

# Isavuconazole versus Caspofungin in the Treatment of Candidemia and Other Invasive *Candida* Infections: The ACTIVE Trial

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**Manuscript Summary**

In a phase 3, randomized, double-blind, multinational clinical trial comparing isavuconazole to caspofungin for primary treatment of patients with proven candidemia or invasive candidiasis, isavuconazole failed to demonstrate noninferiority compared with caspofungin.

This work was presented in part at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2016, Amsterdam, Netherlands.

## ABSTRACT

**Background:** Isavuconazole was compared to caspofungin followed by oral voriconazole in a phase 3, randomized, double-blind, multinational clinical trial (ACTIVE; NCT00413218) for primary treatment of patients with candidemia or invasive candidiasis.

**Methods:** Adult patients were randomized 1:1 to isavuconazole (200 mg IV TID for 2 days, followed by 200 mg IV QD) or caspofungin (70 mg IV QD on day 1, followed by 50 mg IV QD [70 mg in patients >80 kg]) for a maximum of 56 days. After day 10, patients could switch to oral isavuconazole (isavuconazole arm) or voriconazole (caspofungin arm). The primary efficacy endpoint was successful overall response at end of IV therapy (EOIVT) in patients with proven infection who received  $\geq 1$  dose of study drug (modified-intent-to-treat [mITT] population). The pre-specified noninferiority margin was 15%. Secondary outcomes (mITT) were successful overall response at 2 weeks after end of treatment, all-cause mortality at days 14 and 56, and safety.

**Results:** Of 450 patients randomized, 400 comprised the mITT population. Baseline characteristics were balanced between groups. Successful overall response at EOIVT was observed in 60.3% of patients in the isavuconazole arm, and 71.1% in the caspofungin arm, (adjusted difference [95% confidence interval] -10.8 [-19.9, -1.8]). The secondary endpoints, all-cause mortality, and safety were similar between arms, while median time to clearance of the bloodstream was comparable in both groups.

**Conclusions:** This study did not demonstrate the non-inferiority of isavuconazole to caspofungin for primary treatment of invasive candidiasis. Secondary endpoints were similar between both groups.

**Keywords:** isavuconazole, *Candida*, caspofungin, voriconazole

## INTRODUCTION

Invasive *Candida* infections remain a significant source of patient morbidity and mortality [1]. Despite advances in antifungal therapy, mortality among patients with invasive candidiasis is as high as 40% [2, 3]. Currently-available antifungals exhibit shortcomings including nephrotoxicity with polyenes, the need for intravenous (IV) administration with echinocandins, and toxicity, drug–drug interactions, and absorption concerns with some triazoles [4].

Isavuconazole is the newest triazole with a broad-spectrum of antifungal activity, which is administered as the water-soluble prodrug, isavuconazonium sulfate. Isavuconazole offers both IV and oral formulations, has excellent oral bioavailability, no relevant food effects, and little interpatient pharmacokinetic variability [5, 6]. Recent studies have demonstrated its efficacy and safety in the treatment of invasive aspergillosis [7], mucormycosis [8], and certain endemic mycoses [9]. Efficacy against *Candida* species has been demonstrated in preclinical models [10-12]; however, clinical use of isavuconazole for invasive candidiasis has not been reported.

We present the results of ACTIVE, a phase 3, randomized, double-blind, noninferiority trial designed to compare the efficacy and safety of IV isavuconazole followed by oral isavuconazole to IV caspofungin followed by oral voriconazole in the primary treatment of candidemia and invasive candidiasis.

## METHODS

### Study Design

ACTIVE (Clinicaltrials.gov, NCT00413218) was a phase 3, randomized, double-blind, double-dummy, multicenter, noninferiority study of IV isavuconazole followed by oral isavuconazole compared with IV caspofungin followed by oral voriconazole as initial therapy for candidemia and other forms of invasive candidiasis, performed at 116 centers in 25 countries. The study was conducted in accordance with the Declaration of Helsinki (2000) and the International Conference on Harmonization Guidelines for Good Clinical Practice. Independent ethics committees or institutional review boards at the participating sites approved the protocol and all amendments. All patients provided written informed consent prior to enrollment.

### Patients

Male and female patients  $\geq 18$  years of age were eligible if they had candidemia or invasive candidiasis with a positive blood or tissue culture within 96 hours prior to randomization, accompanied by clinical signs and symptoms of infection. Key exclusion criteria at baseline were hepatic dysfunction, *Candida* osteomyelitis, *Candida* endocarditis, *Candida* meningitis, severe immunodeficiency, or more than 48 hours of systemic antifungal therapy for the current episode. Full eligibility and exclusion criteria are provided in Supplementary Appendix.

### Randomization and Blinding

Randomization to receive isavuconazole or caspofungin was performed centrally in a 1:1 ratio using an interactive response computer system, stratified by geographic region and

neutropenia at baseline. All investigators, patients, study personnel, and the sponsor were blinded to treatment assignment, except pharmacy personnel responsible for medication preparation. A placebo was used to maintain blinding by matching the frequency of daily dosing.

## Study Procedures

Patients assigned to isavuconazole received 200 mg (equivalent to isavuconazonium sulfate 372 mg) IV three times a day on days 1 and 2, followed by 200 mg IV once daily. Patients assigned to caspofungin received a single dose of 70 mg IV caspofungin on day 1, followed by 50 mg IV (70 mg in patients >80 kg) once daily. After day 10, patients without neutropenia could be switched from IV to oral therapy at the discretion of the investigator. Patients in the isavuconazole arm received oral 200 mg isavuconazole once daily, and patients in the caspofungin arm received voriconazole 400 mg twice daily on day 1 of oral dosing, followed by 200 mg twice daily orally onwards. Patients continued treatment for a minimum of 14 days after the last positive blood culture. Therapy could be extended up to 56 days. Removal of central venous catheters was recommended for all patients with candidemia.

Patients were followed for 6 weeks after end of therapy (EOT). Clinical and laboratory assessments were performed at baseline, and at days 7, 14, 28, 42, 56, end of IV therapy (EOIVT), EOT, and 2 and 6 weeks after EOT. Blood cultures were performed daily until two sequential negative cultures from two separate days were obtained. Additional radiological and mycological assessments were performed if clinically indicated. Fungal isolates were sent to a central laboratory for identification and susceptibility testing using both the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodologies [13, 14].

## Efficacy and Safety Assessments

All patients who received at least one dose of the study drug were included in the intent-to-treat (ITT) population. Patients in the ITT population who had documented invasive candidiasis or candidemia at baseline, based on the assessment of the independent blinded Data Review Committee (DRC), were included in the modified ITT (mITT) population, used to assess the primary and secondary endpoints.

An independent DRC, masked to treatment allocation, adjudicated the diagnosis and response to study treatment (clinical and mycological) of each patient at EOIVT, EOT, and 2 and 6 weeks after EOT; identified breakthrough, emergent and recurrent infections, and assessed attributable mortality. The primary efficacy endpoint was overall response to therapy (success or failure; Supplementary Appendix 2.2) in the mITT population, defined as mycological eradication and clinical cure or improvement (**Table S1**) at EOIVT, without use of alternative systemic antifungal therapy within 48 hours after the last dose of IV study medication. The secondary endpoints included the overall response to therapy at 2 weeks after EOT. At this point, patients also were required to have no recurrent or emergent fungal infection to be considered a success. Additionally, All-cause mortality at days 14 and 56 was assessed. In mITT patients with positive blood cultures, time to negative blood culture was analyzed on days 3, 7, 14 and 21. Investigators evaluated safety and tolerability by monitoring adverse events (AEs) and findings from physical examinations, vital signs, laboratory tests, electrocardiograms, and concomitant medications/surgery. A treatment-

emergent adverse event (TEAE) was defined as an AE starting or worsening after first study drug administration until 28 days after the last dose.

### **Statistical Analysis**

The primary endpoint of overall response at EOIVT was aimed to demonstrate that isavuconazole was noninferior to caspofungin in the mITT population. A two-sided 95% confidence interval (CI) was calculated for the true difference in efficacy between the study groups, using a stratified Cochran-Mantel-Haenszel method including geographical regions and baseline neutropenic status. Based on an estimated success rate of 70% at EOIVT for both treatment arms, a sample size of 350 mITT patients (175 in each arm) would provide at least 86% power to demonstrate noninferiority of isavuconazole to caspofungin with a noninferiority margin of 15%. Isavuconazole would be considered noninferior to caspofungin if the lower limit of the two-sided 95% CI for the difference in response rates between isavuconazole and caspofungin was greater than -15%. Assuming that 20% of patients would not have baseline invasive candidiasis as confirmed by the blinded DRC, our target enrolment was a total of 438 ITT patients. Time to first negative blood culture and time from randomization to death were analyzed using Kaplan-Meier methods.

All data analyses were performed using SAS® 9.1. Continuous data were summarized descriptively including number of patients, mean, standard deviation (SD), median, minimum, and maximum. Categorical data were summarized by number and percentage of patients within the category.

## RESULTS

### Baseline Characteristics

A total of 473 patients consented for the study (**Figure 1**). Of these, 450 patients were randomized; 440 (97.8%) received at least one dose of study drug and were included in the ITT population. A total of 400 ITT patients (199 patients for isavuconazole and 201 for caspofungin) had documented invasive candidiasis or candidemia at baseline and were included in the mITT population. Demographics and baseline characteristics of the two study arms were comparable for both ITT and mITT populations (**Table 1**). Baseline neutropenia was present in 24 patients (12%) in each study arm of the mITT population. In the mITT population, the majority of patients in the isavuconazole (85.4%), and caspofungin (81.1%) groups had candidemia without other manifestations of invasive candidiasis. The duration of total study drug was similar between the isavuconazole and caspofungin groups (**Table 2**).

### Microbiologic Findings

The distribution of *Candida* species was similar in the two arms of the study (**Table 1**). At baseline, 51.3% of patients in the isavuconazole group and 53.8% in the caspofungin group were infected by a non-albicans *Candida* species as per DRC assessment. The most common species causing infection were *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. glabrata* in both treatment arms (**Table 1**).

The minimal inhibitory concentrations (MICs) for isavuconazole and caspofungin for baseline clinical isolates using CLSI methodology are shown in **Table S2**. Isavuconazole demonstrated a baseline MIC range of 0.0005–0.25 µg/mL (MIC<sub>50</sub>, 0.004; MIC<sub>90</sub>, 0.03 µg/mL) against *Candida* spp. for isavuconazole-treated patients. Caspofungin demonstrated a baseline MIC range of 0.03–2 µg/mL (MIC<sub>50</sub>, 0.25; MIC<sub>90</sub>, 1 µg/mL) for caspofungin-treated patients. The EUCAST MIC values for isavuconazole and caspofungin are presented in **Table S3**.

### Efficacy

For the primary endpoint of overall response at EOIVT, a successful outcome was achieved in 120/199 (60.3%) patients in the isavuconazole group, and 143/201 (71.1%) in the caspofungin group (adjusted difference: -10.8%; 95% CI: -19.9, -1.8; **Table 2**). The lower limit of the 95%CI for the treatment difference (-19.9%) was lower than the prespecified noninferiority margin of -15%; therefore, this study did not demonstrate noninferiority of isavuconazole relative to caspofungin.

The overall response rates at 2 weeks after EOT, the key secondary endpoint according to the study protocol, were similar in the isavuconazole and caspofungin arms (54.8% vs 57.2%; adjusted difference, -2.7%; 95%CI; -12.2, 6.8).

Survival on day 14 and day 56 was comparable between the isavuconazole and caspofungin arms for patients in the ITT population (**Figure 2**).

Among patients with candidemia only (83.3% of all patients), 110/170 (64.7%) had a successful overall response at EOIVT in the isavuconazole group, versus 118/163 (72.4%) in the caspofungin group (adjusted difference, -7.7%; 95%CI: -18.3, 2.9). A total of 67 patients with invasive candidiasis, with or without candidemia, were identified in this study, 29 in the isavuconazole arm and 38 in the caspofungin arms. Response rates were 34.5% (10/29) for isavuconazole and 65.8% (25/38) for caspofungin (adjusted difference, -31.3%; 95%CI: -57.7, -5.0; **Table 2**). No trends in response rates were observed when evaluating the in vitro susceptibility values among the two groups at EOIVT or EOT + 2 weeks. As expected, baseline neutropenia was associated with a lower rate of success in both treatment arms (**Figure 3**), as was an Acute Physiology and Chronic Health Evaluation (APACHE) score of >20 (**Figure 3; Figure S1**). BMI  $\geq$ 25 affected the response rates with a trend towards a lower response rate noted in the isavuconazole arm. While response rates to isavuconazole were lower than to caspofungin in patients with invasive candidiasis, no specific risk groups or sites of infection could be identified at increased risk of failure.

### Oral Step-Down

Of the 400 mITT patients, 69/199 (34.7%) in the isavuconazole group were switched from IV to PO, and 80/201 (39.8%) in the caspofungin group were switched to PO voriconazole. The median (range) total duration of therapy (IV + oral) was 15.0 (1–57) days for isavuconazole and 16.0 (1–59) days for caspofungin→voriconazole groups. Median (range) duration of oral therapy was 8 (1–47) days and 8 (1–45) days in the isavuconazole and caspofungin→voriconazole groups, respectively. Successful overall response at EOIVT in the patients who were switched to oral therapy was 58/69 (84.1%) in the isavuconazole group and 71/80 (88.8%) in the caspofungin→voriconazole group. At 2 weeks after EOT, overall success rates in patients receiving oral therapy were 82.6% for isavuconazole vs. 77.5% for caspofungin→voriconazole (adjusted difference, 4.8%; 95%CI:-7.9, 17.5). More patients switching from IV caspofungin to oral voriconazole (12/80; 15%) transitioned from success to failure between EOIVT and 2 weeks after EOT, compared with patients switching from IV isavuconazole to oral isavuconazole (4/69; 5.8%).

### Emergent or Recurrent Infections

A total of 5 patients in the isavuconazole arm and 11 patients in the caspofungin arm were documented by the DRC to have either a breakthrough, emergent or recurrent *Candida* infection during the study (**Table 2; Table S4**).

In the isavuconazole arm, 3 patients developed a recurrent candidemia after EOT, 1 patient had an emergent fungal infection, and 1 patient had both a emergent and recurrent infection. In the caspofungin arm, breakthrough fungal infections were reported in 5 patients before EOT, along with 5 recurrent infections (3 candidemias and 2 invasive candidiasis) and 1 additional emergent fungal infections reported during follow-up.

### Catheter Management and Bloodstream Clearance



In total, 75.0% of all mITT patients had an intravascular catheter at baseline, (150/199 [75.4%] in the isavuconazole arm vs. 150/201 [74.6%] in the caspofungin arm). In the isavuconazole arm, 98/150 (65.3%) patients had all baseline catheters removed by day 1, an additional 8/150 (5.3%) of patients had all baseline catheters removed by day 2, and in total, 135/150 (90%) of patients had all baseline catheters removed during IV therapy. In the caspofungin arm, 82/150 (54.7%) patients had all baseline catheters removed by day 1, and 133/150 (88.7%) patients had all baseline catheters removed during IV therapy. Overall response was comparable between patients who had their baseline catheters removed and in those that did not (**Table S5**).

The median time to negative blood culture was 4 days in the isavuconazole group and 3 days in the caspofungin group (log rank  $P$ , 0.59; **Figure S2**). At EOIVT, persistent candidemia was documented in 22/120 (18.3%) of patients with baseline candidemia in the isavuconazole arm (*C. tropicalis* [10], *C. albicans* [9], multiple *Candida* spp. [2], and *C. krusei* [1]). Of these patients, 9/12 (75%) had all baseline catheters removed by Day 2, 2/12 (16.7%) patients had baseline catheters removed by EOIVT, and 1/12 (8.3%) patients still had at least one catheter by EOIVT. Persistent candidemia was documented in 21/119 (17.6%) in the caspofungin arm (*C. albicans* [8], *C. tropicalis* [6]), *C. glabrata* [3], multiple *Candida* spp. [3] and *C. krusei* [1]). Of these, 9/13 (69.2%) had baseline catheters removed by Day 2 but all remaining (4/13, 30.8%) patients had baseline catheters removed by the EOIVT.

### Adverse Events

For both the isavuconazole and caspofungin arms, approximately 95% of patients in the safety populations had at least one TEAE (**Table 3**). The safety profiles of isavuconazole and caspofungin were comparable (**Table S6**). More patients in the isavuconazole arm than in the caspofungin arm had TEAEs relating to septic shock (20 [9.1%] vs. 11 [5.0%]), and sepsis (18 [8.2%] vs. 11 [5.0%]). A greater proportion of patients in the isavuconazole arm compared with the caspofungin arm had study drug-related serious TEAEs during the entire treatment period (**Table S6**). More patients in the isavuconazole arm than the caspofungin group had pyrexia (2.3% vs 0.5%) and infusion site pain (2.3% vs 0%), whereas serum alkaline phosphatase was increased more often in the caspofungin arm (2.7%) than in the isavuconazole arm (0.9%). In the subgroup of patients who switched to oral therapy, safety profiles were similar between the isavuconazole and caspofungin→voriconazole arms (**Table S7**).

## DISCUSSION

In this randomized, multicenter study, we compared the efficacy of isavuconazole vs. caspofungin for the treatment of candidemia and other forms of invasive candidiasis. The primary endpoint of successful overall response at EOIVT (isavuconazole, 60.3%; caspofungin, 71.1%) did not meet the prespecified noninferiority margin. Hence, isavuconazole was not shown to be noninferior to caspofungin. The key secondary endpoint of overall response at 2 weeks after EOT was similar in both arms, as were the all-cause mortality rates at days 14 and 56. In addition, in patients with candidemia, the clearance rate of *Candida* from the bloodstream did not differ significantly between isavuconazole and

casprofungin, while the numbers of patients with persistently-positive blood cultures were similar in both arms. Breakthrough and recurrent infections tended to be higher in the casprofungin arm. The MIC<sub>50</sub> for isavuconazole for all *Candida* isolates was ≤0.25 µg/mL. The trend towards higher success rates with casprofungin was consistent across the entire range of APACHE II scores (Fig. S1), underscoring the greater efficacy of echinocandins irrespective of severity of illness.

Previous phase 3 trials involving echinocandins and triazoles have yielded consistently similar results for each drug class [15-20]. The results of the present study are consistent with those of the prior trial comparing the efficacy of an echinocandin and an azole [15], in which overall response rates were significantly higher with anidulafungin (76%) than with fluconazole (60%; P<.01). As in the present study, the echinocandin antifungal was associated with a better outcome than the triazole in infections due to either *C. albicans* or non-*albicans Candida* species. The present study enrolled substantially larger numbers of subjects than the previously published study that compared triazoles vs. echinocandins (400 vs. 245 subjects) [15]. Previously, a pooled analysis of patient-level data from 7 randomized antifungal treatment trials demonstrated that randomization to an echinocandin was associated with improved survival and greater clinical success than treatment with a triazole or amphotericin B [2]. Together, these results suggest that echinocandins are intrinsically more active against invasive candidiasis than azoles, including fluconazole and isavuconazole.

Transition from IV to oral antifungal therapy occurred in 35% of subjects in the isavuconazole arm, and 40% in the casprofungin arm. In these patients, overall success rates were 82.6% for isavuconazole vs. 77.5% for casprofungin→voriconazole. These data suggest that stepdown to oral isavuconazole may be safe and effective once *Candida* has been cleared from the bloodstream as long as the pathogen is triazole-susceptible and the patient is capable of taking oral medications. The reduced success with the oral stepdown of casprofungin→voriconazole may reflect the lack of therapeutic drug monitoring integral to success with voriconazole [21].

Safety and tolerability results were comparable between both study arms. This is largely consistent with a previous meta-analysis that found comparable rates of drug-related TEAEs for echinocandins and triazoles [22].

The limitations of the present study include the exclusion of pediatric patients and the small proportion of patients with neutropenia. Whereas these results provide additional support for the observation that echinocandins are associated with fewer early efficacy failures, we were not able to identify specific predictors of unfavorable outcomes with isavuconazole. However, an evaluation of the exposure-response relationships from this study might be helpful in this regard.

In conclusion, this large, multicenter study did not demonstrate noninferiority of isavuconazole relative to casprofungin for primary treatment of candidemia and invasive candidiasis. Isavuconazole demonstrated comparable all-cause mortality to casprofungin, and the drug safety profile was similar between both groups. Overall success rates with isavuconazole as oral stepdown were favorable.

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## **Potential Conflict of Interest**

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## Figure Legends

### Figure 1: Patient flow

<sup>a</sup>Either EOIVT OR end of all therapy (including completing oral therapy for those who switched to oral)

<sup>b</sup>Other includes violation of selection at entry and other protocol deviation.

<sup>c</sup>One patient was randomized to the isavuconazole group, but received caspofungin treatment on Day 1 and then was switched to isavuconazole treatment; this patient qualified for inclusion in the safety population for caspofungin.

AE, adverse event; ITT, intent-to-treat; mITT, modified-intent-to-treat

### Figure 2. Mortality (ITT Population) Through End of Therapy (EOT)

### Figure 3 Response to Treatment in the mITT Population Subgroups at EOIVT

For each subgroup, the interaction *P* value was calculated using a regression model including treatment group, geographical region, baseline neutropenia status subgroup and treatment by subgroup interaction and is evaluated at a significance level of *P*=0.15

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CI, confidence interval; mITT, modified intent to treat

**Table 1.** Demographics and Baseline Characteristics in ITT Population

| Parameter   | ITT Population           |                        |
|---|--------------------------|------------------------|
|   | Isavuconazole<br>(n=221) | Caspofungin<br>(n=219) |
| Age (years), mean ± SD years                                | 58.0 ± 17.5              | 57.9 ± 16.9            |
| Sex, n (%)  |                          |                        |
| Male  | 143 (64.7)               | 126 (57.5)             |
| Geographic region, n (%)                                    |                          |                        |
| North America   | 38 (17.2)                | 33 (15.1)              |
| Western Europe, Australia and New Zealand                   | 54 (24.4)                | 56 (25.6)              |
| Other   | 129 (58.4)               | 130 (59.4)             |
| Baseline parameters   |                          |                        |
| APACHE II Score, mean ± SD                                  | 13.9 ± 7.2               | 14.1 ± 7.3             |
| Neutropenia, n (%)  | 25 (11.3)                | 24 (11.0)              |
| Mean body-mass index (kg/m <sup>2</sup> )                   | 24.8 ± 6.1               | 24.5 ± 6.9             |
|   | mITT Population          |                        |
|   | Isavuconazole<br>(n=199) | Caspofungin<br>(n=201) |
| Baseline pathogen (mITT population)                         |                          |                        |
| Candidemia only, n (%)                                      | 170 (85.4)               | 163 (81.1)             |
| Invasive candidiasis ± candidemia                           | 29 (14.6)                | 38 (18.9)              |
| Single Organism   |                          |                        |
| <i>C. albicans</i>  | 84 (42.2)                | 74 (36.8)              |
| <i>C. tropicalis</i>  | 41 (20.6)                | 38 (18.9)              |
| <i>C. parapsilosis</i>                                      | 26 (13.1)                | 27 (13.4)              |
| <i>C. glabrata</i>  | 22 (11.1)                | 21 (10.4)              |
| <i>C. krusei</i>  | 4 (2.0)                  | 7 (3.5)                |
| <i>C. guilliermondii</i> <sup>b</sup>                       | 0                        | 5 (2.5)                |
| Other <i>Candida</i> spp.                                   | 4 (2.0)                  | 7 (3.0)                |
| Multiple organisms  | 18 (9.0)                 | 22 (10.9)              |
| <i>Candida</i> spp. only                                    | 13 (6.5)                 | 20 (10.0)              |
| <i>Candida</i> spp. + non- <i>Candida</i> spp. <sup>c</sup> | 5 (2.5)                  | 2 (1.0)                |

<sup>a</sup>Other includes Argentina, Brazil, Chile, China, Hungary, India, Israel, Lebanon, Malaysia, Mexico, Philippines, South Africa, Russia, Singapore, and Thailand

<sup>b</sup>Recently renamed to *Meyerozyma guilliermondii*

<sup>c</sup>In the isavuconazole arm this included; *C. kefyr* and *Saccharomyces cerevisiae* (n=1), *C. parapsilosis* and *Trichosporon ashii* (n=1), *C. albicans*, *C. glabrata* and *Saccharomyces* (n=1) *C. glabrata* and *Trichosporon*

*mucooides* (n=1) and *C. tropicalis*, *C. parasilosis* and *Kodamaea* (n=1); In the caspofungin arm this included; *C. tropicalis* and *Acremonium* (n=1) and *C. tropicalis* and *Geotrichum capitatum* (n=1)

None of the baseline characteristics were significantly different between arms

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II, ITT, intent to treat; IV, intravenous; mITT, modified-intent-to-treat; SD, standard deviation.



**Table 2.** Response to Treatment and All-Cause Mortality in the mITT Population

| mITT Population   | Isavuconazole<br>(n=199) | Caspofungin<br>(n=201) | Adjusted Difference <sup>a</sup><br>(95% CI) |
|---|--------------------------|------------------------|--|
| Response rates, n (%)   |                          |                        |  |
| Overall response at EOIVT   | 120 (60.3)               | 143 (71.1)             | -10.8 (-19.9, -1.8)                          |
| Clinical response <sup>b</sup>                                    | 152 (76.4)               | 169 (84.1)             | -8.2 (-15.4, -0.9)                           |
| Microbiological response  | 141 (70.9)               | 172 (85.6)             | -14.9 (-22.7, -7.0)                          |
| Overall response at EOT   | 122 (61.3)               | 145 (72.1)             | -10.9 (-19.9, -1.9)                          |
| Overall response at 2 weeks after EOT                             | 109 (54.8)               | 115 (57.2)             | -2.7 (-12.2, 6.8)                            |
| Overall response at 6 weeks after EOT                             | 86 (43.2)                | 97 (48.3)              | -5.4 (-15.0, 4.2)                            |
| Overall response at EOIVT by infection type and organism, n/N (%) |                          |                        |  |
| Candidemia only   | 110/170 (64.7)           | 118/163 (72.4)         | -7.7 (-18.3, 2.9)                            |
| Invasive candidiasis with or without candidemia                   | 10/29 (34.5)             | 25/38 (65.8)           | -31.3 (-57.7, -5.0)                          |
| Baseline pathogen   |                          |                        |  |
| <i>C. albicans</i>  | 53/84 (63.1)             | 56/74 (75.7)           | -12.6 (-28.2, 3.0)                           |
| <i>C. tropicalis</i>  | 22/41 (53.7)             | 24/38 (63.2)           | -9.5 (-34.0, 15.0)                           |
| <i>C. parapsilosis</i>  | 15/26 (57.7)             | 20/27 (74.1)           | -16.4 (-45.8, 13.1)                          |
| <i>C. glabrata</i>  | 14/22 (63.6)             | 15/21 (71.4)           | -7.8 (-41.0, 25.4)                           |
| <i>C. krusei</i>  | 2/4 (50.0)               | 6/7 (85.7)             | -  |
| <i>C. guilliermondii</i>  | 0                        | 3/5 (60.0)             | -  |
| Multiple organisms  | 10/18 (55.6)             | 15/22 (68.2)           | -12.6 (-48.6, 23.3)                          |
| All-cause Mortality, n (%)  |                          |                        |  |
| Day 14  | 29 (14.6)                | 25 (12.4)              | 2.5 (-3.8, 8.9)                              |
| Day 56  | 61 (30.7)                | 60 (29.9)              | 1.4 (-7.1, 10.0)                             |
| Study drug exposure   |                          |                        |  |
| Total duration [days], median (min-max)                           | 15 (1-57)                | 16 (1-59)              |  |
| IV duration [days], median (min-max)                              | 11 (1-56)                | 12 (1-56)              |  |

|   |          |          |
|---|----------|----------|
| Patients who switched to oral, n (%)  | 69 (35)  | 80 (40)  |
| Oral duration [days], median (min–max)                                      | 8 (1–47) | 8 (1–45) |
| Breakthrough, emergent and recurrent fungal infections <sup>c</sup> , n (%) |          |          |
| Breakthrough before EOT   | 0 (0)    | 5 (2.5)  |
| Recurrent candidiasis until 6 weeks after EOT                               | 4 (2.0)  | 5 (2.5)  |
| Emergent other fungal infection until 6 weeks after EOT                     | 2 (1.0)  | 1 (0.5)  |

<sup>a</sup>Adjusted treatment difference (Isavuconazole-Caspofungin) and 95% CI are calculated by a stratified minimum-risk analysis. The 95% CI is calculated on a normal approximation with the strata of geographical regions, and baseline neutropenic status.

<sup>b</sup>Complete or partial response as assessed by blinded DRC

<sup>c</sup>An emergent infection is defined as a new infection occurring by a new species in a patient during the study period, a breakthrough infection is defined as any emergent infection occurring up to EOT, and a recurrent infection is any new infection in a patient occurring of the same species recorded at baseline during the study period.

Abbreviations: CI, confidence interval; EOIVT, end of intravenous treatment; EOT, end of treatment; mITT, modified intent to treat.

**Table 3.** Overview of Treatment-Emergent Adverse Events (MedDRA V12.1) and Death<sup>a</sup>

| <b>Safety population, n (%)</b>                    | <b>Isavuconazole<sup>b</sup><br/>(n = 220)</b> | <b>Caspofungin<br/>(n = 220)</b> |
|--|--|----------------------------------|
| Number of subjects ≥1 TEAE                         | 209 (95.0)                                     | 208 (94.5)                       |
| Hypokalaemia                                       | 40 (18.2)                                      | 45 (20.5)                        |
| Pyrexia  | 43 (19.5)                                      | 41 (18.6)                        |
| Diarrhoea  | 34 (15.5)                                      | 41 (18.6)                        |
| Vomiting   | 34 (15.5)                                      | 39 (17.7)                        |
| Constipation                                       | 32 (14.5)                                      | 24 (10.9)                        |
| Hypotension  | 25 (11.4)                                      | 28 (12.7)                        |
| Nausea   | 22 (10.0)                                      | 31 (14.1)                        |
| Hypomagnesaemia                                    | 19 (8.6)                                       | 29 (13.2)                        |
| Study drug-related TEAE                            | 78 (35.5)                                      | 71 (32.3)                        |
| Serious TEAE                                       | 112 (50.9)                                     | 106 (48.2)                       |
| Study drug-related serious TEAE                    | 19 (8.6)                                       | 12 (5.5)                         |
| TEAE leading to discontinuation of study drug      | 22 (10.0)                                      | 23 (10.5)                        |
| Study drug-related TEAE leading to discontinuation | 11 (5.0)                                       | 11 (5.0)                         |
| Death <sup>c</sup>                                 | 66 (30.0)                                      | 68 (30.9)                        |

<sup>a</sup>Data were analyzed according to the study drug that patients received as the first dose irrespective of study group assignment

<sup>b</sup>One patient was randomized to the isavuconazole group, but received caspofungin treatment on Day 1 and then was switched to isavuconazole treatment; this patient qualified for inclusion in the safety population for caspofungin

<sup>c</sup>Includes all deaths reported after the first dose of the study drug

No significant differences for TEAE were observed between arms

Abbreviations: TEAE, treatment-emergent adverse event; MedDRA v.12.1, Medical Dictionary for Regulatory Activities, version 12.1.

## Figure 1

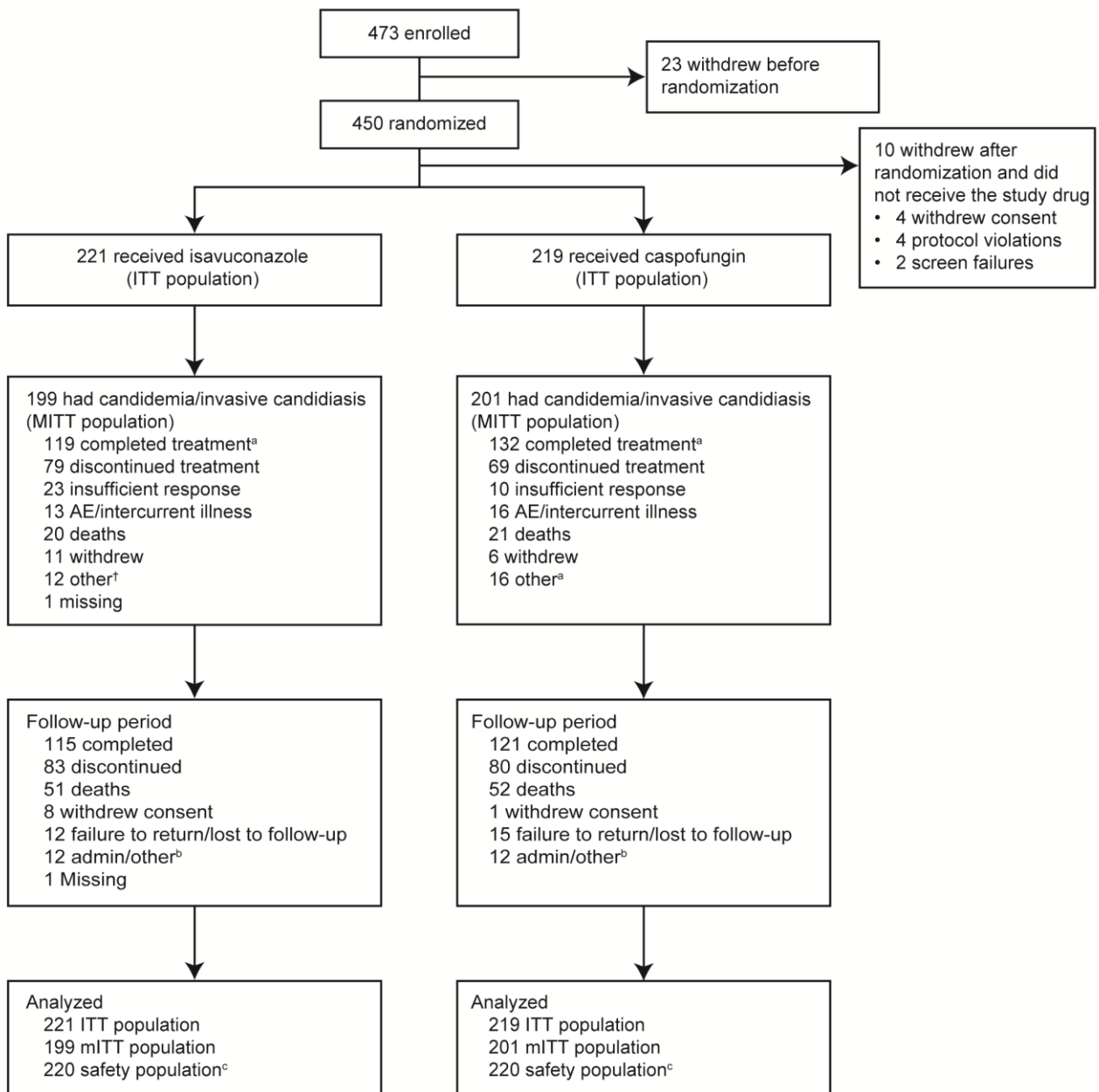
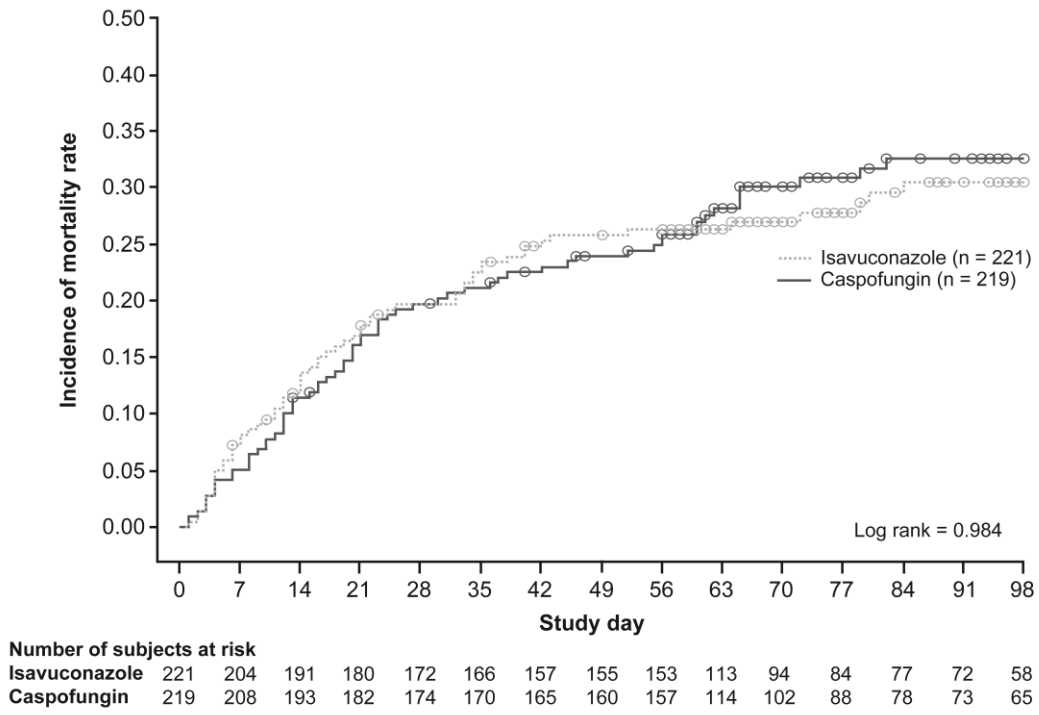


Figure 2



**Figure 3**

