

11-5-2019

## Effect of Caspofungin vs Fluconazole Prophylaxis on Invasive Fungal Disease Among Children and Young Adults With Acute Myeloid Leukemia: A Randomized Clinical Trial.

Brian T Fisher

*Children's Hospital of Philadelphia, Philadelphia, PA, fisherbria@chop.edu*

Theoklis Zaoutis

*Children's Hospital of Philadelphia, Philadelphia, PA, zaoutis@chop.edu*

Christopher C Dvorak

Michael Nieder

Danielle Zerr

*See next page for additional authors*

Follow this and additional works at: <https://digitalrepository.chop.edu/advpractice>



Part of the [Allergy and Immunology Commons](#), [Cancer Biology Commons](#), [Hematology Commons](#), [Infectious Disease Commons](#), [Oncology Commons](#), [Other Immunology and Infectious Disease Commons](#), [Pediatrics Commons](#), and the [Preventive Medicine Commons](#)

---

### Citation

Fisher, B., Zaoutis, T., Dvorak, C., Nieder, M., Zerr, D., Wingard, J., Callahan, C., Villaluna, D., Chen, L., Dang, H., Esbenshade, A., Alexander, S., Wiley, J., & Sung, L. (2019). Effect of Caspofungin vs Fluconazole Prophylaxis on Invasive Fungal Disease Among Children and Young Adults With Acute Myeloid Leukemia: A Randomized Clinical Trial. *JAMA : the journal of the American Medical Association*, 322 (17), 1673-1681. <https://doi.org/10.1001/jama.2019.15702>

This Article is brought to you for free and open access by the Nursing & Clinical Care Services at CHOP Digital Repository. It has been accepted for inclusion in Center for Advanced Practice by an authorized administrator of CHOP Digital Repository.

---

**Authors**

Brian T Fisher, Theoklis Zaoutis, Christopher C Dvorak, Michael Nieder, Danielle Zerr, John R Wingard, Colleen Callahan, Doojduen Villaluna, Lu Chen, Ha Dang, Adam J Esbenshade, Sarah Alexander, Joseph M Wiley, and Lillian Sung

JAMA | Original Investigation

# Effect of Caspofungin vs Fluconazole Prophylaxis on Invasive Fungal Disease Among Children and Young Adults With Acute Myeloid Leukemia

## A Randomized Clinical Trial

Brian T. Fisher, DO, MSCE; Theoklis Zaoutis, MD, MSCE; Christopher C. Dvorak, MD; Michael Nieder, MD; Danielle Zerr, MD, MPH; John R. Wingard, MD; Colleen Callahan, MSN, CRNP; Doojduen Villaluna, MS; Lu Chen, PhD; Ha Dang, PhD; Adam J. Esbenshade, MD, MSCI; Sarah Alexander, MD; Joseph M. Wiley, MD; Lillian Sung, MD, PhD

**IMPORTANCE** Children, adolescents, and young adults with acute myeloid leukemia are at high risk of life-threatening invasive fungal disease with both yeasts and molds.

**OBJECTIVE** To compare the efficacy of caspofungin vs fluconazole prophylaxis against proven or probable invasive fungal disease and invasive aspergillosis during neutropenia following acute myeloid leukemia chemotherapy.

**DESIGN, SETTING, AND PARTICIPANTS** This multicenter, randomized, open-label, clinical trial enrolled patients aged 3 months to 30 years with newly diagnosed de novo, relapsed, or secondary acute myeloid leukemia being treated at 115 US and Canadian institutions (April 2011-November 2016; last follow-up June 30, 2018).

**INTERVENTIONS** Participants were randomly assigned during the first chemotherapy cycle to prophylaxis with caspofungin (n = 257) or fluconazole (n = 260). Prophylaxis was administered during the neutropenic period following each chemotherapy cycle.

**MAIN OUTCOMES AND MEASURES** The primary outcome was proven or probable invasive fungal disease as adjudicated by blinded central review. Secondary outcomes were invasive aspergillosis, empirical antifungal therapy, and overall survival.

**RESULTS** The second interim efficacy analysis and an unplanned futility analysis based on 394 patients appeared to have suggested futility, so the study was closed to accrual. Among the 517 participants who were randomized (median age, 9 years [range, 0-26 years]; 44% female), 508 (98%) completed the trial. The 23 proven or probable invasive fungal disease events (6 caspofungin vs 17 fluconazole) included 14 molds, 7 yeasts, and 2 fungi not further categorized. The 5-month cumulative incidence of proven or probable invasive fungal disease was 3.1% (95% CI, 1.3%-7.0%) in the caspofungin group vs 7.2% (95% CI, 4.4%-11.8%) in the fluconazole group (overall  $P = .03$  by log-rank test) and for cumulative incidence of proven or probable invasive aspergillosis was 0.5% (95% CI, 0.1%-3.5%) with caspofungin vs 3.1% (95% CI, 1.4%-6.9%) with fluconazole (overall  $P = .046$  by log-rank test). No statistically significant differences in empirical antifungal therapy (71.9% caspofungin vs 69.5% fluconazole, overall  $P = .78$  by log-rank test) or 2-year overall survival (68.8% caspofungin vs 70.8% fluconazole, overall  $P = .66$  by log-rank test) were observed. The most common toxicities were hypokalemia (22 caspofungin vs 13 fluconazole), respiratory failure (6 caspofungin vs 9 fluconazole), and elevated alanine transaminase (4 caspofungin vs 8 fluconazole).

**CONCLUSIONS AND RELEVANCE** Among children, adolescents, and young adults with acute myeloid leukemia, prophylaxis with caspofungin compared with fluconazole resulted in significantly lower incidence of invasive fungal disease. The findings suggest that caspofungin may be considered for prophylaxis against invasive fungal disease, although study interpretation is limited by early termination due to an unplanned interim analysis that appeared to have suggested futility.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT01307579](https://clinicaltrials.gov/ct2/show/study/NCT01307579)

JAMA. 2019;322(17):1673-1681. doi:10.1001/jama.2019.15702

 [Visual Abstract](#)

 [Supplemental content](#)

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Brian T. Fisher, DO, MSCE, Division of Infectious Diseases, The Children's Hospital of Philadelphia, 2716 South St, Room 10362, Philadelphia, PA 19146 ([fisherbria@email.chop.edu](mailto:fisherbria@email.chop.edu)).

Children, adolescents, and young adults receiving intensive chemotherapy for acute myeloid leukemia (AML) are at high risk of invasive fungal disease (IFD), with *Candida* and *Aspergillus* species predominating.<sup>1-3</sup> Invasive fungal diseases result in substantial morbidity, increased resource utilization, delayed chemotherapy, and higher treatment-related mortality.<sup>4-7</sup> Interventions to prevent IFD are needed to improve outcomes.

Based on randomized clinical trials, adult clinical practice guidelines recommend posaconazole prophylaxis for patients with AML during prolonged neutropenia.<sup>8,9</sup> However, because of the absence of comparative pediatric data and the lack of a reliable pediatric posaconazole dosing schedule, a pediatric antifungal prophylaxis guideline recommends fluconazole for patients with AML.<sup>10</sup> This guideline identified optimal antifungal prophylaxis among children with AML as an important knowledge gap.

Echinocandins are an option for prophylaxis for children because they are well tolerated, have few drug-drug interactions, and provide antifungal activity against both *Candida* and *Aspergillus* species.<sup>11</sup> Caspofungin has been extensively studied in children and approved for use in patients as young as 3 months of age, making it an ideal candidate for antifungal prophylaxis for pediatric patients.<sup>12-14</sup> The hypothesis of this trial was that caspofungin prophylaxis might be better than fluconazole prophylaxis for IFD prevention because caspofungin is active against both yeast and molds whereas fluconazole is only active against yeasts.

The primary objective was to determine the efficacy of caspofungin vs fluconazole in preventing proven or probable IFD during periods of neutropenia in children, adolescents, and young adults with AML.

## Methods

### Study Design

This was a randomized, open-label, phase 3 clinical trial (ACCL0933) sponsored by the Children's Oncology Group (COG) and approved by the National Cancer Institute's central institutional review board (IRB) and IRBs at each participating institution. The final protocol, statistical analytic plan, and plan amendments are available in Supplement 1. Participants or their guardians provided written informed consent and assent (if appropriate) prior to enrollment.

### Participants

Eligible participants were between 3 months and 30 years of age and had newly diagnosed de novo, relapsed, or secondary AML or had planned treatment with standard AML chemotherapy for other diagnoses (eg, mixed phenotype acute leukemia). Participants had to have adequate kidney function (creatinine clearance or radioisotope glomerular filtration rate  $\geq 70$  mL/min/1.73 m<sup>2</sup> or normal serum creatinine for age and sex) and liver function (total bilirubin  $< 1.5$  times the upper limit of normal [ULN], alanine transaminase  $< 2$  times ULN, and aspartate transaminase  $< 2$  times ULN). Patients were excluded if they had acute promyelocytic leukemia, Down syndrome,

## Key Points

**Question** Does prophylaxis with caspofungin compared with fluconazole reduce the risk of invasive fungal disease during periods of neutropenia after chemotherapy for children, adolescents, and young adults with acute myeloid leukemia?

**Findings** In this randomized clinical trial, which was terminated early after enrolling 517 patients, the incidence of proven or probable invasive fungal disease was statistically significantly lower in the caspofungin group than in the fluconazole group (5-month cumulative incidence, 3.1% vs 7.2%).

**Meaning** The findings suggest that caspofungin may be considered for prophylactic therapy against invasive fungal disease in children, adolescents, and young adults with acute myeloid leukemia.

juvenile myelomonocytic leukemia, documented IFD 30 days prior to enrollment, history of caspofungin or fluconazole hypersensitivity or if they were currently receiving treatment for an IFD. Race/ethnicity information was collected according to the National Institutes of Health inclusion policy ([https://grants.nih.gov/grants/funding/women\\_min/guidelines.htm](https://grants.nih.gov/grants/funding/women_min/guidelines.htm)). A patient's race/ethnicity category were determined by institutional investigators using information documented in the health records and categorizations were based on fixed categories.

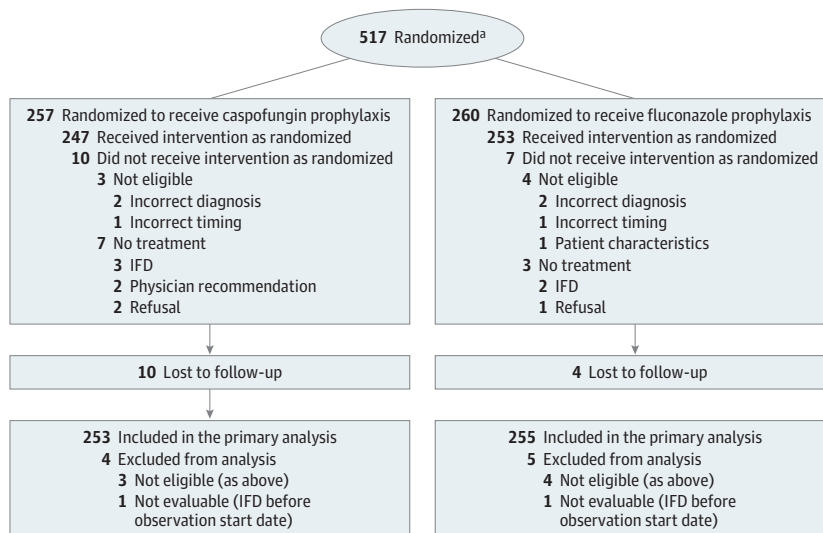
### Randomization and Blinding

Participants were randomized 1:1 to caspofungin (intervention group) or fluconazole (control group) prophylaxis in block sizes of 4 (Figure 1). The allocation sequence, generated by the COG trial management system, and block size were concealed to all investigators, clinicians, and participants. Randomization was stratified by AML type (de novo vs all other types). The study was open label. Consequently, clinicians and participants were aware of treatment allocation. However, IFD outcomes were determined by a central review panel blinded to allocation.

### Procedures

Assigned prophylaxis started between 24 and 72 hours following completion of systemic chemotherapy for each cycle and continued until the absolute neutrophil count ranged from 100/ $\mu$ L to 500/ $\mu$ L following the nadir or start of the next chemotherapy cycle (whichever occurred first). Assigned prophylaxis was administered with each subsequent cycle of chemotherapy until the patient met at least 1 of the following off-protocol therapy criteria: recovery of neutropenia following completion of the final planned AML chemotherapy, had proven or probable IFD according to institutional diagnosis, began conditioning for hematopoietic stem cell transplantation, initiated a new chemotherapy regimen for relapsed or refractory AML, refused to continue prophylaxis, or were withdrawn from the study when the patient's physician determined it was in the patient's best interest to discontinue protocol therapy. The study did not dictate the institutional approach to IFD designation and this designation did not influence the

Figure 1. Flow Through the Trial of Antifungal Prophylaxis in Patients With Acute Myeloid Leukemia



<sup>a</sup> No information about those approached was available. The total number of patients assessed for participation and reason for exclusion were not collected. IFD indicates invasive fungal disease.

study-directed central adjudication of IFD. Because of this variability, patients institutionally diagnosed with IFD continued to be monitored centrally by study investigators for IFD until they met study criteria to discontinue IFD monitoring.

If a participant experienced prolonged fever and neutropenia ( $\geq 96$  hours), the study protocol recommended that the patient be transitioned to empirical antifungal therapy with amphotericin B lipid formulation or voriconazole and undergo chest computerized tomography. This guidance was based on the COG-endorsed guideline for the management of fever and neutropenia.<sup>15</sup> However, this was not mandated and participating centers could elect to follow local care practices. If empirical or directed antifungal therapy was initiated, then the assigned prophylaxis agent was held. The decision to start empirical or directed antifungal therapy was dictated by the institution and was not influenced by the study-directed central adjudication of IFD. Assigned prophylaxis was resumed if empirical or directed antifungal therapy was discontinued prior to absolute neutrophil count recovery. Additional diagnostic investigations were at the discretion of the treating institution. Clinical specimens were processed and reported by local microbiology and pathology laboratory reports.

Regardless of whether patients stopped protocol-assigned prophylaxis therapy, they continued to be followed up for IFD outcomes until they met criteria to discontinue IFD monitoring. Discontinuation of IFD monitoring occurred at the first of the following events: 2 weeks after recovery from neutropenia following completion of the final planned AML chemotherapy, start of conditioning for hematopoietic stem cell transplantation, began a new chemotherapy regimen for relapsed or refractory AML, or withdrew consent. Overall survival was tracked for up to 2 years from enrollment. Maximum follow-up time for all end points was 2 years from enrollment.

### Prophylaxis Dosing

The caspofungin dose of 70 mg/m<sup>2</sup> per day was administered intravenously on day 1 (maximum dose, 70 mg/d) followed by 50 mg/m<sup>2</sup> per day (maximum dose, 50 mg/d).

Fluconazole was administered as follows: participants whose age ranged from 3 months or older to 17.99 years received 12 mg/kg once daily (maximum dose, 400 mg/d) and from age 18 to 30 years, 6 mg/kg once daily (maximum dose, 400 mg/d) either intravenously or orally.

### Outcomes

The primary outcome was proven or probable IFD according to the European Organization for Research and Treatment in Cancer/Mycoses Study Group (EORTC/MSG) criteria.<sup>16</sup> A blinded central review committee systematically applied the criteria to determine the outcome for all enrolled patients. Monitoring for IFD started on the last day of systemic chemotherapy administration of the first chemotherapy cycle and ended when the patient met a criterion for discontinuation of IFD monitoring.

Central reviews were informed by the following clinically available source documents: pathology, autopsy, radiology (computed tomography and magnetic resonance imaging), ophthalmology and bronchoscopy reports, and culture and nonculture mycology results including molecular testing, serologies, and antigen assays (such as galactomannan and  $\beta$ -D-glucan). These documents were deidentified, scanned, and submitted by participating institutions.

Each central review was conducted by 3 reviewers blinded to allocation who viewed the source documents via webinar and made an IFD designation for each cycle. Disagreements were resolved by consensus. For patients designated to have proven, probable or possible IFD, IFD date, site of infection and causative pathogen (proven and probable only) were documented. If galactomannan or  $\beta$ -D-glucan was used to meet

probable IFD mycology criteria, then the pathogen was reported as *Aspergillus* not otherwise specified (NOS) and fungus NOS, respectively. If histopathology was used to meet proven IFD mycology criteria, then the pathogen was reported as yeast NOS or mold NOS.

### Secondary Outcomes

Secondary outcomes included proven or probable invasive aspergillosis (IA), need for empirical antifungal therapy, and overall survival. Proven or probable IA was defined according to the EORTC/MSG criteria and also adjudicated by blinded central review.<sup>16</sup> Determination of empirical antifungal therapy was difficult as the same antifungal agent could be administered as prophylactic, preemptive, empirical, or directed therapy. Therefore, episodes of prolonged or recurrent fever were used as a proxy for the need for empirical antifungal therapy. Prolonged or recurrent fever was defined as daily or recurrent temperature higher than 38.0°C during neutropenia (absolute neutrophil count <500 cells/ $\mu$ L), despite broad-spectrum antibiotics for at least 5 days.<sup>15</sup>

Secondary outcomes collected but not presented in this manuscript were surveillance galactomannan and  $\beta$ -D-glucan and results of single nucleotide polymorphism analysis. Surveillance galactomannan and  $\beta$ -D-glucan testing was performed as part of an ancillary biomarker study. These results were not disclosed to treating clinicians and were not considered in the central review process for this study. The ancillary biomarker study results will be reported separately.

### Post Hoc Outcome

The post hoc outcome was proven, probable, or possible IFD. Possible IFD was adjudicated during central reviews using the EORTC/MSG criteria in a similar fashion to that described for proven and probable IFD.

### Adverse Events

Institutional clinical research assistants monitored enrolled patients for nonhematological grade 4 and grade 5 (fatal) adverse events and reported these events using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.<sup>17</sup>

### Statistical Analysis

Eligible participants were analyzed according to their randomization group irrespective of adherence with protocol therapy. Ineligible and unevaluable patients were not included in the analysis. Ineligible patients included those without AML who did not receive AML chemotherapy. Unevaluable patients were those who developed IFD between enrollment and start of IFD monitoring (last day of systemic chemotherapy administration of the first chemotherapy cycle). Unevaluable patients were not included because in the COG data system, outcomes cannot be entered prior to the day monitoring began. Missing data were handled using available case analysis.

The power calculation assumed IFD rates in the fluconazole and caspofungin groups of 8%<sup>8</sup> and 2%, respectively, at 5 months after enrollment. The projected 5-month follow-up period was based on the anticipated amount of time patients

would undergo chemotherapy for AML. We assumed 35% of the patients would be censored prior to 5 months for reasons including experiencing relapsed or refractory AML or death (10%) and undergoing hematopoietic stem cell transplantation (25%). Under these assumptions, enrollment of at least 275 patients in each group would provide 80% power to detect a difference in time-to-IFD curves between the 2 groups using the log-rank test with a 2-sided  $\alpha$  level of .05. Both IFD failure and the 35% censoring were assumed to follow an exponential distribution.

### Primary Outcome Analysis

The primary analysis was a time-to-event analysis that evaluated time to first proven or probable IFD. Patients without proven or probable IFD were censored when the patient met criteria for discontinuation of IFD monitoring. The cumulative incidence of proven or probable IFD was described using the Kaplan-Meier method and compared between groups using the log-rank test. In a secondary analysis of the primary outcome, hematopoietic stem cell transplant, relapse or refractory AML, and death were considered competing events, and groups were compared using the Gray test.<sup>18</sup> For both approaches, the 5-month estimated cumulative incidence with 95% CIs was described for each group to provide context.

### Secondary Outcome Analysis

A similar analytic approach used for the primary outcome was also used for the secondary outcomes of proven or probable IA and the need for empirical antifungal therapy. For proven or probable IA, any non-IA proven or probable IFD was included as a competing event in addition to hematopoietic stem cell transplant, relapse or refractory AML, and death in the competing risk analysis. For the secondary outcome of overall survival, the time from enrollment to death due to any cause was described using the Kaplan-Meier method.

### Post Hoc Analysis

Hazard ratios and the corresponding 95% CIs were estimated using Cox proportional hazards analysis for primary and secondary outcomes. The cumulative incidence of proven, probable, or possible IFD was compared between groups similar to the primary and secondary IFD outcomes. Post hoc evaluation of the proportional hazard assumption for the primary outcome was performed based on testing an interaction term between groups and natural log of survival time in a Cox regression model. A mixed-effects survival analysis that incorporated site as a random effect was also performed for the primary comparison of time to proven or probable IFD by group.

### Interim Analyses

There were 2 interim efficacy analyses planned for the primary outcome, after approximately one-third and two-thirds of the patients completed IFD observation periods. The monitoring boundary was based on the Lan-DeMets method with power spending function  $\alpha^2$ .<sup>19</sup> The COG data and safety monitoring board (DSMB) requested unplanned futility analyses to be conducted in conjunction with efficacy analyses; this was not adjusted for repeated testing. The ad hoc futility analysis

Table 1. Demographic Baseline Characteristics by Study Group

Characteristic	Caspofungin (n = 254)	Fluconazole (n = 256)
Age, median (range), y <sup>a</sup>	10 (0 to 26)	9 (0 to 21)
Sex, No. (%)		
Male	141 (55.5)	143 (55.9)
Female	113 (44.5)	113 (44.1)
Race, No. (%)		
White	179 (70.5)	175 (68.4)
Black	29 (11.4)	32 (12.5)
Asian	19 (7.5)	19 (7.4)
Other <sup>b</sup>	1 (0.4)	4 (1.6)
Unknown	26 (10.2)	26 (10.2)
Ethnicity, No./total (%)		
Hispanic	41/244 (16.8)	52/251 (20.7)
AML type, No. (%) <sup>c</sup>		
De novo or newly diagnosed	219 (86.2)	218 (85.2)
First or subsequent relapse	17 (6.7)	26 (10.2)
Secondary AML	13 (5.1)	7 (2.7)
Treatment with standard AML therapy without AML diagnosis	5 (2.0)	5 (2.0)
AML protocol therapy, No. (%) <sup>d</sup>		
AAML0523	3 (1.2)	0
AAML0531	22 (8.7)	21 (8.2)
AAML07P1	1 (0.4)	2 (0.8)
AAML1031	201 (79.1)	208 (81.3)
FLAG	9 (3.5)	14 (5.5)
FLAG-idarubicin/liposomal daunorubicin	3 (1.2)	3 (1.2)
Institutional standard of care	7 (2.8)	3 (1.2)
Other <sup>e</sup>	8 (3.1)	5 (2.0)

Abbreviations: AML, acute myeloid leukemia; FLAG, fludarabine, cytarabine [arabinoside], granulocyte colony-stimulating factor.

<sup>a</sup> The number of participants 18 years or older was 22 for caspofungin and 18 for fluconazole.

<sup>b</sup> Includes 4 American Indian/Alaska Native and 1 Native Hawaiian/Pacific Islander.

<sup>c</sup> Randomization was stratified by AML type categorized as de novo AML vs all other AML types.

<sup>d</sup> Specific protocols varied but in general consisted of blocks of intensive myelosuppressive chemotherapy typically including an anthracycline or low- or high-dose cytarabine.

<sup>e</sup> Includes AAML06P1 (n = 1), L-asparaginase, high-dose cytarabine (n = 1), 2 courses of daunorubicin, cytarabine, thioguanine, etoposide, and dexamethasone (DCTER) (n = 1), cytarabine, daunorubicin, etoposide (n = 1), gemtuzumab ozogamicin (n = 1), and not specified (n = 8).

was based on repeated testing of the alternative hypothesis and used a 1-sided *P* value threshold of .024.<sup>20</sup>

Apart from the futility analysis, all tests of significance were 2-sided, and *P* < .05 was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Analyses were conducted using the SAS statistical program (SAS-PC, version 9.4; SAS Institute Inc).

## Results

Between April 4, 2011, and November 11, 2016, a total of 517 patients (257 randomized to caspofungin and 260 randomized to fluconazole) were enrolled from 115 institutions. Median age was 9 years (range, 0-26 years). The number of participants 18 years or older was 22 for caspofungin and 18 for fluconazole. Figure 1 demonstrates the reasons 9 patients (4 caspofungin and 5 fluconazole) were ineligible or unevaluable, resulting in 508 participants (253 caspofungin and 255 fluconazole) included in the primary analysis. Baseline characteristics of the study cohort are described in Table 1. No major differences were observed between the 2 groups. Postrandomization characteristics for the entire cohort and for each chemotherapy cycle are displayed by group in eTable 1 and eTable 2 in Supplement 2, respectively. In particular, dura-

tion of administration of randomized prophylaxis and IFD observation periods were similar by group.

The second interim efficacy (planned) and futility (unplanned) analyses were based on the June 30, 2016, data and included 394 patients (72% of planned enrollment) with complete IFD central review data. The 1-sided *P* value for comparing the observed hazard ratio (HR) of 0.72 at the interim analysis to the design HR of 0.24 was *P* = .01, which appeared to have suggested futility. The study was therefore closed to further enrollment on November 11, 2016; all enrolled patients completed study procedures and observations according to the protocol. Final analysis was based on June 30, 2018, data.

## Outcomes

### Primary Outcome

There were 23 proven or probable IFD events (6 in the caspofungin group and 17 in the fluconazole group) that consisted of 7 yeasts, 14 molds, and 2 fungi NOS (Table 2). Table 3 and Figure 2 show that the estimated 5-month cumulative incidence of proven or probable IFD was 3.1% (95% CI, 1.3%-7.0%) in the caspofungin group and 7.2% (95% CI, 4.4%-11.8%) in the fluconazole group (overall *P* = .03 by log-rank test; HR, 0.37; 95% CI, 0.15-0.94). In the secondary analysis of the primary outcome, time to proven or probable IFD was significantly different when competing risks were considered 2.5% (95% CI, 1.0%-5.1%) in the caspofungin group vs 6.1% (95% CI,

Table 2. Organisms Causing Invasive Fungal Disease by Study Group

	Caspofungin (n = 6)	Fluconazole (n = 17)
Yeast <sup>a</sup>	2	5
<i>Candida albicans</i>	0	2
<i>Candida glabrata</i>	0	1
<i>Candida krusei</i>	0	1
<i>Candida parapsilosis</i>	0	1
<i>Candida</i> not speciated	1	0
Yeast not otherwise specified	1	0
Mold <sup>b</sup>	4	10
<i>Aspergillus flavus</i>	0	1
<i>Aspergillus</i> not otherwise specified	1	6
<i>Rhizomucor</i> species	2	0
<i>Rhizopus</i> species	0	1
<i>Lomentospora prolificans</i>	1	0
<i>Curvularia</i> species	0	1
Mold not otherwise specified	0	1
Fungus not otherwise specified <sup>c</sup>	0	2

<sup>a</sup> All *Candida* species infections were proven events (culture from blood, neck, or lung biopsy tissue). The cases of *Candida* not speciated and yeast not otherwise specified were determined by cutaneous and spleen histopathology, respectively.

<sup>b</sup> *A. flavus* was a probable event (culture from bronchoalveolar lavage). *Aspergillus* not otherwise specified included 1 proven event (lung pathology) and 6 probable events (2 galactomannan positive from bronchoalveolar lavage and 5 galactomannan positive from blood in conjunction with radiographic abnormalities). *Rhizomucor* species were proven events (cultures from skin and lung biopsy) and *Rhizopus* species was a proven event (culture from skin biopsy). *Lomentospora prolificans*, formerly *Scedosporium prolificans*, was a proven event (culture from blood). *Curvularia* species was a proven event (culture from sinus biopsy). Mold not otherwise specified was a proven event (lung biopsy histopathology).

<sup>c</sup> Fungus not otherwise specified included 2 probable events (both  $\beta$ -D-glucan positive from the blood in conjunction with radiographic abnormalities).

3.6%-9.6%) in the fluconazole group (overall  $P = .02$  by the Gray test; HR, 0.35; 95% CI, 0.14-0.89).

The post hoc evaluation of the proportional hazard assumption did not suggest nonproportionality ( $P = .56$ ). In the post hoc analysis that included site as a random effect, the effect of caspofungin was unchanged ( $P = .04$ ).

### Secondary Outcomes

Of the 14 IFD events caused by molds, 8 (57%) were proven or probable IA (Table 2). Table 3 and Figure 2 show that the estimated 5-month cumulative incidence of proven or probable IA was 0.5% (95% CI, 0.1%-3.5%) in the caspofungin group and 3.1% (95% CI, 1.4%-6.9%) in the fluconazole group (overall  $P = .046$  by the log-rank test; HR, 0.16; 95% CI, 0.02-1.27). When competing risks were considered, the estimated 5-month cumulative incidence of proven or probable IA was 0.4% (95% CI, 0.0%-2.1%) in the caspofungin group and 2.5% (95% CI, 1.0%-5.1%) in the fluconazole group (overall  $P = .04$  by the Gray test; HR, 0.15; 95% CI, 0.02-1.18).

Table 3 also shows that there was no statistically significant difference in the need for empirical antifungal therapy.

The estimated 5-month cumulative incidence of the need for empirical antifungal therapy was 71.9% (95% CI, 65.1%-78.4%) for caspofungin and 69.5% (95% CI, 63.1%-75.7%) for fluconazole (overall  $P = .78$  by the log-rank test; HR, 0.97; 95% CI, 0.78-1.21). Considering competing events, these estimates were 62.9% (95% CI, 56.5%-68.6%) for caspofungin and 63.6% (95% CI, 57.3%-69.2%) for fluconazole (overall  $P = .59$  by the Gray test; HR, 0.94; 95% CI, 0.76-1.17). Overall survival at 2 years was 68.8% (95% CI, 62.3%-74.4%) in the caspofungin group and 70.8% (95% CI, 64.6%-76.1%) in the fluconazole group (overall  $P = .66$  by the log-rank test; HR, 1.08; 95% CI, 0.78-1.49).

### Post Hoc Outcomes

Table 3 shows that time to proven, probable, or possible IFD was not statistically significantly different by group. At 5 months, the estimates were 19.9% (95% CI, 14.3%-27.3%) for caspofungin and 18.9% (95% CI, 14.2%-24.9%) for fluconazole when not considering competing events (overall  $P = .33$  by log-rank test; HR, 0.80; 95% CI, 0.52-1.25). The estimates were 14.9% (95% CI, 10.6%-19.8%) for caspofungin and 16.6% (95% CI, 12.2%-21.5%) for fluconazole when considering competing events (overall  $P = .24$  by the Gray test; HR, 0.77; 95% CI, 0.49-1.19).

### Adverse Events

Table 3 in Supplement 2 shows grades 4 or 5 nonhematological adverse events for each chemotherapy cycle. The number of patients with at least 1 of these adverse events was 83 of 253 (32.8%) in the caspofungin group and 98 of 255 (38.4%) in the fluconazole group. The most commonly reported toxicities were hypokalemia (22 caspofungin vs 13 fluconazole), respiratory failure (6 caspofungin vs 9 fluconazole), and elevated alanine transaminase (4 caspofungin vs 8 fluconazole). There were 41 serious adverse events reported for 12 patients, of which 3 were considered possibly due to the study drug by the site investigators. All 3 were in the caspofungin group with 2 grade 4 events in the same patient (elevated alanine aminotransferase and aspartate aminotransferase) and 1 grade 5 hyperammonemia.

## Discussion

In this multicenter randomized trial, antifungal prophylaxis with caspofungin resulted in a significantly lower cumulative incidence of proven or probable IFD in children, adolescents, and young adults with AML compared with fluconazole. A statistically significant difference in proven or probable IA between study groups was also identified.

The observed risk reduction in IFD associated with caspofungin in this study was similar to that of posaconazole prophylaxis in a randomized trial of adolescents and adults with AML.<sup>8</sup> This suggests that the benefit of caspofungin prophylaxis in children with AML may be similar to posaconazole in adults. In the adult study, posaconazole was associated with more frequent adverse events compared with the control treatment. Additionally, there remain continued challenges in establishing a pediatric posaconazole dose that can reliably



**Table 3. Cumulative Incidence of Proven or Probable Invasive Fungal Disease and Invasive Aspergillosis at 5 Months by Study Group<sup>a</sup>**

Study Outcomes	Caspofungin Group (n = 253)				Fluconazole Group (n = 255)				P Value <sup>a</sup>	HR (95% CI)
	No. of Events	No. of Competing Events	No. Censored	Probability (95% CI), %	No. of Events	No. of Competing Events	No. Censored	Probability (95% CI), %		
<b>Primary</b>										
Proven or probable IFD										
No competing risks	6		247	3.1 (1.3-7.0)	17		238	7.2 (4.4-11.8)	.03	0.37 (0.15-0.94)
<b>Secondary</b>										
Proven or probable IFD										
Competing risks	6	112	135	2.5 (1.0-5.1)	17	95	143	6.1 (3.6-9.6)	.02	0.35 (0.14-0.89)
Proven or probable IA										
No competing risk	1		252	0.5 (0.1-3.5)	7		248	3.1 (1.4-6.9)	.046	0.16 (0.02-1.27)
Competing risk	1	117	135	0.4 (0.0-2.1)	7	105	143	2.5 (1.0-5.1)	.04	0.15 (0.02-1.18)
Need for empirical antifungal therapy <sup>b</sup>										
No competing risk	160		93	71.9 (65.1-78.4)	162		93	69.5 (63.1-75.7)	.78	0.97 (0.78-1.21)
Competing risk	160	63	30	62.9 (56.5-68.6)	162	52	41	63.6 (57.3-69.2)	.59	0.94 (0.76-1.17)
<b>Post Hoc</b>										
Proven, probable, or possible IFD										
No competing risk	35		218	19.9 (14.3-27.3)	44		211	18.9 (14.2-24.9)	.33	0.80 (0.52-1.25)
Competing risk	35	104	114	14.9 (10.6-19.8)	44	87	124	16.6 (12.2-21.5)	.24	0.77 (0.49-1.19)

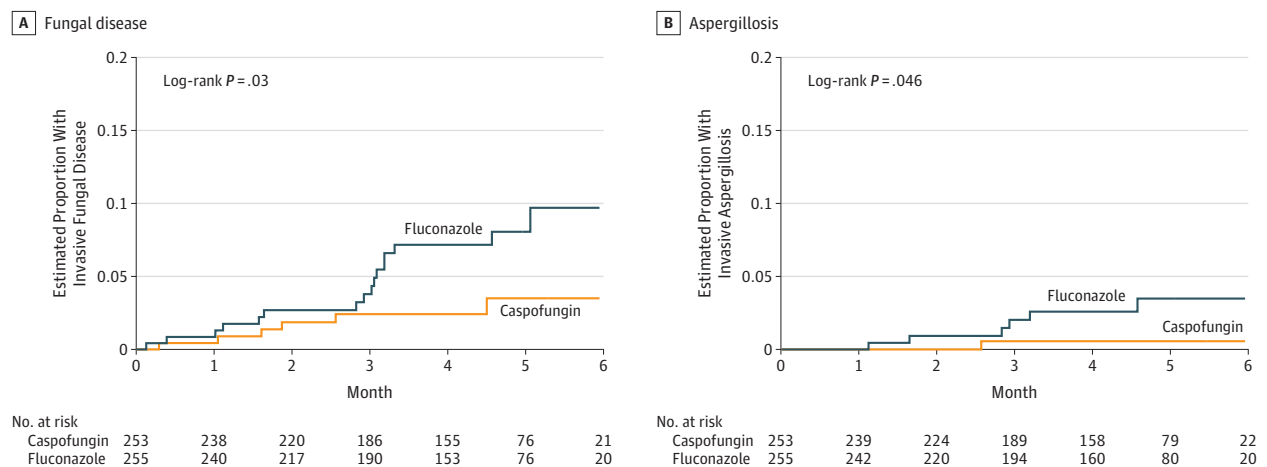
Abbreviations: HR, hazard ratio; IA, invasive aspergillosis; IFD, invasive fungal disease.

competing risks; groups compared by the Gray test. The P values shown reflect these tests.

<sup>a</sup> Primary analytic approach did not consider competing risk; groups compared by log-rank test. Secondary analytic approach considered

<sup>b</sup> Need for empirical antifungal therapy measured by prolonged or recurrent fever despite broad spectrum antibiotics for at least 5 days.<sup>15</sup>

**Figure 2. Time to Proven or Probable Invasive Fungal Disease and Proven or Probable Invasive Aspergillosis**



A, Median follow-up time for invasive fungal disease was 4.4 months (interquartile range [IQR], 3.0-5.2) for caspofungin and 4.6 months (IQR, 3.3-5.2) for fluconazole. B, Median follow-up time for invasive

aspergillosis was 4.4 months (IQR, 3.0-5.2) for caspofungin and 4.6 months (IQR, 3.3-5.3) for fluconazole.

achieve pharmacokinetic targets.<sup>21</sup> These factors suggest that current posaconazole utilization will be limited in children, thus reducing its effect on the uptake of this study’s findings.

This study was closed prior to full accrual based on the result of an unplanned interim futility analysis for the primary outcome requested by an independent DSMB. Futility was concluded by an interim analysis, but the final analysis favored

the alternative hypothesis. There are multiple potential explanations for why the interim and final analyses differed. First, the outcome designations by central review for participants without an IFD were completed more quickly than for patients with an IFD, resulting in an underestimation of the event rate and likely biased comparison due to nonrandom missing data (“nonignorable” missing data) for the second interim

analysis that only included cases with complete IFD data. Second, during the period of interim analysis, follow-up of previously enrolled patients and new patient enrollment continued. As such, the final analysis encompassed an additional 114 participants whose data were not included in the interim analysis, allowing for discrepant results due to random data variation. Similar discrepancy between interim and final analyses has been observed in other large randomized trials.<sup>22</sup> Nuances of trial design should be considered when unplanned futility analyses are implemented.<sup>23,24</sup>

The major strength of this study is that it is a large, multicenter, randomized clinical trial that answers a clinically important question in pediatric cancer supportive care.

### Limitations

This study has several limitations. First, since this was an open-label study, there was potential for differential cessation of assigned prophylaxis. However, the duration of randomized therapy per patient was similar between allocated groups (eTable 1 in Supplement 2). Second, the treating clinician dictated diagnostic testing and thus a differential pursuit for an

IFD pathogen was possible. However, this concern is reduced because patients in the 2 study groups had similar rates of fungal biomarker and bronchoscopy testing (eTable 2 in Supplement 2). Third, early termination of the study hinders interpretability of the results and reduces precision in comparative estimates and adverse event determination. Fourth, centers with historically high rates of mold infection may not have been willing to open this study; thus, generalizability of results to these centers is uncertain.

### Conclusions

Among children, adolescents, and young adults with acute myeloid leukemia, prophylaxis with caspofungin compared with fluconazole resulted in significantly lower incidence of invasive fungal disease. The findings suggest that caspofungin may be considered for prophylaxis against invasive fungal disease, although study interpretation is limited by early termination due to an unplanned interim analysis that appeared to have suggested futility.

#### ARTICLE INFORMATION

**Accepted for Publication:** September 9, 2019.

**Author Affiliations:** Division of Pediatrics Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Fisher, Zaoutis); Division of Pediatric Allergy, Immunology and Bone Marrow Transplant, University of California San Francisco (Dvorak); Division of Blood and Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, Florida (Nieder); Division of Pediatric Infectious Diseases, Seattle Children's Hospital, Seattle, Washington (Zerr); University of Florida College of Medicine, Gainesville (Wingard); Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Callahan); Children's Oncology Group, Monrovia, California (Villaluna); Division of Biostatistics, City of Hope, Duarte, California (Chen); Department of Preventive Medicine, University of Southern California, Los Angeles (Dang); Division of Pediatric Hematology and Oncology, Vanderbilt University Medical Center, Nashville, Tennessee (Esbenshade); Division of Haematology Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada (Alexander, Sung); Division of Pediatric Hematology and Oncology, Sinai Hospital of Baltimore, Baltimore, Maryland (Wiley).

**Author Contributions:** Dr Dang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Concept and design:** Fisher, Zaoutis, Dvorak, Nieder, Wiley, Sung.

**Acquisition, analysis, or interpretation of data:** Fisher, Dvorak, Nieder, Zerr, Wingard, Callahan, Villaluna, Chen, Dang, Esbenshade, Alexander, Wiley, Sung.

**Drafting of the manuscript:** Fisher, Villaluna, Sung.  
**Critical revision of the manuscript for important intellectual content:** Fisher, Zaoutis, Dvorak, Nieder, Zerr, Wingard, Callahan, Chen, Dang, Esbenshade, Alexander, Wiley.

**Statistical analysis:** Fisher, Villaluna, Chen, Dang,

**Obtained funding:** Zaoutis, Sung.

**Administrative, technical, or material support:** Zerr, Wingard, Wiley, Sung.

**Supervision:** Fisher, Zaoutis.

**Other - study conduct:** Alexander.

**Conflict of Interest Disclosures:** Dr Fisher reported that his institution receives funding from Merck and Pfizer for research studies, which are not related to this project, and that he began service on the DSMB for Astellas after this study concluded. Dr Zaoutis reported that he provides consultant services for T2 Biosystems and Nabriva Therapeutics in projects not related to this study. Dr Wingard reported that he serves on the data committees for Astellas, Shire, Merck, and Celgene, none of which are related to this study. Ms Callahan reported that she provides consultant services for Novartis in projects not related to this study. Dr Wiley reported that he is currently employed by Leadiant Biosciences. No other disclosures were reported.

**Funding Support:** This study was supported by the following National Cancer Institute grants: NCORP grant UG1CA189955, NCTN Statistics & Data Center grant U10CA 180899, NCTN Operations Center grant U10CA 180886. Caspofungin was supplied by Merck & Company Inc.

**Role of the Funder/Sponsor:** The National Cancer Institute reviewed and approved the protocol and integrated study and served as the DSMB. Neither the National Cancer Institute nor Merck had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Data Sharing Statement:** See Supplement 3.

**Additional Contributions:** We thank Bayrta Prosvirova, MS, Children's Oncology Group, for her role as study coordinator and her assistance in the data cleaning process. Ms Prosvirova was compensated for her role on this study. We also thank Vicki Nussbaum, PharmD, University of

Wisconsin, for her pharmacological expertise during the course of the study. Dr Nussbaum did not receive compensation for her work.

#### REFERENCES

- Sung L, Lange BJ, Gerbing RB, Alonzo TA, Feusner J. Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia. *Blood*. 2007;110(10):3532-3539. doi:10.1182/blood-2007-05-091942
- Dix D, Cellot S, Price V, et al. Association between corticosteroids and infection, sepsis, and infectious death in pediatric acute myeloid leukemia (AML): results from the Canadian Infections in AML Research Group. *Clin Infect Dis*. 2012;55(12):1608-1614. doi:10.1093/cid/cis774
- Sung L, Gamis A, Alonzo TA, et al. Infections and association with different intensity of chemotherapy in children with acute myeloid leukemia. *Cancer*. 2009;115(5):1100-1108. doi:10.1002/cncr.24107
- Alexander S, Pole JD, Gibson P, et al; International Pediatric Oncology Mortality Classification Group. Classification of treatment-related mortality in children with cancer: a systematic assessment. *Lancet Oncol*. 2015;16(16):e604-e610. doi:10.1016/S1470-2045(15)00197-7
- Zaoutis TE, Heydon K, Chu JH, Walsh TJ, Steinbach WJ. Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the United States, 2000. *Pediatrics*. 2006;117(4):e711-e716. doi:10.1542/peds.2005-1161
- Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. *Clin Infect Dis*. 2005;41(9):1232-1239. doi:10.1086/496922
- Wattier RL, Dvorak CC, Hoffman JA, et al. A prospective, international cohort study of invasive mold infections in children. *J Pediatric*

- Infect Dis Soc.* 2015;4(4):313-322. doi:10.1093/jpids/piu074
8. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med.* 2007;356(4):348-359. doi:10.1056/NEJMoa061094
  9. Freifeld AG, Bow EJ, Sepkowitz KA, et al; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52(4):e56-e93. doi:10.1093/cid/cir073
  10. Science M, Robinson PD, MacDonald T, Rassekh SR, Dupuis LL, Sung L. Guideline for primary antifungal prophylaxis for pediatric patients with cancer or hematopoietic stem cell transplant recipients. *Pediatr Blood Cancer.* 2014;61(3):393-400. doi:10.1002/pbc.24847
  11. Zaoutis TE, Jafri HS, Huang LM, et al. A prospective, multicenter study of caspofungin for the treatment of documented *Candida* or *Aspergillus* infections in pediatric patients. *Pediatrics.* 2009;123(3):877-884. doi:10.1542/peds.2008-1158
  12. Ngai AL, Bourque MR, Lupinacci RJ, Strohmaier KM, Kartsonis NA. Overview of safety experience with caspofungin in clinical trials conducted over the first 15 years: a brief report. *Int J Antimicrob Agents.* 2011;38(6):540-544. doi:10.1016/j.ijantimicag.2011.07.008
  13. Fisher BT, Zaoutis T. Caspofungin for the treatment of pediatric fungal infections. *Pediatr Infect Dis J.* 2008;27(12):1099-1102. doi:10.1097/INF.0b013e3181937fe0
  14. Zaoutis T, Lehrnbecher T, Groll AH, et al. Safety experience with caspofungin in pediatric patients. *Pediatr Infect Dis J.* 2009;28(12):1132-1135. doi:10.1097/INF.0b013e3181af5a15
  15. Lehrnbecher T, Phillips R, Alexander S, et al; International Pediatric Fever and Neutropenia Guideline Panel. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. *J Clin Oncol.* 2012;30(35):4427-4438. doi:10.1200/JCO.2012.42.7161
  16. De Pauw B, Walsh TJ, Donnelly JP, et al; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis.* 2008;46(12):1813-1821. doi:10.1086/588660
  17. Institute NC. CTEP cancer therapy evaluation program: common terminology criteria for adverse events (CTCAE). [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/ctc.htm](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm). Updated March 1, 2018. Accessed December 31, 2018.
  18. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat.* 1988;16(3):1141-1154. doi:10.1214/aos/1176350951
  19. Kim K, DeMets DL. Design and analysis of group sequential tests based on the type I error spending rate function. *Biometrika.* 1987;74(1):149-154. doi:10.1093/biomet/74.1.149
  20. Anderson JR, High R. Alternatives to the standard Fleming, Harrington, and O'Brien futility boundary. *Clin Trials.* 2011;8(3):270-276. doi:10.1177/1740774511401636
  21. Arrieta AC, Sung L, Bradley JS, et al. A non-randomized trial to assess the safety, tolerability, and pharmacokinetics of posaconazole oral suspension in immunocompromised children with neutropenia. *PLoS One.* 2019;14(3):e0212837. doi:10.1371/journal.pone.0212837
  22. Lesaffre E, Edelman MJ, Hanna NH, et al. Statistical controversies in clinical research: futility analyses in oncology-lessons on potential pitfalls from a randomized controlled trial. *Ann Oncol.* 2017;28(7):1419-1426. doi:10.1093/annonc/mdx042
  23. Pocock SJ, Hughes MD. Practical problems in interim analyses, with particular regard to estimation. *Control Clin Trials.* 1989;10(4)(suppl):209S-221S. doi:10.1016/0197-2456(89)90059-7
  24. Walter SD, Han H, Briel M, Guyatt GH. Quantifying the bias in the estimated treatment effect in randomized trials having interim analyses and a rule for early stopping for futility. *Stat Med.* 2017;36(9):1506-1518. doi:10.1002/sim.7242

Copyright of JAMA: Journal of the American Medical Association is the property of American Medical Association and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

Copyright of JAMA: Journal of the American Medical Association is the property of American Medical Association and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.