HCT.

## 9.2 Patient Accrual and Expected Duration of Trial

In North America, from 2006-2008, an average of 688 patients per year were transplanted at COG centers that fit the eligibility criteria for this trial (CIBMTR, personal communication). Presuming constant numbers and a 20% participation rate, this trial would accrue about 138 patients per year and require 4.5-5 years (including an estimated 6 months delay for IRB approvals) to complete the accrual of 560 eligible patients, with a maximum enrollment of 590 patients to account for up to 5% ineligible enrollments. Because we will allow institutions to choose the comparator (fluconazole or voriconazole), we anticipate a high acceptance of this trial by local physicians, and indeed, our survey of the COG Transplant Centers indicated that 89% of the centers who responded would enroll patients on this trial, with a survey response rate of 80%.

## 9.3 Statistical Analysis Methods

### 9.3.1 Study Endpoints

*Primary endpoint*

The primary endpoint is the development of proven or probable IFI defined according to criteria developed by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) (from which time to IFI will be computed).[31] These definitions have been used in major trials of antifungal drug efficacy, in strategy trials, for formulating clinical practice guidelines, for validating diagnostic tests, as well as for undertaking epidemiologic studies. A Data Review Committee, blinded to study drug assignment, will review all clinical documentation used to determine the presence of an IFI and classify it based on the EORTC criteria. The period at risk for primary IFI endpoint will begin at Day 0 and extend until 42 days following stem cell infusion. Some patients at high-risk for IFI may have prolonged inpatient stays, but in order to obtain a relatively homogenous duration of study drug administration, Day +42 was chosen as the maximal period of administration, as was done in the micafungin trial. Based on intent-to-treat principle, the at-risk period will be the same for patients who terminated protocol prophylaxis prior to Day +42 (due to withdrawal or discharge) as long as data regarding IFI are available. For the primary endpoint, deaths that occur in the absence of proven/probable IFI will be counted as censoring events; as a comparison, for the exploratory endpoint of fungal-free-survival (see below), deaths without proven/probable IFI will be counted as events.

The rationale for the duration of therapy and the measurement of the primary endpoint was based upon three issues. First, the major time period that patients are at risk for invasive candidiasis is during the period of combined neutropenia, monocytopenia, and lymphopenia.[53] The second reason is that this time frame was the same as was used in the NIAID-supported micafungin trial by Van Burik *et al.*, and thus, allows us to compare our results to what was seen in that lower-risk, primarily-adult population.[14] The final issue was one of feasibility. The goal was to design a trial that would not mandate a practice that is not standard to local institutions, namely continuing an intravenous medication past the time of hospital discharge, when an acceptable oral medication exists. It was felt that this burden would potentially represent a serious obstacle to widespread acceptance and participation in the trial. This pragmatic trial is designed to determine whether the intervention works under the usual circumstances in which it is used. Once the period of neutropenia and monocytopenia has resolved many patients will be clinically ready for discharge from the hospital. Since caspofungin is only available in an intravenous formulation, continuing the treatment past the time of discharge represents a significant burden of effort and cost, which the data currently do not support undertaking.

*Exploratory Endpoints*

Endpoints for the exploratory objectives include: development of proven or probable IFI during the first 100 days following allogeneic HCT, fungal-free-survival which is defined as time to death or proven/probable IFI during the first 42 and 100 days following allogeneic HCT, and onset and severity of acute GVHD, and results from beta-D glucan assay for the diagnosis of IFI.

### 9.3.2 Central Committee Review

In order to ensure consistent and accurate application of the EORTC/MSG guidelines across all study patients, a Central Review Committee including Pediatric Oncologists and Pediatric Infectious Disease Specialists will be assembled. Through consensus meetings, committee members will review all data pertinent to the EORTC/MSG guidelines and determine whether a patient sustained a possible, probable or proven IFI during the study period. The following data for each study patient will be collected and available at the time of the review: pathology reports, all CT scan and MRI reports, fungal Gram stain and microbiology culture results, non-culture mycology testing results (i.e., Histoplasma urine antigens, cryptococcal CSF and serum antigens), ophthalmology exams, bronchoscopy reports, and dosing and duration of steroid exposures.

All reviewers will be blinded to the patient's antifungal exposures in order to limit any bias in determining the primary and exploratory endpoints.

### 9.3.3 Sample size with power justification

*IFI incidence*

There has never been a randomized prospective trial of anti-fungal prophylaxis in this population of patients. Consequently, it is difficult to measure the expected rate of IFI in the control arm. Pediatric patients have represented less than 10% of the subject population in all but one prospective trial to date.[3,14,19,20,29,54] And every prospective trial to date has had > 50% of their patients undergoing lower-risk forms of transplantation, including matched sibling donor HCTs, and even autologous HCTs in some cases. Given these limitations, the incidence of IFI on these trials has ranged dramatically, from as low as 2.4% at 70 days,[14] to as high as 25% at 180 days post HCT.[20] A simple calculation achieved by combining the results of the 3 trials with 180 day endpoints demonstrates that, in patients receiving fluconazole prophylaxis, there is an approximately 14.5% incidence of IFI at 180 days, while in those receiving mold-active prophylaxis (itraconazole or voriconazole) there was an approximately 9.1% incidence of IFI at 180 days.[3,19,20] If there was an even split between the number of patients receiving fluconazole vs. a mold-active azole, then a very rough estimate of the IFI incidence at 180 days would be 10.9%. Since the distribution of IFIs post-

transplant is bimodal, with one main peak being during the neutropenic period immediately post-HCT,[25,30,53] we would expect roughly half of this, or ~6% to occur during the first 42 days.

Other reports support the hypothesis that roughly half of the "early" (< 180 days post-HCT) IFIs occur within the first 6 weeks. Figure 1A from Wingard *et al.* demonstrates a cumulative incidence curve of IFI; while only the number at 180 days is reported, it is clear that there is a sharp rise between Days 0 and 42, followed by a slower rise from Day 42 to Day 180, so that roughly half of the IFIs have occurred by Day 42.[3] Three retrospective reports show similar conclusions. Hovi *et al.* reported that 5 of 11 (45%) IFI that were found in pediatric allogeneic HCT recipients during the first year post-HCT occurred during the first 6 weeks post-HCT.[27] Dvorak *et al.* reported that 10 of 12 (84%) cases of IFI occurred in the first month after pediatric allogeneic HCT.[26] Benjamin *et al.* reported that, in pediatric patients undergoing unrelated or haploidentical HCT (the population in question in this trial), the number of patients with Aspergillosis or Candidiasis (the 2 most common IFIs) was 22 from Days 0 to 30 post-HCT, 25 from Days 31-100, and only 5 from Days 101-365.[55] Thus, in Benjamin *et al.* 22 of 52 (42%) total IFIs occurring within the first year post-HCT happened within the first 30 days. Combining the small numbers from each of these retrospective studies would suggest that 39 of 77 (51%) of IFIs during the first year post-HCT actually occur within the first 4-6 weeks. Furthermore, a query of the International Pediatric Fungal Network database demonstrates that from July 2008 to December 2010, there were 14 pediatric patients who developed an IFI within 180 days from HCT. Eight of these (57%) occurred by Day 42, 2 between Days 43 and 100, and 4 from Days 101 to 180 (William Steinbach, personal communication). This data provides justification of the use of one-half of the reported Day 180 incidences from the published prospective trial of Wingard *et al.*

However, it should be strongly stressed that these numbers were generated from trials involving a lower-risk patient population in which < 50% of the patients underwent alternative donor HCT, which is the study population proposed for this trial. None of the prospective trials report whether alternative donors demonstrated a higher incidence of IFI than matched-siblings, but based on the largest available series of retrospective data the risk of IFI at 1 year in alternate donors is ~2% higher than seen in matched-siblings.[56] Benjamin *et al.* report a greater difference between matched sibling donor recipients and alternative donor recipients of 16% vs. 22% (at 100 days),[55] but we will use the more conservative 2% estimate. Once again, based on a bimodal distribution, we would expect approximately half of that increased IFI incidence to occur early post-transplant, thus increasing our overall estimate to ~7%.

Another source of data to inform this estimate is the various retrospective studies that have been performed, although these have inherent biases. There have been three pediatric-specific studies, which unfortunately have used different end-point times and methods.[26,27,55] One study demonstrated an 8.7% incidence of IFI at 30 days in a mixed-risk patient population utilizing fluconazole prophylaxis.[26] Another demonstrated a 10.9% incidence of IFI at 30 days in our exact population of high-risk patients, but utilizing low-dose amphotericin B as prophylaxis.[55] Another informative study involved a very high number (> 2500) of primarily adult patients undergoing transplant from alternative donors and demonstrated an approximately 8% risk of IFI at 365 days post-HCT.[56] However, this population included ~30% non-myeloablative HCTs, which have a very different pattern of IFI than those undergoing myeloablative transplant[57] (the study population for this trial), making it difficult to fully utilize this data. Another group of patients who appear to be at high-risk for the development of IFI post-HCT are those undergoing HCT utilizing an umbilical cord blood (UCB), likely due to the extended period of neutropenia commonly seen in these patients. A report by Sadfar *et al*. demonstrated that 12.4% of their UCB HCT patients had developed an IFI by Day 30, and 22.6% by Day 100.[58] The prospective trials to date have included very few UCB recipients, including only 2 of 600 in the trial by Wingard *et al*.[3] Finally, a report analyzed the infectious complications of high-risk (unrelated donor) HCTs done on the NHLBI-funded trial of *ex vivo* T-cell depletion vs. standard cyclosporine and methotrexate for GVHD prophylaxis.[30] The methodology of this study did not report an IFI incidence at 180 days, but at the time of data censoring, 31% of patients had ultimately gone on to

develop an IFI. This highlights the elevated risk of IFI in this population of patients, and underscores the danger of utilizing data generated from a lower-risk population to inform an IFI estimate for this trial.

We determined the magnitude of absolute IFI risk reduction by starting with the rate of 4% seen in the trial by Wingard *et al*.[3] On that trial, in the early post-HCT period only 2 infections were due to organisms other than *Candida* and *Aspergillus*, (which would thus also not be covered by caspofungin). There are several theories why patients receiving a mold-active agent developed breakthrough *Aspergillus* or *Candida.* One possible reason is the inherent variability in voriconazole pharmacokinetics (as noted above), which may have led to inadequate serum levels in a significant number of patients.[5,49] We would not expect a similar problem utilizing caspofungin, which has very predictable pharmacokinetics,[59] even in the setting of renal or hepatic insufficiency. Another possible reason is that 36% of the IFIs occurred after premature withdrawal of voriconazole.[3] Since echinocandins are generally exceptionally well-tolerated, we expect a lower rate of premature stoppage of caspofungin when compared to the azole group, a finding also demonstrated in the trial by Van Burik *et al*.[14] Given these inherent benefits of the echinocandin class, we therefore expect that caspofungin's magnitude of benefit will be slightly higher than seen in trials of other mold-active agents.

Therefore, we assume that the incidence of IFI during the period at risk for the primary objective (Day 0 to Day 42) is 7% in the control patients (with fluconazole or voriconazole) and that the incidence of IFI is 2% with caspofungin prophylaxis, which is a clinically important decrease in the risk of IFI.

*Sample Size and Estimated Power*

Assuming the incidence of IFI during the period at risk for the primary objective (Day 0 to Day 42) is 7% in the control patients (with fluconazole or voriconazole) and that the incidence of IFI is 2% with caspofungin prophylaxis, we will require 560 randomized patients (approximately 280 per arm) to achieve 80% power at 2-sided alpha level of 0.05. The power consideration is based on a 2-sample log rank test comparing the time to (first occurrence of proven/probable) IFI. Time to IFI is assumed to follow an exponential distribution. The observation period for the primary endpoint is from Day 0 till Day +42 following high-risk allogeneic HCT. Under an exponential time-to-IFI model with these parameters, the incidence of IFI is distributed almost evenly during the at-risk period; for each one-third of at-risk period (~14 days), the incidence of IFI is 2.3%-2.4% for patients on the azole arm and is 0.66%-0.67% for patients on the caspofungin arm. A 5% exponential loss-to-follow-up during the at-risk period is also included in the power consideration. Considering up to 5% of the enrolled patients might be deemed ineligible, the maximum enrollment number is adjusted to 590. The expected number of IFI among 280 eligible azole arm patients is 19.6.

### 9.3.4 Analysis Plans

*Descriptive Analyses*

Standard descriptive statistics will be used to describe subjects' baseline characteristics and study outcome measures overall and within each treatment group. Summary statistics such as means, standard deviations, medians, and ranges will be produced for all measured variables. The balance of baseline measures across the treatment groups will be examined using appropriate two-sample tests.

*Analysis for Primary Objective*

For the primary endpoint, the at-risk period for IFI is from Day 0 until Day +42. Events that will shorten the at-risk IFI observation period (including death, withdrawal consent for data submission, or patient loss to follow-up) prior to Day +42 are expected to be rare. Since death (a true competing risk event) prior to Day +42 is expected to be rare, in the primary analysis all these events will be treated as censoring events and standard survival data methods will be performed. The primary analysis will be based on the principle of intention to treat (i.e., by the treatment assignment of patients at randomization, regardless of subsequent

compliance with the assigned treatment). All eligible and randomized patients with available IFI data will be included in this analysis. A modified intention to treat analysis which only includes patients who complied with the randomized treatment will also be performed as an exploratory analysis to evaluate whether its result differs from that of the intention to treat analysis. Kaplan-Meier curves will be used to estimate the time to onset of proven/probable IFI for patients randomized to the 2 arms. Log rank test will be used to compare the incidence of IFI between the 2 randomized arms during the at-risk period up to Day +42. The primary analyses will be performed at overall 2-sided alpha level of 0.05, with two planned interim efficacy analyses (see Section 9.3.5). Cox proportional hazards models will also be used to explore the treatment difference between the 2 arms on time to IFI with adjustment for covariates such as stratification factors or other potential risk factors.

*Exploratory Analyses on Clinical Endpoints*

For exploratory objective 1, to examine the longer term treatment effect, a similar log rank test will be performed comparing the incidence of proven/probable IFI between the 2 randomization arms by extending the observation period up to Day +100. For exploratory objective 2 & 3, log rank test will be used to compare the incidence of proven/probable IFI of patients randomized to caspofungin within the particular randomization stratum defined by the comparator (fluconazole or voriconazole) to that of patients randomized to the comparator within the same stratum. For exploratory objective 4 on fungal-free-survival, failures for this endpoint will include death or proven/probable invasive fungal infection. Log rank test will be used to explore any treatment differences between the 2 arms on fungal-free-survival. For exploratory objectives 1-4, Cox proportional hazards models will also be used to examine the treatment difference between the 2 arms on time to IFI or fungal-free-survival with adjustment for other risk factors. For exploratory objective 5, the binary incidence of acute GVHD and the percentage distribution of acute GVHD by stage and by overall clinical grade will be estimated for each arm and compared between the 2 arms by Chi-square test. Logistic regression models (for the binary GVHD incidence data) or proportional odds models (for the ordinal GVHD data by stage or overall clinical grade) will also be used to explore the treatment difference between the 2 arms with adjustment for other risk factors such as donor HLA match score.

Based on the survey we performed, we expect about half of the enrolled patients will use fluconazole as the comparator and the other half will use voriconazole as the comparator. For the exploratory objective on comparing the incidence of IFI during the first 42 days between caspofungin and fluconazole or between caspofungin and voriconazole, with 140 patients per arm, the power to detect a difference in IFI incidence of 7% (comparator) vs. 2% (caspofungin) will be only about 51%. The power for a difference in IFI incidence of 7% (comparator) vs. 1% (caspofungin), 8% (comparator) vs. 2% (caspofungin), and 9% (comparator) vs. 2% (caspofungin) are 71%, 62%, and 71% respectively. These power considerations follow the same assumptions as those for the primary objective. For the exploratory objective on comparing the incidence of IFI during the first 100 days following high risk allogeneic HCT using the entire study population, assuming IFI incidence of 12% (with fluconazole or voriconazole) vs. 5% (caspofungin), the power to detect the difference is 81%. The incidence of IFI during this longer at-risk-period might be bimodal with the main peak during neutropenic period immediately after HCT; however due to lack of good estimate for such bimodal distribution, this power consideration is still based on exponential models and the incidence is distributed roughly evenly under these incidence assumptions. The power consideration for IFI up to Day 100 also includes a 15% exponential loss-to-follow-up. When only comparing patients randomized between caspofungin and one comparator (fluconazole or voriconazole), again with about half of the sample size (about 140 per arm), the power to detect IFI incidence during the first 100 days of 12% (comparator) vs. 5% (caspofungin) is only 52%. The power will be about 78% if the IFI incidence during the first 100 days is 14% (comparator) vs. 3% (caspofungin).

*Analysis of beta-D Glucan Assay*
Sensitivity, specificity, positive predictive value, and negative predictive value of the beta-D glucan assay will be determined using standard formulas and EORTC/MSG criteria as the gold standard. Please see Section 13.9 for additional statistical considerations for this aim.

9.3.5 Interim Monitoring
Study data will be reviewed by DSMC twice a year during the first 2 years of study activation, and once a year thereafter upon their approval if the study goes smoothly. Two formal interim efficacy analyses on the primary endpoint will be performed, after approximately one third and two thirds of the patients have completed study treatment and IFI observation. Monitoring boundary for the primary endpoint on IFI will be based on Lan-Demet's method with spending function $\alpha t^2$.

At the time of primary efficacy monitoring, the observed incidence of IFI during the first 42 days following HCT in patients randomized to the comparator arm will be monitored. If the 95% 1-sided confidence interval does not contain the assumed rate of 7%, the study will be referred to DSMC for consideration of study closure. Roughly speaking, if $\leq 2$ IFI out of 93 patients, or $\leq 7$ out of 187 patients, the rule will be met. However, the exact rule at the time of monitoring will depend on the exact N at the time of the interim analysis and whether there is censoring and how much. If no censoring and exactly at the numbers listed above, the rule will be those above.

Informal safety analyses will also be performed on the observed adverse events at each DSMC review. This analysis will include all patients who receive at least one dose of study medication. The proportion of patients experiencing any reportable grade 4 or higher adverse event will be compared between the 2 arms using chi-square tests. For such informal safety analyses, each test will be at two-sided level of 0.05 without adjustment for multiple testing. If a significant difference between the 2 arms is found ($P < .05$), the study committee will perform a review of the adverse event profiles and report the finding to DSMC for their evaluation, with a recommendation about action with respect to the study.

## 9.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

| **Accrual Targets** | | | |
|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | |
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 66 | 96 | 162 |
| Not Hispanic or Latino | 179 | 249 | 428 |
| **Ethnic Category: Total of all subjects** | 245 | 345 | 590 |
| **Racial Category** | | | |
| American Indian or Alaskan Native | 0 | 0 | 0 |
| Asian | 5 | 9 | 14 |
| Black or African American | 24 | 29 | 53 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 216 | 307 | 523 |
| **Racial Category: Total of all subjects** | 245 | 345 | 590 |

This distribution was derived from ASCT0431.

## 10.0 EVALUATION CRITERIA

### 10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate data collection forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (i.e. v4.02 and all subsequent iterations prior to version 5.0).

### 10.2 IFI Checklist: Submission & Central Review

Institutions will be provided with CRA worksheets (IFI Checklist) to complete which will help to identify whether patients had an IFI. Biopsy and imaging reports are requested rather than report interpretation in order to minimize the work load for sites. An independent data review committee including infectious disease and oncology experts who are unaware of treatment assignments will review and classify all cases of proven/probable IFI by EORTC/MSG criteria.[60] The committee will then submit a Central Review CRF via eRDES.

The following IFI checklist materials will be submitted (via the Document Imaging System: (626) 447-2204) as of Day 42 and as of Day 100, only if they were performed to investigate an IFI according to local physician discretion:

- Pathology reports (including autopsy reports),
- CT scan and MRI reports,
- Fungal Gram stain and microbiology culture results,
- Non-culture mycology testing results (i.e. Histoplasma urine antigens, cryptococcal CSF and serum antigens),
- Ophthalmology exams, and
- Bronchoscopy reports.

In addition, dosing and duration of steroid exposure will be collected and entered via eRDES. All reviewers will be blinded to the patient's antifungal exposures in order to limit any bias in determining the primary and secondary endpoints.

### 10.3 Acute GVHD

The staging of acute GVHD will follow National Marrow Donor Program (NMDP) guidelines (Appendix III).

# 11.0 ADVERSE EVENT REPORTING REQUIREMENTS

## 11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

## 11.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution); and 3) the *prior experience* (expectedness) of the adverse event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- ***the current known toxicities for each commercial agent as provided in the Drug Information for Commercial Agents Used by the Children's Oncology Group posted on the COG website; or***
- ***the drug package insert.***

Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment need to be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

## 11.3 Reporting of Adverse Events for Commercial Agents - via CTEP-AERS

Expedited AE reporting must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via https://eapps-ctep.nci.nih.gov/ctepaers

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol immediately following the Study Committee roster.

- COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

**Table B**
**Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.**

**CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or Within 30 Days[1]**

| Attribution | Grade 4 | | Grade 5 |
|---|---|---|---|
| | Unexpected | Expected | |
| Unrelated or Unlikely | | | CTEP-AERS |
| Possible, Probable, Definite | CTEP-AERS | | CTEP-AERS |

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via **CTEP-AERS**.

### 11.4 Routine Adverse Event Reporting

**Note:** The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for **CTEP-AERS** S reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via **CTEP-AERS** and all Grade 4 and higher non-hematological Adverse Events.

## 12.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

### 12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

## 13.0 PROSPECTIVE EVALUATION OF (1→3) BETA-D GLUCAN ASSAY AS A DIAGNOSTIC TOOL FOR INVASIVE FUNGAL INFECTION IN CHILDREN UNDERGOING ALLOGENEIC HCT RECEIVING FUNGAL PROPHYLAXIS. (FOR PATIENTS THAT CONSENT ONLY)

### 13.1 Background

The crippling mortality associated with IFI in HCT recipients is in part related to the difficulty in diagnosing them in a reasonable time frame. In fact, IFI are frequently only diagnosed on autopsy.[61] As noted above, almost all major pediatric HCT centers prescribe some form of antifungal prophylaxis during periods of immune suppression. Fluconazole is frequently used but it does not have activity against mold organisms such as Aspergillus. This fact has led many to theorize that using an antifungal agent with anti-Aspergillus activity would provide additional benefits. However, the studies comparing fluconazole to a mold active agent have been conflicting.[3,19,42] In an effort to standardize antifungal prophylaxis, the parent randomized clinical trial described above will compare the efficacy of an azole agent (voriconazole or fluconazole) to that of caspofungin. This study will potentially define the appropriate antifungal prophylactic agent.

Regardless of the antifungal agent ultimately chosen, prophylaxis will not prevent all IFI. In those patients with a breakthrough IFI, a modification to the antifungal regimen will be necessary. The challenge is to identify those patients sustaining breakthrough IFI at the earliest possible point. The recent Infectious Disease Society of America (IDSA) guidelines for fever and neutropenia suggests a pre-emptive therapeutic approach.[62] This approach requires the use of adjunctive diagnostic biomarker assays such as the Fungitell Assay, to help inform the decision to modify antifungal therapy. The utility of this assay has been well defined in adult immunocompromised patients but to date there are limited data on the operating characteristics of this assay in pediatric patients undergoing HCT and receiving antifungal prophylaxis. In order to endorse this as a useful adjunctive study, the operating characteristics must be defined in a high-risk pediatric population. We propose to prospectively study this biomarker in the parent COG trial. This parent study cohort provides a one-time opportunity to rigorously evaluate the ability of this fungal biomarker to identify IFI in a homogeneous cohort of pediatric HCT patients receiving antifungal prophylaxis. Knowledge of the operating characteristics of the Fungitell Assay under these study conditions is necessary to inform its potential future utility.

#### 13.1.2 Traditional diagnostic studies to identify patients with suspected IFI

Traditional diagnostic modalities for IFI are limited to radiologic imaging and blood or tissue culture techniques. Radiologic studies may show visceral involvement but an invasive biopsy procedure is necessary to differentiate between a fungal or non-fungal infectious process. Although blood cultures may be used to isolate Candida spp. during candidemia, they are not helpful in the setting of invasive candidiasis without fungemia. Furthermore, traditional blood cultures are not typically successful at isolating mold infections such as Aspergillus. Cultures of tissue specimens can be definitive but require invasive techniques for sample procurement.

#### 13.1.3 Beta-D Glucan (Fungitell) Assay

The testing approach of this ancillary study involves the serial evaluation of a patient's serum for the presence of BG. The Fungitell Assay is a commercially available kit from the Associates of Cape Cod, Inc. for the identification of BG, present in a vast majority of pathogenic fungi, in the serum of patients with IFI. This assay received FDA approval for use in adults in May of 2004 to assist in the diagnosis of most IFI (including IA). The operating characteristics of the assay have been elucidated in two separate adult cohorts and are reassuring.[63,64] The first included adult patients with newly diagnosed AML or myelodysplastic syndrome undergoing initial induction chemotherapy and receiving fungal prophylaxis with either caspofungin or itraconazole.[64] The assay was performed in 283 patients twice a week for the duration of neutropenia resulting in sensitivity, specificity, PPV and NPV for diagnosing proven or probable IFI of 100%, 90%, 43%, and 100%, respectively. More importantly, a positive Fungitell Assay result was

identified at a median of 10 days prior to the clinical diagnosis of IFI in this cohort. The second study evaluated 95 adult patients with fever and neutropenia down to 16 years of age. Thirty-eight patients with proven, probable or possible IFI were identified. The resultant sensitivity, specificity, PPV and NPV were 97.4%, 28.6%, 55.2%, and 92.3%. The specificity reported was reduced as compared to results from the prior publication as they included possible as well as probable and proven cases of IFI. Positive Fungitell Assay results preceded clinical diagnosis of IFI by a median of 5 days.[63] More recently, a meta-analysis including 16 prospective and retrospective studies evaluating BG levels reported a combined sensitivity of 77% and specificity of 85%.[65]

One pediatric study evaluated BG levels in children using the Fungitell Assay. This study was limited to healthy children and revealed elevated baseline levels of BG in a subset of the patients.[66] To date, the Fungitell Assay testing has never been performed prospectively in immunocompromised pediatric patients and never in a population of only HCT recipients. Even if one tried to extrapolate the previously described adult data for BG testing, the results are conflicting with some studies revealing a reassuringly high sensitivity and others with a poor sensitivity. This variation likely stems from the variation across each study for testing frequency, timing of testing, and variation in the type of immunosuppressed patients. Furthermore, the elevated baseline BG levels in the one study of healthy children suggest that a higher threshold for a positive test would be necessary in a pediatric patient population.

#### 13.1.5 Gaps in knowledge

The Fungitell Assay has shown reassuring operating characteristics in adults. Because of the proven utility of this test in adults, guidelines from the Infectious Disease Society of America have endorsed it as adjunctive diagnostic tool to guide the clinical choice for pre-emptive antifungal therapy in neutropenic adult patients at high risk for IFI despite receiving antifungal prophylaxis. A similar approach is certainly attractive to those clinicians caring for children undergoing HCT. However, there is a paucity of data regarding the operating characteristics of the Fungitell Assay in large homogeneous cohorts of children undergoing an HCT and receiving antifungal prophylaxis. It is not reasonable or appropriate to extrapolate results from adult studies and employ a similar pre-emptive approach in children. Prospective study in children is absolutely necessary to allow clinicians to transition from the traditional empiric antifungal approach to a pre-emptive strategy. The planned COG multicenter randomized controlled trial comparing the efficacy of an azole agent to caspofungin for prophylaxis against IFI in children undergoing an HCT offers a unique and likely one-time-only opportunity to establish the utility of the Fungitell Assay in a large cohort of pediatric HCT recipients.

### 13.2 Specific Aims and Hypotheses

**Specific Aim:** To define the test characteristics of weekly Fungitell beta-D-glucan Assay testing for identifying IFI in pediatric HSCT recipients receiving antifungal prophylaxis during the post-transplant neutropenic period.

***Hypothesis***: The Fungitell beta-D-glucan Assay will have a sensitivity that is > 90% for identifying IFI in this population of pediatric HSCT recipients. Alternatively stated, more than 90% of patients that ultimately are diagnosed with an IFI will have at least one positive Fungitell beta-D-glucan Assay prior to the actual IFI diagnosis.

### 13.3 Study Design

This ancillary study is a prospective observational cohort study for defining the operating characteristics of the Fungitell Assay in children enrolled on ACCL1131.

### 13.4 Patient Accrual

All patients to be enrolled on ACCL1131 will be offered the chance to participate in this ancillary fungal infection screening study. Those who consent will undergo weekly Fungitell Assay testing from the time of the HCT until Day +42 or until withdrawal from the study for any reason. It is suggested that specimens be obtained on Thursdays but other days are acceptable if more convenient. For those patients discharged prior to Day +42 weekly outpatient testing will be performed when possible. Each patient will have the potential for 7 separate testing points (once a week for 7 weeks). The proposed ancillary study will concurrently enroll patients from the parent trial with a goal of enrolling 400 patients.

### 13.5 Sample Collection and Testing Procedures (For Consenting Patients Only)

13.5.1 Sample:

In order to perform the Fungitell® beta-D-glucan Assay 5 mL of whole blood will be collected in a gold top serum-separator tube and labeled with the site number, COG ID number, and date (labels will be provided with the sample shipping kit). Although the above volume of blood testing will likely represent a small fraction of the blood testing performed on a HCT recipient during the period of 1 week, it may result in an important increase in certain patients (e.g., smaller children or anemic children). Therefore, we have set the following maximum limits per kilogram for blood draws related to this ancillary study: 3 mL of blood/kg body weight in an 8-week period.

13.5.2 Specimen processing:

Each specimen should be processed as follows prior to shipping:

1. Allow the blood to clot for 30-60 minutes at room temperature
2. Centrifuge the specimen for 15 minutes at 1,000 – 1,300 x *g*.
3. Remove the serum from the clot and place it into the provided polypropylene storage tube and label the tube.
4. A total minimum volume of 1.8 mL of serum is required to run the Fungitell® beta-D-glucan Assay.

13.5.3 Storing specimens:

1. Specimens should be frozen at -70°C the day of collection after following the above processing steps.
2. Specimens can be stored at -70°C until shipment. Specimens stored at -70°C may be stored indefinitely.

13.5.4 Shipping of specimens:

Each center will be provided with specimen collection kits that will be shipped to the center after patient enrollment. These kits will contain specimen collection tubes, Styrofoam lined boxes, sealing tape, labels, the ACCL1131 Fungitell® beta-D-glucan Assay Requisition form and a gel pack. The boxes can hold multiple frozen serum specimens. In order to optimize efficiency, specimens should not be sent until 10 specimens have been collected or every 6 months whichever comes first. As soon as a patient is enrolled, please email Sarah Klieger, at the Children's Hospital of Philadelphia (Klieger@email.chop.edu) to order a specimen collection kit. The shipping kit will be shipped by two-day courier. Kit requests placed on the weekend will be shipped the following Monday.

Requisitions:

Complete an ACCL1131 Fungitell® beta-D-glucan Assay Requisition Form for each specimen sent for testing. All areas of the requisition form must be completed to assure accurate result reporting.

Packaging:

1. Assure all specimen labels and packaging labels are correct and legible. Please use the labels provided in the kits as they are designed to withstand specimen freezing and thawing without disruption of the written patient identification information. A Sharpie marker is most effective for writing on these labels and should be used to avoid smudging of labels.
2. Place the labeled vials containing the patient serum into a biohazard plastic bag along with absorbent material such as gauze or paper towel and seal. Use the biohazard plastic bags provided in the kit.
3. Ship specimens in the boxes provided along with the frozen gel pack that should be frozen.
4. Open the box and remove the Styrofoam liner lid.
5. Place the frozen cold pack into the liner. The frozen cold pack will ensure specimen integrity during overnight shipment.
6. Place the biohazard plastic bag containing the requisition forms and specimens directly on top of the frozen cold pack.
7. Replace the Styrofoam liner lid.
8. Add the completed ACCL1131 Fungitell® beta-D-glucan Assay Requisition Form for each specimen and place on top of the Styrofoam liner before sealing the box.
9. Wet the sealing tape provided in the kit and seal the cardboard box.
10. Affix the UN3373 "Biological Substance Category B" label to a vertical side of the box.
11. If the specimen tube labels and requisition forms do not match when received at the testing site the specimens will not be considered valid and testing will not be performed.

Shipping Instructions:

The courier account information can be found on the ACCL1131 Fungitell® beta-D-glucan Assay Requisition Form provided with the shipping kit.

1. Refer to UPS website http://www.ups.com/content/us/en/resources/ship/hazardous/biological_substances.html to learn the current guidelines, in accordance with IATA (International Air Transport Association) for the shipping and Packaging Requirements of human body fluids.
2. Affix the UPS label to the top of the box. (The UPS label will be included in the shipping kit.) Take care not to cover any of the UN markings.
3. If your institution has a mailroom that uses UPS, take the package to the pickup area.
4. Ship packages to the following address:

   UT Health Science Center at Houston
   Attention: Jose Rodriguez
   6431 Fannin R219 MSE
   Houston TX, 77030
   (713)-500-6755
5. Do not ship on a Friday, Saturday, or the day before a holiday.

13.5.5 Testing of specimens:

1. Testing of serum specimens for this study will be performed in batches.
   a. Negative results are final.
   b. Positive results are retested on the next work-day for confirmation. If original test is performed on Friday, repeat testing of positive specimens will be performed the following Monday.
2. Testing will not occur under the following conditions:
   a. The specimen stored under unacceptable storage times and/or temperatures.
   b. The specimen has been shipped under unacceptable time and/or temperature conditions

c. The specimen volume is less than needed to complete the testing process.
d. The specimen cannot be pipetted due to viscosity.
e. The specimen is hemolyzed or icteric
f. The specimen is of a type other than serum separated off the clot.

3. If a specimen is received and falls under one of the five criteria listed above, a call will be made to the study site to inform them that testing on the specimen could not be performed.
4. Fungitell® beta-D glucan Assay results are reported as pg/mL.

13.5.7 Laboratory of Mycology Research key personnel:

Technical Assistance:
Jose Rodriguez
713-500-6755
jose.rodriguez@uth.tmc.edu
Director: Luis Ostrosky-Zeichner, MD, 713-500-6733

Testing will be performed by technicians blinded to each patient's clinical information. **Test results will not be made available to treating physicians since the utility of these tests is not yet established in children and because we will not be conducting testing in real time. Thus, results will not be utilized for clinical decision-making.**

To our knowledge BG testing is not routinely performed at many pediatric centers but may be performed at some of the COG sites. Regardless of the number of institutions offering such BG testing, we anticipate that such testing will be ordered by a subset of treating physicians. The local BG results will not be included in our final analysis of the biomarker assay's operating characteristics. However, these results may effect a change from fungal prophylaxis to preemptive or empiric therapy and may encourage or discourage more comprehensive efforts to diagnose a proven or probable IFI in any given patient. This in turn may falsely influence our evaluation of the Fungitell beta-D-glucan Assay's operating characteristics. For each patient we will identify whether local BG testing has been performed and, via a sensitivity analysis, explore whether such a practice influences the operating characteristics. The plans for this sensitivity analysis are described in more detail in Section 13.9.4 below.

The Fungitell beta-D-glucan Assay is reported in pg/ mL of patient's serum. The manufacturer recommendation for a single positive Fungitell Assay result of > 80 pg/mL will be used to define a positive test.

## 13.6 Gold Standards for IFI Infections

The criteria established by the EORTC/MSG for proven or probable IFI IA will be used as the gold standard. These definitions have been used as the primary endpoints for prior studies validating the Fungitell beta-D-glucan Assay.

13.6.1 Methodology to Identify IFI:

The EORTC/MSG guidelines incorporate clinical, microbiologic, histopathologic, and radiographic data for classification of proven or probable IFI. Therefore, in order to establish these diagnoses, the following data will be obtained on the IFI checklist (Section 10.2): pathology reports (including autopsy reports), CT scan and MRI reports, fungal gram stain and microbiology culture results, non-culture mycology testing results (i.e. histoplasma urine antigens, cryptococcal CSF and serum antigens), ophthalmology exams, and bronchoscopy reports. An independent data review committee including infectious disease and oncology experts who are unaware of treatment assignments will review and classify all cases of fungal infection as proven, probable, or possible, according to the consensus criteria of the EORTC/MSG.

## 13.7 Justification of Methodologic Choices

### 13.7.1 Justification for Chosen Threshold for the Fungitell beta-D-glucan Assay:

IFI outcomes are often devastating; thus it is desirable to optimize sensitivity at the potential expense of specificity. Furthermore, a highly sensitive test will likely result in few false negatives. Clinicians caring for patients with positive tests would then have a heightened concern for IFI while a negative test result would reassure them that no further modifications to antifungal therapy are necessary at that time. It was with these intentions that the following threshold value was chosen to conclude negative and positive results.

The Fungitell beta-D-glucan Assay threshold result of ≥ 80 pg/mL was chosen based on manufacturer recommendations and available data. For two adult studies that evaluated this test, the cut-off for a positive test was lowered to > 60 pg/mL.[63,64] Lowering of the manufacturer threshold in these two studies resulted in high sensitivity, which is consistent with the goals of our study. However, analysis of BG levels in 120 healthy children revealed that 22% of them had BG levels greater than 60 pg/mL.[66] Although this level would optimize sensitivity, the likelihood for false positivity is too high. There were still 15% of healthy children in this study that had a level of ≥ 80 pg/mL. This suggests that even at a level of ≥ 80 pg/mL, sensitivity of this assay in children would be preserved. Therefore, the manufacturer threshold of ≥ 80 pg/mL was chosen. A post hoc analysis of various cutoffs as well as assessment of sequential positive testing will be performed in an attempt to identify the most ideal cut-off for future use of this assay (please see statistical analysis below).

### 13.7.2 Justification for IFI Gold Standard:

We have chosen to use EORTC/MSG defined proven or probable IFI as the gold standard. The ideal gold standard to compare the biomarker would be a positive culture of a fungal organism from blood or infected tissue. However, there are significant challenges to establish the presence of fungal infection based on just the isolation of the fungal organism itself. Certain molds such as Aspergillus do not grow routinely in blood cultures, the ability to obtain tissue for culture can be impacted by the size and location of a visceral lesion, and the clinical status of a patient may preclude invasive procedures to obtain cultures. Therefore, an alternate endpoint to identify all patients who truly have IFI is necessary. This issue has been addressed by the EORTC/MSG. This group of experts initially created criteria based on clinical, radiographic and culture data to define possible, probable and proven IFI in 2002 and revised these criteria in 2008.[31,67] These criteria have served as the primary endpoint for major trials of antifungal drug efficacy, in strategy trials, for formulating clinical practice guidelines, as well as for undertaking epidemiologic studies. Consistent use of these criteria as the primary endpoint will allow for comparison of our resultant data to prior and future studies.

## 13.8 Factors Resulting in False Positive Results

A number of medications, medical interventions, and infections have been suggested as possible causes of false positive results for BG testing.[68-70] Table 2 lists the potential causes of false positive results reported in the literature. It is anticipated that recipients of a HCT will have reason to be exposed to a number of these medications, infusions and/or medical interventions. Additionally, *Pneumocystis jiroveci* infection is also considered a cause of a "false positive" BG test. Technically this is not a true false positive as the Fungitell Assay is detecting BG from the cell wall of *Pneumocystis jiroveci* as it would for other fungal infections. However, in this instance it is considered a "false positive" as the treatment of choice for this infection is trimethoprim-sulfamethoxazole as opposed to a typical anti-fungal agent. A sensitivity analysis (as described in Section 13.9.4 below) will be performed to investigate the impact of these false positive inducing factors on the operating characteristics of the 2 biomarkers. The starred factors are likely to be the most clinically relevant and thus they will be focused on.

| **Table 2.** Potential factors resulting in false positive testing for (1→3) beta-D glucan | |
|---|---|
| Medications | *Amoxicillin-clavulanate |
| Infusions | *Intravenous immune globulin<br>Cellulose filters for IV infusion<br>Albumin |
| Medical interventions | Hemodialysis with cellulose filter<br>Gauze packing on serosal Surfaces |
| Other infections | **Pneumocystis jiroveci* |

### 13.9 Statistical Design

13.9.1 Sample Size and Estimated Event Rates:

The parent trial comparing prophylaxis with an azole (fluconazole or voriconazole) to caspofungin in newly diagnosed AML patients anticipates enrollment of at least 280 patients for each arm with a total cohort of approximately 560 patients. As noted above we anticipate enrollment of approximately 400 patients. This will result in 200 patients from each study arm. Consent for testing will be included as a part of the parent trial enrollment, thus significantly limiting the need for additional resources to complete this biomarker study.

The estimated number of probable or proven IFI events for final analyses will vary by study arm. The Fungitell beta-D-glucan Assay has the potential to identify most pathogenic fungi (with the exception of *Mucorales* species and Cryptococci) and thus a majority of the probable or proven IFIs will be considered as true events.

It is challenging to establish an estimate of the event rate for IFI in this patient population as a prospective trial of anti-fungal prophylaxis in pediatric HCT recipients has never been performed. There have been three retrospective pediatric-specific studies that have attempted to define these event rates.[26,27,55] The cumulative incidence of IFI in these three studies ranged from 8- 13%. It should be noted that these studies varied in follow-up time, in the types of transplants included, in the antifungal prophylaxis utilized and in the definition for IFI used to define the outcome. More recently an adult randomized and double blind controlled trial compared the efficacy of fluconazole prophylaxis to that of voriconazole in HCT recipients.[3] Within 180 days from transplantation, 8.1% of patients on fluconazole and 4.6% of patients on voriconazole developed a breakthrough IFI. This patient population had almost no unrelated umbilical cord blood transplant patients making it a much lower risk group for IFI than our proposed patient population.

In the proposed parent trial included patients will be the recipients of allogeneic stem cells (bone marrow, peripheral blood stem cells, or umbilical cord blood). These HCT patients are those at high-risk for an IFI and thus the anticipated incidence rate of IFI may be higher than that reported in the above referenced adult trial. Alternatively, the proposed trial will only follow patients for 100 days from transplantation and thus later onset IFI will not be identifiable. Considering the data presented above and the proposed study parameters, the COG parent trial has conservatively estimated that the IFI incidence rate will be 7% (20 events) in the azole treatment arm and 2% (6 events) in the caspofungin study arm. Because this ancillary study plans to enroll 70% (400 patients) of the parent trial patients over a three-year period the estimated event rates for the azole and caspofungin arms are 14 and 4 respectively (table 3).

| Table 3. Estimated IFI and IA event rates | | | |
|---|---|---|---|
| | Total | Azole Arm | Caspofungin Arm |
| Number | 400 | 200 | 200 |
| IFI Rate | 4.6% | 7.0% | 2.0% |
| IFI Events | 18 | 14 | 4 |

13.9.2 Sensitivity, Specificity, PPV, and NPV:

The validity of a biomarker is based on whether the study appropriately categorizes patients with and without the illness in question (sensitivity and specificity). Alternatively the validity of a test can be measured by how well the test results predict the presence or absence of the disease (PPV and NPV). Collectively, sensitivity, specificity, PPV, and NPV are often referred to as the test's operating characteristics. Each component of the operating characteristics will be calculated based first on the entire cohort. As indicated in the estimates above, the incidence of is expected to vary between the two study arms. It is well documented that variations in the incidence/prevalence of a disease will impact the operating characteristics of a diagnostic test specifically for the PPV and NPV. Therefore, each assay's sensitivity, specificity, PPV and NPV will also be calculated separately for each study arm.

The operating characteristics for the Fungitellbeta-D-glucan Assay will be computed as follows:

- Outcome of all IFI defined as a single positive test for the Fungitell beta-D-glucan Assay as compared to the EORTC/MSG criteria for all proven or probable IFI.

Sensitivity, specificity, PPV and NPV and their accompanying 95% confidence intervals will be calculated using STATA statistical software version 12.0 (College Station, TX). As noted above, these parameters will first be calculated for the entire cohort and then for each study arm separately. A patient with multiple episodes of IFI will only be included in the analyses as a single IFI. As would be expected in the setting of low incidence, we anticipate that the results will show a low PPV and high NPV. This will not be an indication that the assay is not useful. The intended goal of the assay is to identify all patients with IFI at the earliest time point. In order to identify all such patients there will need to be a tolerance for a certain number of false positive results. Thus in this clinical setting the sensitivity of these assays is the most relevant parameter assuming the number of false positive results is not excessive.

13.9.3 Receiver Operator Characteristics Curve:

In addition to understanding the operating characteristics of a diagnostic test at a single defined threshold, it is also important to understand how variations in the test's threshold can alter the test's operating characteristics. The receiver operating characteristics (ROC) curve is a useful approach to illustrate how these operating characteristics will change as the threshold changes. Therefore, a receiver-operating-characteristics (ROC) curve will be generated with a series of sensitivities and specificities derived from various cutoff values. For the Fungitell Assay cutoffs of $\geq 60$, $\geq 80$, $\geq 100$, and $\geq 120$ pg/mL will be used to create the ROC. The ROC curve will be displayed graphically (sensitivity vs. 1-specificity) and evaluated numerically (c-statistic). The c-statistic (also referred to as the area under the curve (AUC)) varies from 0.5 to 1.0 and is a measure of the test's ability to discriminate between patients with and without the gold standard diagnosis.[71] A c-statistic of 0.5 is possible by chance alone while a perfectly discriminating test will result in a c-statistic of 1.0.

Additionally, the ROC curves will be used in an exploratory analysis to identify the threshold for the biomarker assay that optimizes the diagnostic test's sensitivity while maintaining a reasonable specificity. The identified thresholds will be used to categorize each patient as "likely to have IFI " and "not likely to have IFI ". Once these 2 sub-groups are defined we will calculate the incidence rates of IFI for each sub-group and compare them. Because the anticipated incidence for IFI may be variable between the two study

arms (those receiving an azole and those receiving caspofungin) this approach will have to be done at the level of each study arm. The incidence rates will be compared statistically using Pearson's Chi-square analysis.

Finally, to further explore the ideal utility and interpretation of each biomarker, serial testing results will be explored. For this analysis the Fungitell beta-D-glucan Assay will be considered positive when a patient has 2 consecutive test results ≥ 80 pg/mL. Operating characteristics and ROC curves will be constructed in a similar manner as discussed above.

13.9.4 Sensitivity Analysis:

Sensitivity analyses will be explored for the reasons expressed in Section 13.7.1 and 13.8. The first sensitivity analysis will attempt to identify the direction and magnitude of the bias resulting from the availability of clinical BG testing performed outside of the ancillary study. Such testing has the potential to change the treating clinician's approach for diagnosing an IFI. It is possible that these test results could result in more or less investigation (e.g. radiologic imaging) to identify an IFI, which could ultimately impact on the incidence of identified IFI. Therefore, in addition to calculating the operating characteristics for all patients enrolled, the same operating characteristics will be calculated after excluding all patients that had at least 1 biomarker test result available to the treating clinician.

The second sensitivity analysis will be performed to explore the impact of the various factors described in Section 13.8 that may contribute to a positive result for the biomarker. False positive results would impact the final interpretation of sensitivity and PPV for each of the assays. However, it is also possible that one of the factors listed in Table 2 is present in a patient that truly has an IFI. Therefore, we plan to still include all patients in the primary analysis for calculation of the assay's operating characteristics. In this sensitivity analysis, we will eliminate all patients with a positive test that correlates in time with at least 1 of the starred factors listed in Table 2.

### 13.10 Significance

Fungal infections continue to be major contributors to morbidity and mortality in children undergoing HCT. Although antifungal prophylaxis in these patients will reduce the frequency of IFI, it will not eliminate the risk of these devastating infections. Early diagnosis and therapeutic modifications are paramount to improving patient outcomes. The Fungitell beta-D-glucan Assay is a potential diagnostic tool that could improve the time to diagnosis of IFI. More definitive data regarding the operating characteristics of these 2 biomarkers interpreted separately and simultaneously in the setting of a large pediatric cohort receiving anti-fungal prophylaxis are necessary. Evaluating the biomarker first as an integrated test will provide valuable information regarding the utility of each test for future pediatric patients being treated under similar circumstances. It is important to realize that the results of this study (either to support or not support the routine clinical use of the biomarker) will have an important impact on the provision of future clinical care. If the results support the biomarker as an adjunctive diagnostic tool for identifying IFI, then clinicians will be better informed on the clinical application of the assay results. However, if the assay does not perform well in identifying IFI, then clinicians will know that this assay is not useful in this clinical scenario and thus will not order the test. This would result in the conservation of finite resources and redirect the focus of researchers to other modalities for diagnosing fungal infections.

## 14.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS FOR PATIENTS THAT CONSENT ONLY

### 14.1 Single Nucleotide Polymorphisms

Genotypes of interest in genes mediating immune function will be determined by review of the literature. Analysis will be performed on the Taqman Open Array Platform according to the manufacturer's instructions.

14.1.1 Sample Collection
Collect 5 mL of peripheral blood in a purple top (EDTA) tube at study entry and at end of study (Day +100 +/- 7 days), optimally when the patient has an ANC >1000/μL. Patients with weights less than 20 kg may have only 3 mL collected. Specimens may be shipped fresh to the BPC, where the plasma and buffy coat will be stored at -20°C.

14.1.2 Labeling:
Label the tubes with the patient's BPC #, specimen type, and date of collection.

14.1.3 Shipping:
Ship sample at room temperature by FedEx priority overnight delivery. Shipping labels can be obtained via the Biopathology Center's Kit Management application. Blood may be shipped Monday through Friday for receipt on Tuesday through Saturday. Include a COG Specimen Transmittal Form with each shipment.

The SNP sample should be shipped to:

COG Biopathology Center – ACCL1131
Nationwide Children's Hospital
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: 614-722-2865
Fax: 614-722-2897

*Be sure to include the room number. Packages received without the room number may be returned to the sender.

## 15.0 BANKING SPECIMENS

If the patient consents, leftover blood samples (from the studies described in Section 14) will be returned to the BPC and banked for future research studies.

## APPENDIX I: YOUTH INFORMATION SHEETS

### INFORMATION SHEET REGARDING RESEARCH STUDY ACCL1131
### (for children from 7 through 12 years of age)

A Research Study Comparing Drugs Used To Prevent Serious Fungal Infections In Children Receiving a Stem Cell Transplant

1. We have been talking with you about your likelihood of getting Invasive Fungal Infections. Invasive Fungal Infections are infections which occur in people whose natural infection-fighting ability (also called immunity) have been reduced. The strong cancer fighting drugs (called chemotherapy) and radiation used in stem cell transplants reduce your immunity and make you more likely to get invasive fungal infections.

2. We are asking you to take part in a research study because you are at risk of invasive fungal infections. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to find better ways to prevent invasive fungal infections in children receiving a stem cell transplant.

3. Children who are part of this study will be given medicines that help prevent invasive fungal infections. These drugs are called antifungal agents. In this study, one group of children will get the usual antifungal drugs called fluconazole or voriconazole. The other group will get a newer antifungal agent called caspofungin. Your doctor will tell you which group you are in. We do not know if the newer antifungal agent will be better than the usual treatment. That is why we are doing this study.

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is a better chance of avoiding invasive fungal infections during your stem cell transplant, but we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” There is a risk that you will have bad effects from the newer antifungal agent or that it will not be better at preventing you from getting invasive fungal infections during your stem cell transplant. Other things may happen to you that we don’t yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood for some special tests. We want to collect extra blood samples to see if doctors can detect fungal infections as early as possible, and better than the usual tests used. We also want extra blood samples to look at your genes for any changes that may make a person more likely to get invasive fungal infections. Samples for these tests would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

**INFORMATION SHEET REGARDING RESEARCH STUDY ACCL1131**
**(for teens from 13 through 17 years of age)**

A Research Study Comparing Drugs Used To Prevent Serious Fungal Infections In Children and Adolescents Receiving a Stem Cell Transplant

1. We have been talking with you about your likelihood of getting Invasive Fungal Infections. Invasive Fungal Infections are infections which occur in people whose natural infection-fighting ability (also called immunity) have been reduced. The strong cancer fighting drugs (called chemotherapy) and radiation used in stem cell transplants reduce your immunity and make you more likely to get invasive fungal infections.

2. We are asking you to take part in a research study because you are at risk of invasive fungal infections. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to find better ways to prevent invasive fungal infections in children receiving a stem cell transplant.

3. Children who are part of this study will be given medicines that help prevent invasive fungal infections. These drugs are called antifungal agents. Children and adolescents that are part of this study will be placed into 1 of 2 treatment groups by a process called randomization. Randomization means that the study treatment groups are assigned by chance, and is like flipping a coin, only it is done by a computer. In this study, one group of children will get one of the usual antifungal drugs, called fluconazole or voriconazole. The other group will get a newer antifungal agent called caspofungin. Your doctor will tell you which group you are in. We do not know if the newer antifungal agent will be better than the usual treatment at preventing invasive fungal infections. That is why we are doing this study.

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is a better chance of avoiding invasive fungal infections during your stem cell transplant, but we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” There is a risk that you will have bad effects from the newer antifungal agent or that it will not be better at preventing you from getting invasive fungal infections during your stem cell transplant. Other things may happen to you that we don’t yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood for some special tests. We want to see if a new blood tests can help doctors detect fungal infections as early as possible, and better than the usual tests used. This new test is called beta-D glucan. We also want extra blood samples to look at your genes for any changes that may make an individual more likely to get invasive fungal infections. This is called single nucleotide polymorphism (SNP) analysis. Blood for these tests would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

## APPENDIX II: EORTC/MSG CRITERIA

### Criteria for proven invasive fungal disease except for endemic mycoses[31]

| 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.

## Criteria for probable invasive fungal disease except for endemic mycoses

- Host factors[a]
  - Recent history of neutropenia (< 0.5 X $10^9$ 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.

## APPENDIX III: COG STEM CELL COMMITTEE CONSENSUS GUIDELINES FOR ESTABLISHING ORGAN STAGE AND OVERALL GRADE OF ACUTE GRAFT VERSUS HOST DISEASE (GVHD)

Reporting Requirements for Acute GVHD in COG Studies

In an attempt to standardize reporting of acute GVHD, the COG Stem Cell Transplantation Committee has adopted a modification of guidelines that were originally developed at the University of Michigan.

***Table 1*** outlines standard criteria for GVHD organ staging. However, confounding clinical syndromes (such as non-GVHD causes of hyperbilirubinemia) may make staging GVHD in a given organ difficult. In addition, timing of organ specific symptoms affects whether that symptom is more or less likely to be true GVHD. Please refer to ***Tables 2 and 3*** to assist you in deciding whether to attribute these clinical findings to GVHD, especially in situations where a biopsy is not possible. For additional help, please see the text which follows the tables.

***Table 4*** reviews the approach to assessing GVHD as acute, chronic, or the overlap between the two.

Finally, *engraftment syndrome* will be reported separately from the GVHD scoring presented below.

Engraftment Syndrome

A clinical syndrome of fever, rash, respiratory distress, and diarrhea has been described just prior to engraftment in patients undergoing unrelated cord blood and mismatched transplantation. If in the judgment of the local investigator a patient experiences this syndrome, details of the event should be reported when requested in the study CRFs.

Modified Glucksberg Staging Criteria for Acute Graft versus Host Disease

**Table 1. Organ Staging (See tables and text below for details)**

| Stage | Skin | Liver (bilirubin) | Gut (stool output/day) |
|---|---|---|---|
| **0** | No GVHD rash | < 2 mg/dL | Adult: < 500 mL/day<br>Child: < 10 mL/kg/day |
| **1** | Maculopapular rash<br>< 25% BSA | 2-3 mg/dL | Adult: 500-999 mL/day<br>Child: 10-19.9 mL/kg/day<br>***Or persistent nausea, vomiting, or anorexia, with a positive upper GI biopsy.*** |
| **2** | Maculopapular rash<br>25% – 50% BSA | 3.1-6 mg/dL | Adult: 1000-1500 mL/day<br>Child: 20-30 mL/kg/day |
| **3** | Maculopapular rash<br>> 50% BSA | 6.1-15 mg/dL | Adult: >1500 mL/day<br>Child: > 30 mL/kg/day |
| **4** | Generalized erythroderma plus bullous formation and desquamation > 5% BSA | >15 mg/dL | Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume). |

For GI staging: The "adult" stool output values should be used for patients > 50 kg in weight. Use 3 day averages for GI staging based on stool output. If stool and urine are mixed, stool output is presumed to be 50% of total stool/urine mix.

For Stage 4 GI: the term "severe abdominal pain" will be defined as:
(a) Pain control requiring institution of opioid use, or an increase in on-going opioid use, PLUS
(b) Pain that significantly impacts performance status, as determined by the treating MD.

If colon or rectal biopsy is +, but stool output is < 500 mL/day (< 10 mL/kg/day), then consider as GI Stage 0.

There is no modification of liver staging for other causes of hyperbilirubinemia

**Overall Clinical Grade (based on the highest stage obtained):**
**Grade 0:** No Stage 1-4 of any organ
**Grade I:** Stage 1-2 skin and no liver or gut involvement
**Grade II:** Stage 3 skin, or Stage 1 liver involvement, or Stage 1 GI
**Grade III:** Stage 0-3 skin, with Stage 2-3 liver, or Stage 2-3 GI
**Grade IV:** Stage 4 skin, liver or GI involvement

**Table 2. Evaluating Liver GVHD in the Absence of Biopsy Confirmation**

**Establishing liver GVHD with no skin or GI GVHD**

| | | |
|---|---|---|
| **No Skin/GI GVHD Day 0-35** | **Assume no liver GVHD** unless proven by biopsy | |
| **No Skin/GI GVHD Day 36-100** | If NO other etiology identified, NO improvement with stopping hepatotoxic medications/TPN: **Stage as liver GVHD** | If other etiology identified or improves with stopping hepatotoxic drugs/TPN: **Do not stage as liver GVHD** |

**Establishing liver GVHD with skin or GI GVHD and other cause of hyperbilirubinemia**

| | | |
|---|---|---|
| **Skin and/or GI GVHD present** | Worsening bilirubin level (includes worsening just prior to onset of skin or GI tract GVHD) OR stable elevated bilirubin despite resolution of non-GVHD cause of increased bilirubin: **Stage as liver GVHD** | Stable or improving bilirubin after diagnosis of skin or GI GVHD, irrespective of treatment: **Do not stage as liver GVHD** |

**Changing liver GVHD stage with other cause of hyperbilirubinemia**

| | |
|---|---|
| **Skin and GI GVHD stable, improving, or absent** | Liver GVHD staging is carried forward without increase in stage until other disease process resolves (e.g., if TTP is diagnosed in the presence of Stage 2 liver GVHD, the liver GVHD Stage 2 is carried forward despite rising bilirubin level until TTP is resolved. If there is no liver GVHD – Stage 0 – and new onset TTP, the Stage 0 is carried forward until TTP is resolved). |

| | |
|---|---|
| **Skin and/or GI GVHD worsening** | **Liver GVHD is staged according to the Glucksberg criteria. The elevated bili is attributed to GVHD alone.**<br><br>Thus, when skin or GI GVHD is worsening, there is no downgrading of liver GVHD staging for other causes of hyperbilirubinemia. (e.g., if TTP is diagnosed in the presence of Stage 2 liver GVHD and worsening skin or GI GVHD, the liver is staged according to the actual bilirubin level even if some of the rise in bilirubin is attributed to TTP).<br><br>Similarly, even if there is no liver GVHD at onset of a new process, (such as TPN cholestasis), but skin or GI GVHD worsen during that process, then liver GVHD is diagnosed and staged according to the height of the bilirubin.<br><br>There is one exception to this: the diagnosis of TTP, with high LDH and **unconjugated** bilirubin precludes the diagnosis and staging of new liver GVHD in the absence of a confirmatory liver biopsy. |

**Table 3. Evaluating GI GVHD in the Absence of Biopsy Confirmation**

**Establishing GI GVHD with new onset diarrhea and no skin or liver GVHD**

| | | |
|---|---|---|
| **No Skin/liver GVHD Day 0 through engraftment** | Assume no GI GVHD unless proven by biopsy | |
| **No Skin/liver GVHD Engraftment through Day 100** | NO other etiology of diarrhea identified:<br>**Stage as GI GVHD** | Any other etiology of diarrhea identified:<br>**Do not stage as GI GVHD** |

**Establishing GI GVHD with pre-existing diarrhea and skin or liver GVHD**

| | | |
|---|---|---|
| **Skin and/or liver GVHD present** | Worsening diarrhea (includes worsening just prior to onset of skin or liver GVHD) OR persistent diarrhea despite resolution of non-GVHD cause:<br>**Stage as GI GVHD** | Improving diarrhea after the diagnosis of skin or liver GVHD (irrespective of treatment) OR persistent diarrhea without resolution of underlying non-GVHD cause:<br>**Do not stage as GI GVHD** |

Differentiating Acute GVHD, Chronic GVHD, and Overlap Syndrome

There is often confusion differentiating acute from chronic GVHD, especially in the setting of reduced intensity transplants, DLI and new prophylactic treatments. The NIH Working Group recently published new classifications for GVHD:

**Table 4. Acute GVHD, Chronic GVHD, and Overlap Syndrome**

| Category | Time of Symptoms after HCT or DLI | Presence of Acute GVHD features | Presence of Chronic GVHD features |
|---|---|---|---|
| **Acute GVHD** | | | |
| Classic acute GVHD | ≤100 d | Yes | No |
| Persistent, recurrent, or late-onset acute GVHD | >100 d | Yes | No |
| **Chronic GVHD** | | | |
| Classic chronic GVHD | No time limit | No | Yes |
| Overlap syndrome | No time limit | Yes | Yes |

- Scoring of acute GVHD may need to occur past Day 100. In particular, patients should continue to be scored for acute GVHD when classic acute GVHD symptoms (maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea - particularly if bloody and ileus) persist past Day 100 or if identical symptoms previously scored as acute GVHD resolve and then recur within 30 days during immunosuppression taper but past Day 100.

- Those patients being scored as having acute GVHD should NOT have diagnostic or distinctive signs of chronic GVHD.

- Patients with both acute and chronic symptoms should be diagnosed as having Overlap Syndrome and scored according to their chronic GVHD score.

Further Explanation of Criteria presented in Tables 2 and 3

Assessment of Skin GVHD

**Presence or Absence of Skin GVHD:** Skin GVHD will be considered present if a rash characteristic of acute GVHD develops after allogeneic marrow transplantation involving more than 25% of the body surface not clearly attributable to causes such as drug administration or infection. The extent of the body surface area involved can be estimated by the "Rule of Nines". In estimating the extent of skin GVHD, the area involved is calculated for individual anatomic areas, such as the arm or leg, and then the total is derived from a simple summation. Areas that are non-blanching should not be considered involved regardless of the overlying color of the rash (red, brown, etc.). Limited distribution erythema (with the exception of palms and soles) in the absence of associated rash elsewhere on the body will not be considered GVHD.

Assessment of Liver GVHD

**Assessing for the Presence or Absence of Liver GVHD**

A. Hyperbilirubinemia (total bilirubin ≥ 2.0 mg/dL) in the **absence** of other signs of acute GVHD in the skin or GI tract:

   i) Day 0-35: If hyperbilirubinemia alone is present with no other signs of acute GVHD in other organ systems, acute GVHD will not be diagnosed based solely on laboratory abnormalities. Acute GVHD will be diagnosed if findings on histopathology studies of liver from a biopsy or autopsy are confirmatory.

ii) Day 35-100: If hyperbilirubinemia (must be conjugated bilirubin) is not improving or is exacerbated (especially if serum alkaline phosphatase is increased), in the absence of acute GVHD in other organ systems, no other etiologies are identified, and does not improve with discontinuation of hepatotoxic drugs, acute GVHD will be diagnosed. However, it is distinctly unusual to develop ascites or a coagulopathy in the early stages of acute GVHD of the liver alone. In the absence of histopathology studies of liver from a biopsy or autopsy specimen, ascites or a coagulopathy secondary to liver dysfunction will be considered to indicate the presence of another disease process (e.g., veno-occlusive disease). Recommended non-invasive studies to define an etiology for hyperbilirubinemia are:

a. Imaging of liver (CT or ultrasound)
b. Hepatitis screen (only if ALT is elevated)
c. PT
d. Blood cultures
e. Review of medication list for potentially hepatotoxic drugs
f. Review of risk factors for viral liver infection (HSV, CMV, VZV, adenovirus, EBV, HBV, HCV)
g. Hemolysis screen

B. Pre-existing hyperbilirubinemia clearly attributed to an etiology other than acute GVHD in the presence of signs of acute GVHD in other organ systems.

i) If pre-existing non-GVHD liver disease (documented clinically, by lab assessment, or by imaging studies) is stable or improving at the onset of signs of acute GVHD in other organs, then acute GVHD of the liver will not be considered to be present unless proven by liver biopsy or autopsy.

ii) If hyperbilirubinemia worsens several days before or at the time of onset of signs of acute GVHD in other organ systems, GVHD will be considered to be present unless histopathology studies of liver are available and negative on a biopsy during that time interval or autopsy results exclude GVHD.

iii) If hyperbilirubinemia persists and is not improving after resolution of a pre-existing non-GVHD liver disease process (e.g. localized infection of liver, systemic sepsis, biliary tract obstruction) when signs of acute GVHD are present in other organ systems or no other intervening cause has been diagnosed, then acute GVHD will be considered to be present in the absence of a new, clearly identifiable cause of non-GVHD liver disease or unless a liver biopsy or autopsy specimen is negative.

C. Prior acute GVHD in liver with new onset of a disease process that exacerbates pre-existing or recently resolved hyperbilirubinemia:

i) If an etiology other than acute GVHD is clearly identified as causing or exacerbating hyperbilirubinemia and acute liver GVHD has been diagnosed and has been stable, improving, or resolved, then the liver will not be restaged for acute GVHD until the resolution or stabilizing of the concurrent disease process (i.e., the liver stage prior to the onset of the new disease process will be carried forward until the new disease process resolves). Example: Acute GVHD of the liver and gut is diagnosed on Day 20. Treatment of acute GVHD results in falling bilirubin levels to liver Stage 1. Sepsis or TTP develops with transient worsening of the hyperbilirubinemia. The liver stage is not increased, despite a higher bilirubin level, because the cause of worsening hyperbilirubinemia is attributed to sepsis or TTP.

ii) If an etiology other than acute GVHD is clearly identified as causing or exacerbating hyperbilirubinemia in the presence of already worsening acute liver GVHD **or** GVHD of the skin or GI tract is simultaneously worsening, then the liver GVHD will be staged according to the actual bilirubin level, even though another cause of hyperbilirubinemia is present.

Assessment of GVHD of the Gastrointestinal Tract

**Assessing for the Presence or Absence of GVHD of the Gastrointestinal Tract**

A. Diarrhea (≥ 500 mL/day in adults or > 10 mL/kg in pediatric patients) in the absence of other signs of acute GVHD in other organ systems

i) Day 0-engraftment: If diarrhea alone is present without other signs of acute GVHD in other organ systems, acute GVHD will not be considered present. Diarrhea will be attributed to acute GVHD if histopathology studies of gastrointestinal tract from a biopsy or autopsy are diagnostic.

ii) Engraftment-Day 100: If diarrhea persists and is not improving, is exacerbated, or develops *de novo* in the absence of acute GVHD in other organ systems, histopathology studies of gut biopsies or from autopsy specimens are not available, and no other etiologies are clearly identified, acute GVHD will be considered to be the cause. A stool specimen should be examined to rule out infectious causes (e.g., rotavirus, adenovirus, and C. difficile toxin). It is recommended, if at all possible, that biopsies be obtained for diagnostic purposes.

B. Pre-existing diarrhea clearly attributed to an etiology other than acute GVHD in the presence of signs of acute GVHD in other organ systems:

i) If pre-existing diarrhea caused by a process other than GVHD has been documented clinically or by lab assessment and is stable or improving at the onset of signs of acute GVHD in the skin or liver, then acute GVHD of the intestine will not be considered to be present in the absence of biopsy confirmation or autopsy report.
ii) If diarrhea or gastrointestinal symptoms are already present, but worsen significantly at the time of onset of signs of acute GVHD in the skin or liver, GVHD will be considered present, unless biopsy or autopsy are negative.
iii) If diarrhea persists after resolution of a pre-existing disease process with signs of acute GVHD present in other organ systems, GVHD will be considered present, unless biopsy or autopsy are negative.

C. Prior or present acute GVHD in other organ systems with new onset of diarrhea:

If diarrhea is **clearly** attributable to an etiology other than acute GVHD (e.g., infection) and a history of acute GVHD exists or acute GVHD is present in other organ systems and is stable, then the gastrointestinal tract will not be evaluable for acute GVHD until the resolution or stabilizing of the other disease process (e.g., infection) in the absence of biopsy or autopsy confirmation.

D. Persistent anorexia, nausea or vomiting in the absence of signs of acute GVHD in other organ systems:

Persistent anorexia, nausea or vomiting in the absence of other known causes of these symptoms will be considered Stage 1 acute GVHD if confirmed by endoscopic biopsy.

If a biopsy is not possible (e.g., secondary to thrombocytopenia) but the clinical findings are compatible with acute GVHD, then the patient will be treated and recorded as having acute GVHD.

**Staging of the Gastrointestinal Tract for the Severity of Acute GVHD**

The severity of gastrointestinal tract GVHD will be staged according to modified Glucksberg criteria. To minimize errors caused by large day-to-day variation, diarrhea volume is measured as an average over 3 days and reported as the volume in ml per day. When urinary mixing is noted the stool volume will be considered half of the total volume unless nursing staff is able to give a better estimate from direct observation. Abdominal cramps are considered significant for staging if the severity results in a clinical intervention (e.g., analgesia, fasting, etc.). Blood in the stools is considered significant if the blood is visible or hematochezia/melena is present and not clearly attributed to a cause other than GVHD (e.g. epistaxis/hemorrhoids).

## APPENDIX IV: POSSIBLE DRUG INTERACTIONS

***The lists below do not include everything that may interact with chemotherapy. Study patients and/or their parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in the diet.***

**Caspofungin**

| **Drugs that may interact with caspofungin** |
|---|
| • Anti-rejection medications<br>  o Cyclosporine, tacrolimus<br>• Anti-seizure medications<br>  o Carbamazepine, phenytoin<br>• Other medications such as dexamethasone, efavirenz, nevirapine, and rifampin |

| **Food and supplements that may interact with caspofungin*** |
|---|
| • Florastor |

*Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

**Fluconazole**

| **Drugs that may interact with fluconazole** |
|---|
| • Antibiotics, antifungals, and other drugs for infections<br>  o Artemether/lumefantrine, ciprofloxacin, clarithromycin, erythromycin, levofloxacin, moxifloxacin, pentamidine, rifabutin, rifampin<br>• Antidepressants and antipsychotics<br>  o Buspirone, citalopram, clozapine, escitalopram, fluoxetine, lurasidone, nefazodone, olanzapine, paliperidone, quetiapine, sertraline, thioridazine, trazodone<br>• Anti-rejection medications<br>  o Cyclosporine, sirolimus, tacrolimus<br>• Antiretrovirals and antivirals<br>  o Atazanavir, boceprevir, darunavir, delavirdine, didanosine, efavirenz, etravirine, fosamprenavir, maraviroc, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, telaprevir, zidovudine<br>• Anti-seizure medications<br>  o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone<br>• Cholesterol, heart and blood pressure medications<br>  o Amiodarone, atorvastatin, carvedilol, clopidogrel, dofetilide, eplerenone, gemfibrozil, lovastatin, nicardipine, nisoldipine, procainamide, simvastatin, sotalol, verapamil<br>• Diabetes medications<br>  o Glipizide, glyburide, repaglinide, saxagliptin<br>• Nausea medications<br>  o Aprepitant, dolasetron, droperidol, haloperidol<br>• Oral contraceptives (“birth control”), including emergency oral contraceptives<br>• Some chemotherapy (be sure to talk to your doctor about this)<br>• Stomach and reflux medications<br>  o Cimetidine, esomeprazole, lansoprazole, omeprazole<br>• Many other drugs, including the following: |

| |
|---|
| ○ Apixaban, bosentan, budesonide, diazepam, dihydroergotamine, eletriptan, ergotamine, eszopiclone, guanfacine, ivacaftor, lomitapide, methadone, methylprednisolone, mifepristone, oxycodone, pimozide, salmeterol, sitaxentan, sildenafil, tofacitinib, warfarin, zolpidem |

| **Food and supplements that may interact with fluconazole*** |
|---|
| • Florastor<br>• Milk thistle<br>• Red rice yeast<br>• St. John's Wort<br>• Grapefruit, grapefruit juice, Seville oranges, star fruit |

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

**Voriconazole**

| **Drugs that may interact with voriconazole** |
|---|
| • Antibiotics, antifungals, and other drugs for infections<br>○ Artemether/lumefantrine, ciprofloxacin, clarithromycin, erythromycin, isoniazid, levofloxacin, moxifloxacin, pentamidine, rifabutin, rifampin<br>• Antidepressants and antipsychotics<br>○ Buspirone, citalopram, clozapine, escitalopram, fluoxetine, fluvoxamine, lurasidone, nefazodone, olanzapine, paliperidone, quetiapine, sertraline, thioridazine, trazodone<br>• Anti-rejection medications<br>○ Cyclosporine, sirolimus, tacrolimus<br>• Antiretrovirals and antivirals<br>○ Atazanavir, boceprevir, darunavir, delavirdine, didanosine, efavirenz, etravirine, fosamprenavir, lopinavir, maraviroc, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir<br>• Anti-seizure medications<br>○ Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone<br>• Cholesterol, heart and blood pressure medications<br>○ Amiodarone, atorvastatin, carvedilol, clopidogrel, dofetilide, eplerenone, gemfibrozil, lovastatin, nicardipine, nisoldipine, procainamide, simvastatin, sotalol, verapamil<br>• Diabetes medications<br>○ Glipizide, glyburide, repaglinide, saxagliptin<br>• Nausea medications<br>○ Aprepitant, dolasetron, droperidol, haloperidol<br>• Oral contraceptives ("birth control"), including emergency oral contraceptives<br>• Some chemotherapy (be sure to talk to your doctor about this)<br>• Stomach and reflux medications<br>○ Cimetidine, esomeprazole, lansoprazole, omeprazole<br>• Many other drugs, including the following:<br>○ Apixaban, bosentan, budesonide, dihydroergotamine, eletriptan, ergotamine, eszopiclone, guanfacine, ivacaftor, lomitapide, methadone, methylprednisolone, mifepristone, oxycodone, pimozide, salmeterol, sitaxentan, sildenafil, tofacitinib, warfarin, zolpidem |

| **Food and supplements that may interact with voriconazole*** |
|---|
| • Florastor |

- Milk thistle
- Red rice yeast
- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

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This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

**SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM –FOR INSTITUTIONS WITH STANDARD USE OF FLUCONAZOLE**

**ACCL1131**

**A Phase III Open-Label Trial of Caspofungin vs. Azole Prophylaxis for Patients at High-Risk for Invasive Fungal Infections (IFI) Following Allogeneic Hematopoietic Cell Transplantation (HCT)**

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

## Why am I being invited to take part in this study?

You are being asked to take part in this research study because you are about to undergo a stem cell transplant (SCT). More information about SCT can be found in the COG Family Handbook for Children with Cancer. Patients undergoing SCT are at risk of getting an invasive fungal infection.

Invasive fungal infections are infections caused by organisms called fungi that enter the blood stream and spread to different organs in the body. Treatment with high doses of chemotherapy and radiation, which are used as part of SCT, severely reduces the body's natural infection fighting ability. In patients who died from infections while receiving SCT, an invasive fungal infection was the cause in more than half of the cases. Preventing invasive fungal infections is therefore very important for the treatment success of people receiving SCT.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard preventive treatment for invasive fungal infections and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

## What is the current standard of treatment for this disease?

The current standard preventive treatment for people who are at risk of invasive fungal infections due to SCT is the use of fungi fighting drugs (called antifungal therapy). The current standard antifungal drugs are called fluconazole and voriconazole. Fluconazole and voriconazole are part of a group of agents called *azoles*. The azole utilized by your center is fluconazole.

## Why is this study being done?

Current standard antifungal therapy agents (fluconazole and voriconazole) have been shown to be equally effective in preventing invasive fungal infections in people receiving a SCT; especially those caused by the fungi *Candida*. However, previous studies have shown that they do not fully prevent infections caused by some types of fungi called *filamentous fungi*. Aspergillus is a type of filamentous fungi.

In this study, researchers want to find out if using a newer antifungal drug called caspofungin will be better than the current standard antifungal drugs at preventing invasive fungal infections when given to people receiving SCT.

The drug caspofungin was chosen because a drug very similar to caspofungin has been shown to be effective in the prevention of various fungal infections, including *Candida* and *Aspergillus* in a study for adult patients. Caspofungin is an antifungal drug that has been approved by the Food and Drug Administration (FDA) for use in children as well as adults.

The use of caspofungin to prevent invasive fungal infections is experimental.

The overall goal of this study is to:

- **Compare the effects, good and/or bad, of caspofungin vs azole antifungals on people receiving SCT, who are at risk of getting invasive fungal infections, to find out which is better. In this study, you will get either caspofungin or an azole antifungal (fluconazole or voriconazole). You will not get both.**

## What will happen on this study that is research?

Before you take part in this study, you will first get the SCT conditioning regimen (high doses of chemotherapy or radiation). Taking part in this study will not change the cancer treatment plan you get.

Treatment on this study involves antifungal drugs used to prevent invasive fungal infections. In this study you will get 1 of *2* treatment plans. The 2 treatment arms are called:

- **Azole Antifungal Arm –** Current standard treatment; patients will get therapy with fluconazole. The azole utilized by your center was determined to be fluconazole.

- **Caspofungin Arm –** Experimental treatment; patients will get therapy with caspofungin.

**Random Assignment**

You will receive 1 of 2 different treatment plans. The treatment plan that you receive is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer. You and your doctor will not pick which treatment you get. You will have an equal chance of being on either the caspofungin arm or the azole (fluconazole) arm. The randomization process is described in the COG Family Handbook for Children with Cancer.

Subjects (people who agree to be part of this study) will receive their planned SCT conditioning regimen. Before the SCT conditioning regimen is completed, some subjects will be randomized to receive fluconazole while others will get caspofungin. On the day of the SCT (called Day 0) you will begin receiving the assigned antifungal treatment to prevent you from developing an invasive fungal infection.

**Diagram of Treatment**

This chart shows the treatments on the study.


**Treatment Plan Tables**

Preventive treatment that is standard for invasive fungal infections as well as standard tests and procedures are described in **Attachment #1**. The following drug therapies relate to the experimental comparison of the treatment groups in this study.

Various methods are used to give drugs:

- **IV** - Drug is given using a needle or tubing inserted into a vein. Drugs can be given rapidly over a few minutes ("push") or slowly over minutes or hours ("infusion").
- **PO**- Drug is given by tablet or liquid swallowed through the mouth.

***Treatment for participants who are on the Azole (Fluconazole) Arm- Standard Treatment***

| ***Drug*** | ***How the drug will be given*** | ***Days*** |
|---|---|---|
| *Fluconazole* | *IV Infusion over 1-2 hours (or longer) or PO* | *Start on SCT Day 0 & continue until Day +42 or discharge from hospital.* |

***Treatment for participants who are on Caspofungin Arm – Experimental Treatment***

| ***Drug*** | ***How the drug will be given*** | ***Days*** |
|---|---|---|
| *Caspofungin* | *IV Infusion over 1 hour (Dose on first day is different from dose given in the days that follow) This medication is not available PO* | *Start on SCT Day 0 & continue until Day +42 or discharge from hospital.* |

**Research Study Procedures**

If you have a fungal infection while you are on this study, copies of some of the scans or tests that identify the infection will be sent to a central review center as part of COG quality control.

**Optional Research Study Tests**

We would like to do the following tests because you are a part of this study. These tests are not part of standard care and you do not need to take part in these tests to be on this study. The results of these tests will not be returned to you and no treatment decisions will be based on the results. The results of these tests will not be a part of your medical record. If you provide specimens to the researchers, there are no plans for you to profit from any new products developed from research done on your specimens.

At the end of this consent, there are questions for you to indicate if you want to take part in these optional research tests.

Serum Beta–D Glucan Testing - *Biomarker Study*

Researchers would like to see if they can identify certain *biomarkers* in the blood. Biomarkers are substances in the blood produced from the fungal organisms that cause invasive fungal infections. The biomarker that will be measured in your blood is called beta-D glucan. Findings from this research will help researchers know more about fungal infections, as well how to diagnose and treat them better in future patients.

If you agree, about a teaspoon of blood will be taken from you once a week while you are receiving antifungal treatment. This will be drawn from your central line when other routine blood tests are being performed.

Single Nucleotide Polymorphisms (SNP) Analysis – *Genetic Study*

Researchers would like to look for genetic changes that may put subjects at an increased risk of invasive fungal infections. This test is called single nucleotide polymorphism (SNP) analysis. Information learned from this study may be useful in the future for identifying patients that are more likely to have invasive fungal infections.

If you agree, about a teaspoon of blood will be collected at 2 time points for SNP analysis. The samples will be collected prior to transplant and about 100 days after transplant when other routine blood tests are performed.

Future Studies:
If you agree, we would like to store (bank) any leftover blood for future studies. The research that may be done with the samples is not designed to help you during your present treatment. It might help people who have cancer and other diseases in the future.

Research on the banked specimens is **very unlikely** to discover results that are important to your current or future health. However, if it does, COG will try to contact your doctor about what the research tests might mean. Only the doctor will be notified and the information will not become part of your medical record. Your doctor will decide whether to discuss the results with you. Your doctor may recommend repeat testing, meeting with a genetic counselor, or no further action.

## What side effects or risks can I expect from being in the study?

**Treatment Risks**
**You may have side effects while on this study. All people taking part in this study will be carefully monitored for side effects. Side effects may be mild or very serious; and you may be given care to lessen side effects. Many side effects go away soon after you stop taking the drug causing the side effects, but in some cases, may last longer or never go away.**

The risks of the individual drug given as standard treatment are listed in **Attachment #2**.

**Reproductive risks: Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex 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 birth control methods might not be approved for use in this study. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).**

**Risks of Study**
**The use of caspofungin may cause more complications than the use of fluconazole.**

**The caspofungin treatment that is being studied could be less effective than the current standard treatment with fluconazole.**

**In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.**

**Risks and side effects reported or expected with <u>caspofungin</u> include:**

| **COMMON, SOME MAY BE SERIOUS**<br>In 100 people receiving caspofungin, more than 20 may have: |
|---|
| • **Reaction during or following infusion of the drug which may cause fever, chills, rash, low blood pressure** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving caspofungin, from 4 to 20 may have: |
|---|
| • **Low blood pressure which may cause feeling faint**<br>• **High blood pressure which may cause dizziness, blurred vision**<br>• **Swelling of the body**<br>• **Blood clot**<br>• **Abnormal heartbeat**<br>• **Rash, itching**<br>• **Pain in the belly**<br>• **Diarrhea, nausea, vomiting**<br>• **Anemia which may require blood transfusion**<br>• **Damage to the liver which may cause belly pain, bleeding**<br>• **Severe blood infection**<br>• **Headache**<br>• **Kidney damage which may require dialysis**<br>• **Cough**<br>• **Damage to or fluid around the lungs which may cause shortness of breath**<br>• **Low levels of certain salts in the body which may require you to take another medicine to correct the salt level** |

| **RARE, AND SERIOUS**<br>In 100 people receiving caspofungin, 3 or fewer may have: |
|---|
| • **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body**<br>• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** |

Although caspofungin has the potential risks noted above, it may be better at preventing invasive fungal infections caused by *Aspergillus* as compared to fluconazole, but there is no proof of this yet.

For the optional studies, the greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

## Are there benefits to taking part in the study?

We hope that this study will help you personally, but we do not know if it will.

Potential benefits to you could include a better chance of preventing invasive fungal infections during treatment with a SCT.

We expect that the information learned from this study will benefit other patients in the future.

## What other options are there?

Instead of being in this study, you have these options:

- **Current standard therapy even if you do not take part in the study. Standard therapy is described on page 1. It is the Azole (fluconazole) Arm of this study.**
- **Receiving no prevention against fungal infections.**
- **Taking part in another study**

Please talk to your doctor about these and other options.

## How many people will take part in the study?

The total number of people enrolled on this study is expected to be 590.

## How long is the study?

Subjects in this clinical trial are expected to receive treatment on this study for up to 45 days. After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health for 100 days after your SCT.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

## What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included in **Attachment #3**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include groups such as:

- **The Children's Oncology Group**
- **The Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this hospital**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The drug company that makes the drug caspofungin or their designated reviewers.**

## What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

The drug company that makes caspofungin is supplying the drug at no charge for subjects on this study. Therefore, if you are randomized to the caspofungin arm, you or your insurance company will not be charged for the caspofungin. The drug company does not cover the cost of getting the caspofungin ready and giving it to you, so you or your insurance company may have to pay for this. Please direct any questions related the cost of getting caspofungin ready and giving it to you to _____ *[please insert contact information for the appropriate institutional representative].*

Fluconazole is a standard antifungal drug and would most likely be given to you if you did not take part in the study. Therefore, if you are randomized to the azole antifungal arm, you or your insurance company will be charged for the fluconazole.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

## Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

This study includes providing specimens to the researcher. There are no plans for you to profit from any new product developed from research done on your specimens.

## What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. *A summary of the study results will also be posted on the Children's Oncology Group website (http://www.childrensoncologygroup.org/).* To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all children on the study is completed, and not only when your child completes treatment.

## Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. XXXX or your doctor at XXXXX.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at XXXX.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at XXXX.

## Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at:
http://www.childrensoncologygroup.org/familyhandbook

Visit the *NCI's Web site* at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at:
1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at anytime.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

## Specimens for optional research tests

This section of the informed consent is about samples for the optional research tests (biomarker and SNP studies).

The choice to let us use specimens for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies.

There are few risks to you from the genetic research studies, either from the SNP studies described above or other potential genomic studies performed if you consent to bank your samples for future research. The greatest risk is the release of information from your health records, but the tissue bank will protect your records so that your name, date of birth, and other identifiable information will be kept private. The chance of these personal facts being given to someone else is very small. Special precautions will be taken with studies that involve genetic information about the normal cells in your body. Studies of this type will only be performed on samples that have a second de-identified number (instead of your name or the COG patient number).

Researchers will only be allowed to have access to your genetic information if they sign a special agreement and certify that they will keep all records confidential. Those researchers will not receive any personal information about you such as your name, date of birth, address, or phone number. This type of genetic research is also protected by a recent federal law in the United States called the Genetic Information Nondiscrimination Act (GINA), which generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on genetic information.

Some of your genetic and health information may be placed in a central database along with information from many other people. This database will be available only to those with authorized access. There is a risk that someone could trace the information in the controlled-access database back to you. Even without your name or other identifiers, your genetic information is unique to you. In spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.

The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

If you decide now that your specimens can be used for research and banking you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any leftover specimens that we have will be destroyed.

If you want to learn more about tissue research with banked specimens, the NCI website has an information sheet called "Providing Your Tissue For Research: What You Need To Know." This sheet can be found at: http://www.cancer.gov/clinicaltrials/resources/providingtissue.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

1. I agree to the collection of extra blood samples for the research studies called biomarkers in the blood to study fungal infections.

   Yes_____ No_____ _____ / _____
   Initials Date

2. I agree to the collection of extra blood for SNP analysis that will look at genetic risk factors for fungal infections.

   Yes_____ No_____ _____ / _____
   Initials Date

3. If some blood is leftover after the SNP studies above are completed, I agree that it may be kept (banked) for future research to learn about, prevent, or treat cancer.

   Yes_____ No_____ _____ / _____
   Initials Date

4. If some blood is leftover after the SNP studies above are completed, I agree that it may be kept (banked) for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes_____ No_____ _____ / _____
   Initials Date

## SIGNATURE

**I have been given a copy of all _____ pages of this form. The form includes three (3) attachments.**

I have reviewed the information and have had my questions answered.

I agree to take part in this study (ACCL1131)

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

IRB# IRB Approved:

**Attachment #1**
**Treatment and Procedures Common to all Patients at Risk of IFI**

**Method for Giving Drugs**

- **IV** - Drug is given using a needle or tubing inserted into a vein. Drugs can be given rapidly over a few minutes ("push") or slowly over minutes or hours ("infusion").
- **PO**- Drug is given by tablet or liquid swallowed through the mouth.

**Central Line**

Your doctor may recommend that you get a special kind of IV called a "central line." This is a kind of IV placed into a big vein in your chest that can stay in for a long time. The risks associated with central lines will be explained to you and all of your questions will be answered. If you are to have a central line inserted, you will be given a separate informed consent document to read and sign for this procedure. A description of the types of central lines is in the COG Family Handbook for Children with Cancer.

**Therapy for Patient on the Azole Arm: Fluconazole Treatment Plan (Standard Treatment Arm)**

The purpose of fluconazole therapy is to prevent the development of invasive fungal infections following SCT.

| Drug | How the drug will be given | Days |
|---|---|---|
| Fluconazole | IV infusion over 1-2 hours (or longer) or PO once a day | Start on SCT Day 0 & continue until Day +42 or discharge from hospital. |

**Standard Tests and Procedures**

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- History and physical exam.
- Frequent labs to monitor blood counts and blood chemistries.
- Urine tests to measure how the kidneys are functioning.
- Pregnancy test for females of childbearing age before treatment begins.

**Attachment #2**

**Possible Side Effects of fluconazole**

| **COMMON, SOME MAY BE SERIOUS**<br>In 100 people receiving fluconazole, more than 20 may have: |
|---|
| • **None known** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving fluconazole, from 4 to 20 may have: |
|---|
| • **Nausea, vomiting, diarrhea**<br>• **Pain in the belly**<br>• **Headache**<br>• **Rash, itching**<br>• **Increased blood level of liver tests which may mean there has been damage to the liver** |

| **RARE, AND SERIOUS**<br>In 100 people receiving fluconazole, 3 or fewer may have: |
|---|
| • **Abnormal heartbeat which may cause fainting**<br>• **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body**<br>• **Infection, especially when white blood cell count is low**<br>• **Bruising, bleeding**<br>• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**<br>• **Seizure** |

**Attachment #3**
**Certificate of Confidentiality**

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

**SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM –FOR INSTITUTIONS WITH STANDARD USE OF VORICONAZOLE**

**ACCL1131**
**A Phase III Open-Label Trial of Caspofungin vs. Azole Prophylaxis for Patients at High-Risk for Invasive Fungal Infections (IFI) Following Allogeneic Hematopoietic Cell Transplantation (HCT)**

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

## Why am I being invited to take part in this study?

You are being asked to take part in this research study because you are about to undergo a stem cell transplant (SCT). More information about SCT can be found in the COG Family Handbook for Children with Cancer. Patients undergoing SCT are at risk of getting an invasive fungal infection.

Invasive fungal infections are infections caused by organisms called fungi that enter the blood stream and spread to different organs in the body. Treatment with high doses of chemotherapy and radiation, which are used as part of SCT, severely reduces the body's natural infection fighting ability. In patients who died from infections while receiving SCT, an invasive fungal infection was the cause in more than half of the cases. Preventing invasive fungal infections is therefore very important for the treatment success of people receiving SCT.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard preventive treatment for invasive fungal infections and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

## What is the current standard of treatment for this disease?

The current standard preventive treatment for people who are at risk of invasive fungal infections due to SCT is the use of fungi fighting drugs (called antifungal therapy). The current standard antifungal drugs are called fluconazole and voriconazole. Fluconazole and voriconazole are part of a group of agents called *azoles*. The azole utilized by your center is voriconazole.

## Why is this study being done?

Current standard antifungal therapy agents (fluconazole and voriconazole) have been shown to be equally effective in preventing invasive fungal infections in people receiving a SCT; especially those caused by the fungi *Candida*. However, previous studies have shown that they do not fully prevent infections caused by some types of fungi called *filamentous fungi*. *Aspergillus is a type of filamentous fungi.*

In this study, researchers want to find out if using a newer antifungal drug called caspofungin will be better than the current standard antifungal drugs at preventing invasive fungal infections when given to people receiving SCT.

The drug caspofungin was chosen because a drug very similar to caspofungin has been shown to be effective in the prevention of various fungal infections, including *Candida* and *Aspergillus* in a study for adult patients. Caspofungin is an antifungal drug that has been approved by the Food and Drug Administration (FDA) for use in children as well as adults.

The use of caspofungin to prevent invasive fungal infections is experimental.

The overall goal of this study is to:

- **Compare the effects, good and/or bad, of caspofungin vs azole antifungals on people receiving SCT, who are at risk of getting invasive fungal infections, to find out which is better. In this study, you will get either caspofungin or an azole antifungal (fluconazole or voriconazole). You will not get both.**

## What will happen on this study that is research?

Before you take part in this study, you will first get the SCT conditioning regimen (high doses of chemotherapy or radiation). Taking part in this study will not change the cancer treatment plan you get.

Treatment on this study involves antifungal drugs used to prevent invasive fungal infections. In this study you will get 1 of *2* treatment plans. The 2 treatment arms are called:

- **Azole Antifungal Arm –** Current standard treatment; patients will get therapy with voriconazole. The azole utilized by your center was determined to be voriconazole.

- **Caspofungin Arm –** Experimental treatment; patients will get therapy with caspofungin.

**Random Assignment**

You will receive 1 of 2 different treatment plans. The treatment plan that you receive is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer. You and your doctor will not pick which treatment you get. You will have an equal chance of being on either the caspofungin arm or the azole (voriconazole) arm. The randomization process is described in the COG Family Handbook for Children with Cancer.

Subjects (people who agree to be part of this study) will receive their planned SCT conditioning regimen. Before the SCT conditioning regimen is completed, some subjects will be randomized to receive voriconazole while others will get caspofungin. On the day of the SCT (called Day 0) you will begin receiving the assigned antifungal treatment to prevent you from developing an invasive fungal infection.

**Diagram of Treatment**

This chart shows the treatments on the study.


**Treatment Plan Tables**

Preventive treatment that is standard for invasive fungal infections as well as standard tests and procedures are described in **Attachment #1**. The following drug therapies relate to the experimental comparison of the treatment groups in this study.

Various methods are used to give drugs:

- **IV** - Drug is given using a needle or tubing inserted into a vein. Drugs can be given rapidly over a few minutes ("push") or slowly over minutes or hours ("infusion").
- **PO**- Drug is given by tablet or liquid swallowed through the mouth.

***Treatment for participants who are on the Azole (voriconazole) Arm- Standard Treatment***

| ***Drug*** | ***How the drug will be given*** | ***Days*** |
|---|---|---|
| *Voriconazole* | *IV Infusion over 1-2 hours (or longer) or PO twice a day*<br>*(Dose on first day is different from dose given in the days that follow)* | *Start on SCT Day 0 & continue until Day +42 or discharge from hospital.* |

***Treatment for participants who are on Caspofungin Arm – Experimental Treatment***

| ***Drug*** | ***How the drug will be given*** | ***Days*** |
|---|---|---|
| *Caspofungin* | *IV Infusion over 1 hour*<br>*(Dose on first day is different from dose given in the days that follow)*<br>*This medication is not available PO* | *Start on SCT Day 0 & continue until Day +42 or discharge from hospital.* |

**Research Study Procedures**

If you have a fungal infection while you are on this study, copies of some of the scans or tests that identify the infection will be sent to a central review center as part of COG quality control.

**Optional Research Study Tests**

We would like to do the following tests because you are a part of this study. These tests are not part of standard care and you do not need to take part in these tests to be on this study. The results of these tests will not be returned to you and no treatment decisions will be based on the results. The results of these tests will not be a part of your medical record. If you provide specimens to the researchers, there are no plans for you to profit from any new products developed from research done on your specimens.

At the end of this consent, there are questions for you to indicate if you want to take part in these optional research tests.

Serum Beta–D Glucan Testing - *Biomarker Study*

Researchers would like to see if they can identify certain *biomarkers* in the blood. Biomarkers are substances in the blood produced from the fungal organisms that cause invasive fungal infections. The biomarker that will be measured in your blood is called beta-D glucan. Findings from this research will help researchers know more about fungal infections, as well how to diagnose and treat them better in future patients.

If you agree, about a teaspoon of blood will be taken from you once a week while you are receiving antifungal treatment. This will be drawn from your central line when other routine blood tests are being performed.

Single Nucleotide Polymorphisms (SNP) Analysis – *Genetic Study*

Researchers would like to look for genetic changes that may put subjects at an increased risk of invasive fungal infections. This test is called single nucleotide polymorphism (SNP) analysis. Information learned from this study may be useful in the future for identifying patients that are more likely to have invasive fungal infections.

If you agree, about a teaspoon of blood will be collected at 2 time points for SNP analysis. The samples will be collected prior to transplant and about 100 days after transplant when other routine blood tests are performed.

Future Studies:
If you agree, we would like to store (bank) any leftover blood for future studies. The research that may be done with the samples is not designed to help you during your present treatment. It might help people who have cancer and other diseases in the future.

Research on the banked specimens is **very unlikely** to discover results that are important to your current or future health. However, if it does, COG will try to contact your doctor about what the research tests might mean. Only the doctor will be notified and the information will not become part of your medical record. Your doctor will decide whether to discuss the results with you. Your doctor may recommend repeat testing, meeting with a genetic counselor, or no further action.

## What side effects or risks can I expect from being in the study?

**Treatment Risks**

**You may have side effects while on this study. All people taking part in this study will be carefully monitored for side effects. Side effects may be mild or very serious; and you may be given care to lessen side effects. Many side effects go away soon after you stop taking the drug causing the side effects, but in some cases, may last longer or never go away.**

The risks of the individual drug given as standard treatment are listed in **Attachment #2**.

**Reproductive risks: Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex 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 birth control methods might not be approved for use in this study. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).**

**Risks of Study**

**The use of caspofungin may cause more complications than the use of voriconazole.**

**The caspofungin treatment that is being studied could be less effective than the current standard treatment with voriconazole.**

**In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.**

**Possible Side Effects of Caspofungin**

| **COMMON, SOME MAY BE SERIOUS**<br>In 100 people receiving caspofungin, more than 20 may have: |
|---|
| • **Reaction during or following infusion of the drug which may cause fever, chills, rash, low blood pressure** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving caspofungin, from 4 to 20 may have: |
|---|
| • **Low blood pressure which may cause feeling faint**<br>• **High blood pressure which may cause dizziness, blurred vision**<br>• **Swelling of the body**<br>• **Blood clot**<br>• **Abnormal heartbeat**<br>• **Rash, itching**<br>• **Pain in the belly**<br>• **Diarrhea, nausea, vomiting**<br>• **Anemia which may require blood transfusion**<br>• **Damage to the liver which may cause belly pain, bleeding**<br>• **Severe blood infection**<br>• **Headache**<br>• **Kidney damage which may require dialysis**<br>• **Cough**<br>• **Damage to or fluid around the lungs which may cause shortness of breath**<br>• **Low levels of certain salts in the body which may require you to take another medicine to correct the salt level** |

| **RARE, AND SERIOUS**<br>In 100 people receiving caspofungin, 3 or fewer may have: |
|---|
| • **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body**<br>• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** |

Although caspofungin has the potential risks noted above, it may be better at preventing invasive fungal infections caused by *Aspergillus* as compared to voriconazole, but there is no proof of this yet.

For the optional studies, the greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

## Are there benefits to taking part in the study?

We hope that this study will help you personally, but we do not know if it will.

Potential benefits to you could include a better chance of preventing invasive fungal infections during treatment with a SCT.
We expect that the information learned from this study will benefit other patients in the future.

## What other options are there?

Instead of being in this study, you have these options:

- Current standard therapy even if you do not take part in the study. Standard therapy is described on page 1. It is the Azole (voriconazole) Arm of this study.
- Receiving no prevention against fungal infections.
- Taking part in another study

Please talk to your doctor about these and other options.

## How many people will take part in the study?

The total number of people enrolled on this study is expected to be 590.

## How long is the study?

Subjects in this clinical trial are expected to receive treatment on this study for up to 45 days. After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health for 100 days after your SCT.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

## What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included in **Attachment #3**.
Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include groups such as:

- **The Children's Oncology Group**
- **The Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this hospital**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**

- **The drug company that makes the drug caspofungin or their designated reviewers.**

## What are the costs?

**Taking part in this study may lead to added** costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

The drug company that makes caspofungin is supplying the drug at no charge for subjects on this study. Therefore, if you are randomized to the caspofungin arm, you or your insurance company will not be charged for the caspofungin. The drug company does not cover the cost of getting the caspofungin ready and giving it to you, so you or your insurance company may have to pay for this. Please direct any questions related the cost of getting caspofungin ready and giving it to you to _____ *[please insert contact information for the appropriate institutional representative].*

Voriconazole is a standard antifungal drug and would most likely be given to you if you did not take part in the study. Therefore, if you are randomized to the azole antifungal arm, you or your insurance company will be charged for the voriconazole.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

## Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

This study includes providing specimens to the researcher. There are no plans for you to profit from any new product developed from research done on your specimens.

## What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. *A summary of the study results will also be posted on the Children's Oncology Group website (http://www.childrensoncologygroup.org/).* To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all children on the study is completed, and not only when your child completes treatment.

## Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. XXXX or your doctor at XXXXX

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at XXXX.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at XXXX.

## Where can I get more information?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at http://www.childrensoncologygroup.org/familyhandbook.

Visit the *NCI's Web site* at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at anytime.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

## Specimens for optional research tests

This section of the informed consent is about samples for the optional research tests (biomarker and SNP studies).

The choice to let us use specimens for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies.

There are few risks to you from the genetic research studies, either from the SNP studies described above or other potential genomic studies performed if you consent to bank your samples for future research. The greatest risk is the release of information from your health records, but the tissue bank will protect your records so that your name, date of birth, and other identifiable information will be kept private. The chance of these personal facts being given to someone else is very small. Special precautions will be taken with studies that involve genetic information about the normal cells in your body. Studies of this type will only be performed on samples that have a second de-identified number (instead of your name or the COG patient number).

Researchers will only be allowed to have access to your genetic information if they sign a special agreement and certify that they will keep all records confidential. Those researchers will not receive any personal information about you such as your name, date of birth, address, or phone number. This type of genetic research is also protected by a recent federal law in the United States called the Genetic Information Nondiscrimination Act (GINA), which generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on genetic information.

Some of your genetic and health information may be placed in a central database along with information from many other people. This database will be available only to those with authorized access. There is a risk that someone could trace the information in the controlled-access database back to you. Even without your name or other identifiers, your **genetic information is** unique to you. In spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.

The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

If you decide now that your specimens can be used for research and banking you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any specimens that we have will be destroyed.

If you want to learn more about tissue research with banked specimens, the NCI website has an information sheet called "Providing Your Tissue For Research: What You Need To Know." This sheet can be found at: http://www.cancer.gov/clinicaltrials/resources/providingtissue.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any

questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

1. I agree to the collection of extra blood samples for the research studies called biomarkers in the blood to study fungal infections.

   Yes_____ No_____ _____ / _____
   Initials Date

2. I agree to the collection of extra blood for SNP analysis that will look at genetic risk factors for fungal infections.

   Yes_____ No_____ _____ / _____
   Initials Date

3. If some blood is left over after the SNP studies above are completed, I agree that it may be kept (banked) for future research to learn about, prevent, or treat cancer.

   Yes_____ No_____ _____ / _____
   Initials Date

4. If some blood is left over after the SNP studies above are completed, I agree that it may be kept (banked) for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes_____ No_____ _____ / _____
   Initials Date

## SIGNATURE

**I have been given a copy of all _____ pages of this form. The form includes three (3) attachments.**

I have reviewed the information and have had my questions answered.

I agree to take part in this study (ACCL1131)

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

IRB# IRB Approved:

## Attachment #1

## Treatment and Procedures Common to all Patients at Risk of IFI

### Method for Giving Drugs

- **IV** - Drug is given using a needle or tubing inserted into a vein. Drugs can be given rapidly over a few minutes ("push") or slowly over minutes or hours ("infusion").
- **PO**- Drug is given by tablet or liquid swallowed through the mouth.

### Central Line

Your doctor may recommend that you get a special kind of IV called a "central line." This is a kind of IV placed into a big vein in your chest that can stay in for a long time. The risks associated with central lines will be explained to you and all of your questions will be answered. If you are to have a central line inserted, you will be given a separate informed consent document to read and sign for this procedure. A description of the types of central lines is in the COG Family Handbook for Children with Cancer.

### Therapy for Patient on the Azole Arm: Voriconazole Treatment Plan (Standard Treatment Arm)

The purpose of voriconazole therapy is to prevent the development of invasive fungal infections following SCT.

| Drug | How the drug will be given | Days |
|---|---|---|
| Voriconazole | IV infusion over 1-2 hours (or longer) or PO twice a day. (Dose on first day is different from dose given in the days that follow) | Start on SCT Day 0 & continue until Day +42 or discharge from hospital. |

### Standard Tests and Procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- History and physical exam.
- Frequent labs to monitor blood counts and blood chemistries.
- Urine tests to measure how the kidneys are functioning.
- Pregnancy test for females of childbearing age before treatment begins.

**Attachment #2**

**Possible Side Effects of Voriconazole**

| **COMMON, SOME MAY BE SERIOUS**<br>In 100 people receiving voriconazole, more than 20 may have: |
|---|
| • **Blurred vision, vision changes, discomfort from light** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving voriconazole, from 4 to 20 may have: |
|---|
| • **Rash**<br>• **Fever**<br>• **Nausea, vomiting**<br>• **Damage to the liver which may cause belly pain, bleeding**<br>• **Hepatitis which may cause yellow eyes and skin, tiredness**<br>• **Muscle weakness**<br>• **Numbness and tingling of the arms and legs**<br>• **Confusion, sensing things that are not there** |

| **RARE, AND SERIOUS**<br>In 100 people receiving voriconazole, 3 or fewer may have: |
|---|
| • **Low blood pressure which may cause you to feel faint**<br>• **High blood pressure which may cause headaches, dizziness, blurred vision**<br>• **Swelling of the body**<br>• **Pain in the belly**<br>• **Abnormal heartbeat which may cause fainting**<br>• **Increased risk of sunburn**<br>• **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body**<br>• **A new cancer of the skin**<br>• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**<br>• **Blurred vision with a chance of blindness**<br>• **Kidney damage which may require dialysis** |

**Attachment #3**
**Certificate of Confidentiality**

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.