Clinical Infectious Diseases

MAJOR ARTICLE

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

Bart Jan Kullberg,[1] Claudio Viscoli,[2,3] Peter G. Pappas,[4] Jose Vazquez,[5] Luis Ostrosky-Zeichner,[6] Coleman Rotstein,[7] Jack D. Sobel,[8] Raoul Herbrecht,[9] Galia Rahav,[10] Sutep Jaruratanasirikul,[11] Ploenchan Chetchotisakd,[12] Eric Van Wijngaerden,[13] Jan De Waele,[14] Christopher Lademacher,[15] Marc Engelhardt,[16] Laura Kovanda,[15] Rodney Croos-Dabrera,[15] Christine Fredericks,[15] and George R. Thompson III[17]

[1]Radboud Center for Infectious Diseases, and Department of Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; [2]Dipartimento di Scienze della Salute, University of Genova, and [3]Ospedale Policlinico San Martino, Genova, Italy; [4]University of Alabama at Birmingham; [5]Medical College of Georgia/Augusta University; [6]University of Texas, Houston; [7]University Health Network, University of Toronto, Ontario, Canada; [8]Wayne State University, Detroit, Michigan; [9]Hôpitaux Universitaires de Strasbourg and Université de Strasbourg, Inserm, UMR-S1113/IRFAC, France; [10]Sheba Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Israel; [11]Songklanagarind Hospital, Hat Yai; and [12]Srinagarind Hospital, Khon Kaen University, Thailand; [13]Ku Leuven, Belgium; [14]Ghent University Hospital, Belgium; [15]Astellas Pharma Global Development, Inc, Northbrook, Illinois; [16]Basilea Pharmaceutica International Ltd., Basel, Switzerland; and [17]Department of Medicine, University of California Davis

Background. Isavuconazole was compared to caspofungin followed by oral voriconazole in a Phase 3, randomized, double-blind, multinational clinical trial for the primary treatment of patients with candidemia or invasive candidiasis.

Methods. Adult patients were randomized 1:1 to isavuconazole (200 mg intravenous [IV] three-times-daily [TID] for 2 days, followed by 200 mg IV once-daily [OD]) or caspofungin (70 mg IV OD on day 1, followed by 50 mg IV OD [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). Primary efficacy endpoint was successful overall response at the end of IV therapy (EOIVT) in patients with proven infections who received ≥1 dose of study drug (modified-intent-to-treat [mITT] population). The pre-specified noninferiority margin was 15%. Secondary outcomes in the mITT population were successful overall response at 2 weeks after the 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 -10.8, 95% confidence interval -19.9–-1.8). The secondary endpoints, all-cause mortality, and safety were similar between arms. Median time to clearance of the bloodstream was comparable between groups.

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

Clinical Trials Registration. NCT00413218.

Keywords. isavuconazole; *Candida*; caspofungin; voriconazole.

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 that is administered as a water-soluble pro-drug, isavuconazonium sulfate. Isavuconazole offers both IV and oral formulations, has excellent oral bioavailability, has no relevant food effects, and has little inter-patient 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]. Its efficacy against the *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.

Received 22 May 2018; editorial decision 3 August 2018; accepted 4 October 2018; published online October 5, 2018.

Presented in part: European Congress of Clinical Microbiology and Infectious Diseases, Amsterdam, Netherlands; April 9–12, 2016; O423.

Correspondence: B. J. Kullberg, Radboud Center for Infectious Diseases, Department of Medicine (463), Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands (bj.kullberg@radboudumc.nl).

Clinical Infectious Diseases® 2018;XX(XX):1–9

DOI: 10.1093/cid/ciy827

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 as compared with IV caspofungin followed by oral voriconazole as initial therapies 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 ≥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 the 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, and was stratified by geographic region and neutropenia at baseline. All investigators, patients, study personnel, and the sponsor were blinded to treatment assignment, except the 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 3 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 who were switched received 200 mg of oral isavuconazole once daily, while patients in the caspofungin arm received voriconazole at 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. The removal of central venous catheters was recommended for all patients with candidemia.

Patients were followed for 6 weeks after the end of therapy (EOT). Clinical and laboratory assessments were performed at baseline; days 7, 14, 28, 42, and 56; the end of IV therapy (EOIVT); the EOT; and 2 and 6 weeks after EOT. Blood cultures were performed daily until 2 sequential negative cultures from 2 separate days were obtained (1 on each day). 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 and European Committee on Antimicrobial Susceptibility Testing methodologies [13, 14].

Efficacy and Safety Assessments

All patients who received at least 1 dose of the study drug were included in the intent-to-treat (ITT) population. Patients in the ITT population who had invasive candidiasis or candidemia documented 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 (Supplementary Table S1) at EOIVT, without use of alternative, systemic, antifungal therapy within 48 hours after the last dose of the 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, the 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 AE (TEAE) was defined as an AE starting or worsening between the first study drug administration and 28 days after the last dose.

Statistical Analysis

The primary endpoint of overall response at EOIVT was intended to demonstrate that isavuconazole was noninferior to caspofungin in the mITT population. A 2-sided 95% confidence interval (CI) was calculated for the true difference in efficacy between the study groups, using a stratified Cochran-Mantel-Haenszel method and 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 2-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 enrollment was a total of 438 ITT patients. The 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 the number of patients, mean, standard deviation, 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 1 dose of the study drug and were included in the ITT population. A total of 400 ITT patients (199 patients for

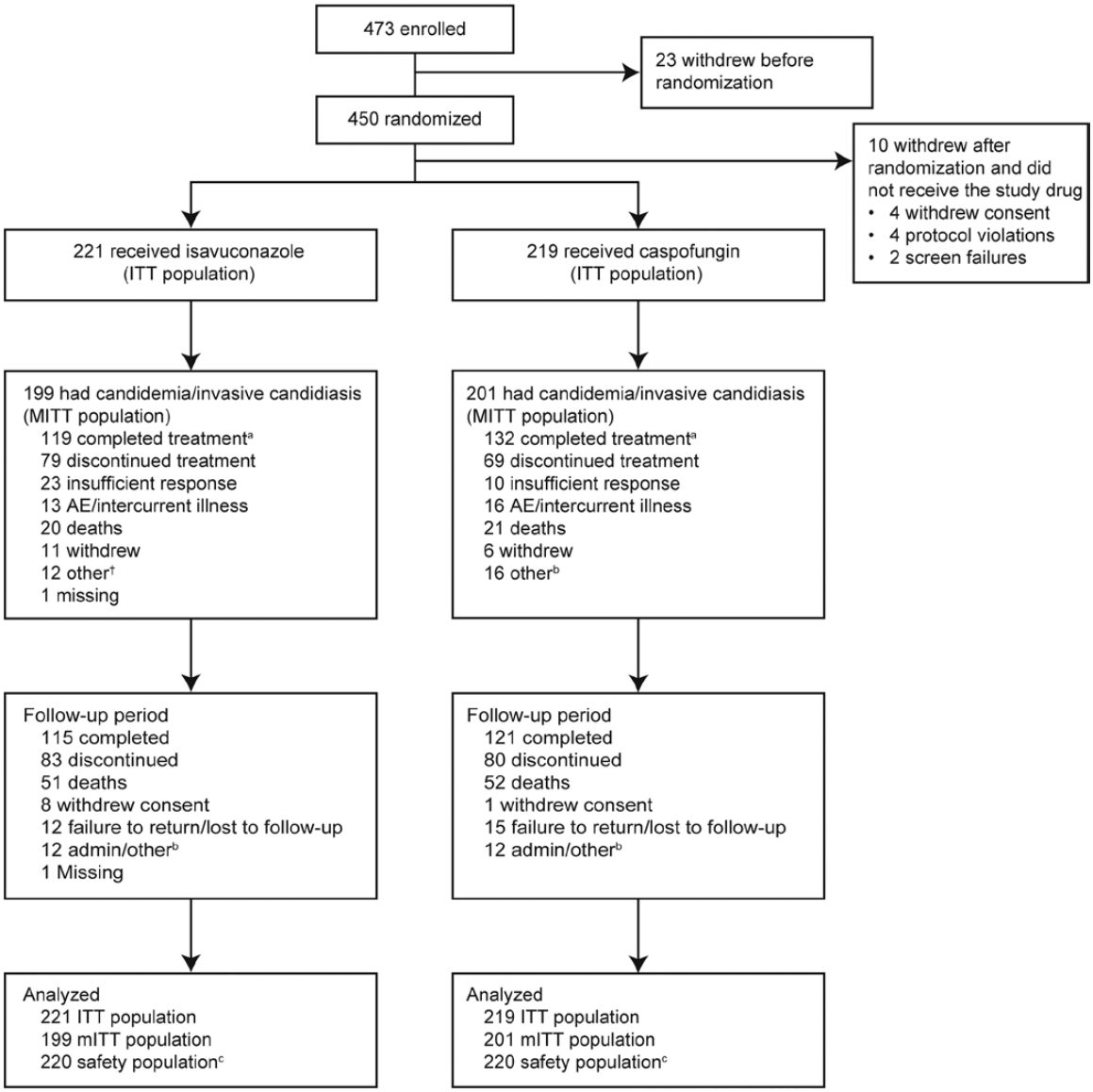

Figure 1. Patient flow. Abbreviations: AE, adverse event; ITT, intent-to-treat; mITT, modified-intent-to-treat. [a]Either end of intravenous therapy or end of all therapy (including completing oral therapy for those who switched to oral). [b]Other includes violation of selection at entry and other protocol deviations. [c]There was 1 patient randomized to the isavuconazole group who received caspofungin treatment on Day 1 and then was switched to isavuconazole treatment; this patient qualified for inclusion in the safety population for caspofungin.

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 2 study arms were comparable for both the 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 study drug administration was similar between the isavuconazole and caspofungin groups (Table 2).

Table 1. Demographics and Baseline Characteristics in Intent-to-treat Population

	ITT Population	
	Isavuconazole	Caspofungin
Parameter	(n = 221)	(n = 219)
Age in 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[a]	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^2)	24.8 ± 6.1	24.5 ± 6.9
	mITT Population	
	Isavuconazole	Caspofungin
	(n = 199)	(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		
C. albicans	84 (42.2)	74 (36.8)
C. tropicalis	41 (20.6)	38 (18.9)
C. parapsilosis	26 (13.1)	27 (13.4)
C. glabrata	22 (11.1)	21 (10.4)
C. krusei	4 (2.0)	7 (3.5)
C. guillermondii[b]	0	5 (2.5)
Other *Candida* spp.	4 (2.0)	7 (3.0)
Multiple organisms	18 (9.0)	22 (10.9)
Candida spp. only	13 (6.5)	20 (10.0)
Candida spp. + non-*Candida* spp.[c]	5 (2.5)	2 (1.0)

None of the baseline characteristics were significantly different between arms.

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

[a]Other includes Argentina, Brazil, Chile, China, Hungary, India, Israel, Lebanon, Malaysia, Mexico, Philippines, South Africa, Russia, Singapore, and Thailand.

[b]Recently renamed to *Meyerozyma guillermondii*.

[c]In the isavuconazole arm, this included *C. kefyr* and *Saccharomyces cerevisae* (n = 1); *C. parasilosis* and *Trichosporon ashii* (n = 1); *C. albicans, C glabrata,* and *Saccharomyces* (n = 1); *C. glabrata* and *Trichosporon mucoides* (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).

Microbiologic Findings

The distribution of *Candida* species was similar in the 2 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 minimum inhibitory concentrations (MICs) for isavuconazole and caspofungin for baseline clinical isolates using the Clinical and Laboratory Standards Institute's methodology are shown in Supplementary Table S2. Isavuconazole demonstrated a baseline MIC range of 0.0005–0.25 µg/mL (MIC_{50}, 0.004; MIC_{90}, 0.03 µg/mL) against *Candida* spp. for isavuconazole-treated patients. Caspofungin demonstrated a baseline MIC range of 0.03–2 µg/mL (MIC_{50}, 0.25; MIC_{90}, 1 µg/mL) for caspofungin-treated patients. The European Committee on Antimicrobial Susceptibility Testing's MIC values for isavuconazole and caspofungin are presented in Supplementary 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%, respectively; 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 2 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 II score of >20 (Figure 3; Supplementary

Table 2. Response to Treatment and All-cause Mortality in the Modified Intent-to-treat Population

mITT Population	Isavuconazole (n = 199)	Caspofungin (n=201)	Adjusted Difference[a] (95% CI)
Response rates, n (%)			
Overall response at EOIVT	120 (60.3)	143 (71.1)	−10.8 (−19.9, −1.8)
Clinical response[b]	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			
C. albicans	53/84 (63.1)	56/74 (75.7)	−12.6 (−28.2, 3.0)
C. tropicalis	22/41 (53.7)	24/38 (63.2)	−9.5 (−34.0, 15.0)
C. parapsilosis	15/26 (57.7)	20/27 (74.1)	−16.4 (−45.8, 13.1)
C. glabrata	14/22 (63.6)	15/21 (71.4)	−7.8 (−41.0, 25.4)
C. krusei	2/4 (50.0)	6/7 (85.7)	…
C. guilliermondii	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 in days, median (min–max)	15 (1–57)	16 (1–59)	
IV duration in days, median (min–max)	11 (1–56)	12 (1–56)	
Patients who switched to oral, n (%)	69 (35)	80 (40)	
Oral duration in days, median (min–max)	8 (1–47)	8 (1–45)	
Breakthrough, emergent, and recurrent fungal infections,[c] 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)	

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

[a]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.

[b]Complete or partial response, as assessed by blinded Data Review Committee.

[c]An emergent infection is defined as an 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, of the same species recorded at baseline, occurring during the study period.

Figure S1). A body mass index ≥ 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 as having an 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 oral and 80/201 (39.8%) in the caspofungin group were switched to oral 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 the 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, the 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; Supplementary Table S4).

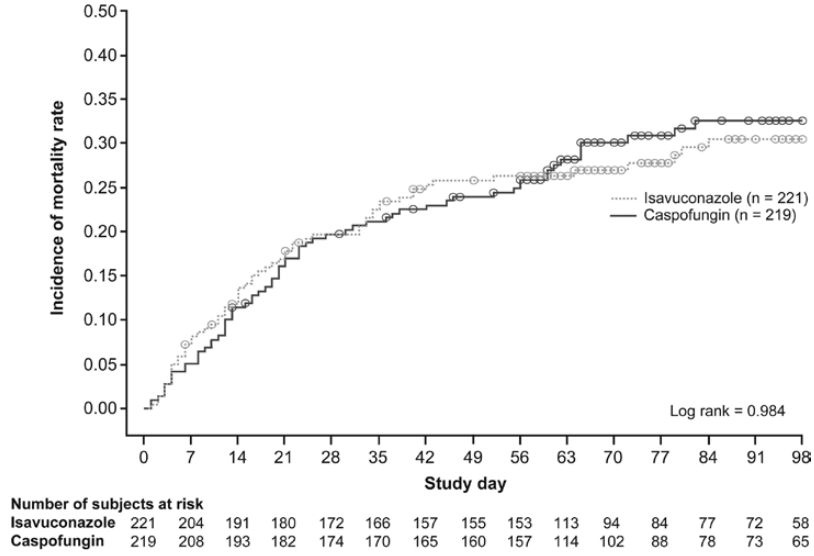

Figure 2. Mortality (intent-to-treat population) through end of therapy.

In the isavuconazole arm, 3 patients developed a recurrent candidemia after EOT, 1 patient had an emergent fungal infection, and 1 patient had both emergent and recurrent infections. 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 infection 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

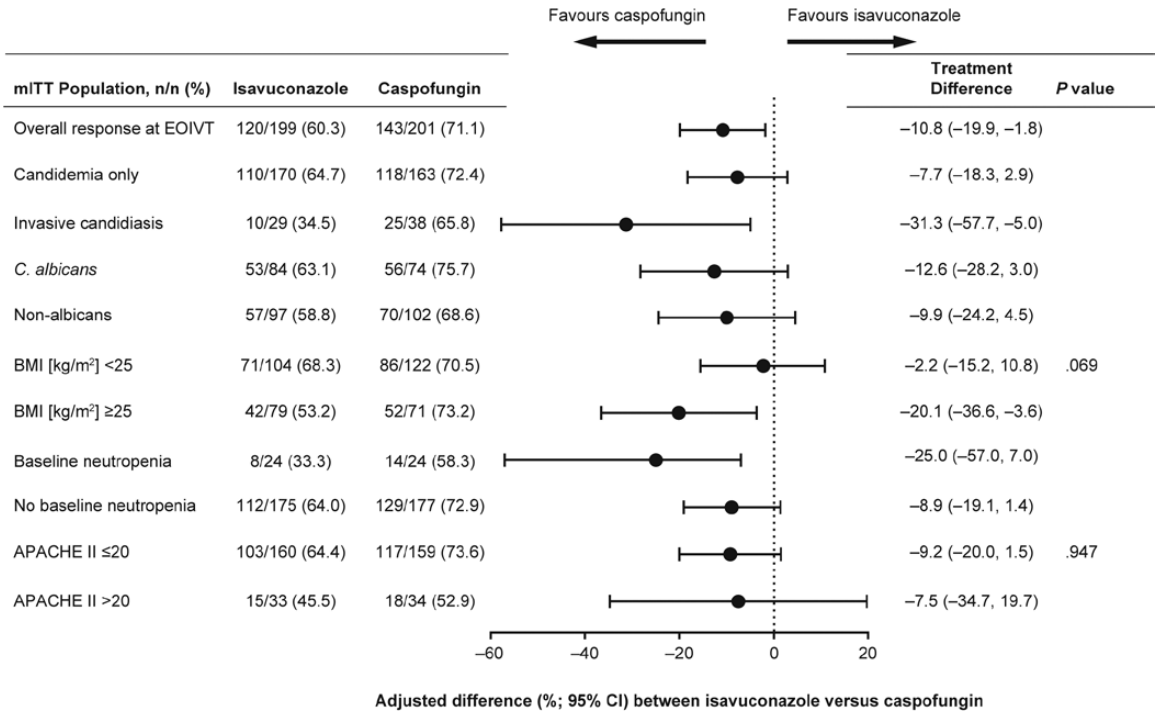

Figure 3. Response to treatment in the modified intent-to-treat population subgroups at end of intravenous therapy. For each subgroup, the interaction *P* value was calculated using a regression model that included treatment group, geographical region, baseline neutropenia status subgroup, and treatment by subgroup interaction, and is evaluated at a significance level of *P* = .15. Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CI, confidence interval; EOIVT, end of intravenous therapy; mITT, modified intent-to-treat.

[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 patents had all baseline catheters removed during IV therapy. In the caspofungin arm, 82/150 (54.7%) of patients had all baseline catheters removed by day 1 and 133/150 (88.7%) of patients had all baseline catheters removed during IV therapy. The overall response was comparable between patients who had their baseline catheters removed and those that did not (Supplementary 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 $P = 0.59$; Supplementary 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 1 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 1 TEAE (Table 3). The safety profiles of isavuconazole and caspofungin were comparable (Supplementary 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%], respectively) and sepsis (18 [8.2%] vs 11 [5.0%], respectively). 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 (Supplementary 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 (Supplementary Table S7).

Table 3. Overview of Treatment-emergent Adverse Events (MedDRA V12.1) and Death[a]

Safety Population, n (%)	Isavuconazole[b] (n = 220)	Caspofungin (n = 220)
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)
Diarrhea	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[c]	66 (30.0)	68 (30.9)

No significant differences for TEAE were observed between arms. Data were analyzed according to the study drug that patients received as the first dose irrespective of study group assignment

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

[a]Data were analyzed according to the study drug that patients received as the first dose irrespective of study group assignment.

[b]There was 1 patient randomized to the isavuconazole group who received caspofungin treatment on Day 1 and then was switched to isavuconazole treatment; this patient qualified for inclusion in the safety population for caspofungin

[c]Includes all deaths reported after the first dose of the study drug.

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 caspofungin, 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 caspofungin arm. The MIC_{50} for isavuconazole for all *Candida* isolates was ≤0.25 µg/mL. The trend towards higher success rates with caspofungin was consistent across the entire range of Acute Physiology and Chronic Health Evaluation II scores (Supplementary Figure 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 a 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 those 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 caspofungin arm. In these patients, the overall success rates were 82.6% for isavuconazole vs 77.5% for caspofungin → 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 caspofungin → voriconazole may reflect the lack of therapeutic drug monitoring, which is 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 caspofungin for the primary treatment of candidemia and invasive candidiasis. Isavuconazole demonstrated comparable all-cause mortality to caspofungin, and the drug safety profile was similar between both groups. Overall success rates with isavuconazole as an oral stepdown were favorable.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank Barrie J. Anthony, PhD, CMPP, of Envision Scientific Solutions, funded by Astellas Pharma, Inc., for editorial assistance. The authors thank the investigators and study center staff who conducted the studies for their contributions, as well as the patients who participated in the ACTIVE trial.

Financial support. This work was funded by Astellas Pharma, Inc. Isavuconazole has been co-developed by Basilea Pharmaceutica International Ltd and Astellas Pharma Global Development, Inc.

Potential conflicts of interest. B. J. K. has received support from Astellas for being a member of the data review committee; from Amplyx, Basilea, Cidara, Gilead, and Scynexis for advisory board membership; and from Pfizer for speaker fees. G. R. T. has received grant and consultant fees from Astellas, Scynexis, and Cidara; grant support from Merck and Mayne; and consultant fees from Amplyx and Vical. J. V. has received support from Astellas for being a member of the data review committee. P. G. P. has received grant support from Astellas, T2 Biosystems, and Merck; and grant support and fees for Scientific Advisory Committee from Cidara. C. V. has received speaker fees and advisory board membership from Astellas, Pfizer, Gilead, Merck Sharp & Dohme (MSD), Angelini, and Basilea. L. O.-Z. has received support from Astellas for being a member of the data review committee; grant support and personal fees from Astellas, Pfizer, Cidara, and Scynexis; and personal fees from Merck, Gilead, and F2G. C. R. has received grant/research support from Astellas, Cidara, Chimerix Inc, Pfizer, and Merck; paid consultancy fees from Astellas, Merck, Pendopharm, and Pfizer; and speakers fees from Merck, Pfizer, Sunovion Pharmaceuticals, and Teva Pharmaceutical Industries Ltd. E. VW. has received study support to his institution from Astellas; educational grants from Merck and Pfizer; and has an advisory board membership from Pfizer. R. H. has received personal fees for advisory board membership and speakers fees from Basilea, Gilead, and MAS; advisory board membership for Astellas; and grant support, advisory board membership, and speakers fees from Pfizer. G. R. has received speakers fees and grant support from MSD and Pfizer. P. C. has received grant support from Astellas, Gilead, GlaxoSmithKline, the National Institutes of Health, and MSD. L. K., C. L., R. C.-D., and C. F. are employees of Astellas Pharma Global Development, Inc. M. E. is an employee of Basilea Pharmaceutica International Ltd. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Kullberg BJ, Arendrup MC. Invasive candidiasis. N Engl J Med **2015**; 373:1445–56.
2. Andes DR, Safdar N, Baddley JW, et al.; Mycoses Study Group. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis **2012**; 54:1110–22.
3. Puig-Asensio M, Pemán J, Zaragoza R, et al.; Prospective Population Study on Candidemia in Spain (CANDIPOP) Project; Hospital Infection Study Group (GEIH); Medical Mycology Study Group (GEMICOMED) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC); Spanish Network for Research in Infectious Diseases. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. Crit Care Med **2014**; 42:1423–32.
4. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 62:e1–50.
5. Desai A, Kovanda L, Kowalski D, Lu Q, Townsend R, Bonate PL. Population pharmacokinetics of isavuconazole from Phase 1 and Phase 3 (SECURE) trials in adults and target attainment in patients with invasive infections due to *Aspergillus* and other filamentous fungi. Antimicrob Agents Chemother **2016**; 60:5483–91.
6. Schmitt-Hoffmann A, Desai A, Kowalski D, Pearlman H, Yamazaki T, Townsend R. Isavuconazole absorption following oral administration in healthy subjects is comparable to intravenous dosing, and is not affected by food, or drugs that alter stomach pH. Int J Clin Pharmacol Ther **2016**; 54:572–80.
7. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a Phase 3, randomised-controlled, non-inferiority trial. Lancet **2016**; 387:760–9.
8. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al.; VITAL and FungiScope Mucormycosis Investigators. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis **2016**; 16:828–37.
9. Thompson GR 3rd, Rendon A, Ribeiro Dos Santos R, et al. Isavuconazole treatment of cryptococcosis and dimorphic mycoses. Clin Infect Dis **2016**; 63:356–62.
10. Lepak AJ, Marchillo K, VanHecker J, Diekema D, Andes DR. Isavuconazole pharmacodynamic target determination for *Candida* species in an in vivo murine disseminated candidiasis model. Antimicrob Agents Chemother **2013**; 57:5642–8.

11. Majithiya J, Sharp A, Parmar A, Denning DW, Warn PA. Efficacy of isavuconazole, voriconazole and fluconazole in temporarily neutropenic murine models of disseminated *Candida tropicalis* and *Candida krusei*. J Antimicrob Chemother **2009**; 63:161–6.
12. Thompson GR 3rd, Wiederhold NP. Isavuconazole: a comprehensive review of spectrum of activity of a new triazole. Mycopathologia **2010**; 170:291–313.
13. Rodriquez-Tudela JL, Donnelly JP, Arendrup MC, et al. EUCAST technical note on the method for the determination of broth dilution minimum inhibitory concentrations of antifungal agents for conidia-forming moulds. Clin Microbiol Infect **2008**; 14:982–4.
14. Clinical and Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi: approved standard. 2nd ed. Available at: https://clsi.org/media/1455/m38a2_sample.pdf. Accessed 24 August 2017.
15. Reboli AC, Rotstein C, Pappas PG, et al.; Anidulafungin Study Group. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med **2007**; 356:2472–82.
16. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis **2007**; 45:883–93.
17. Mora-Duarte J, Betts R, Rotstein C, et al.; Caspofungin Invasive Candidiasis Study Group. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med **2002**; 347:2020–9.
18. Kuse ER, Chetchotisakd P, da Cunha CA, et al.; Micafungin Invasive Candidiasis Working Group. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a Phase III randomised double-blind trial. Lancet **2007**; 369:1519–27.
19. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet **2005**; 366:1435–42.
20. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. N Engl J Med **1994**; 331:1325–30.
21. Smith J, Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother **2006**; 50:1570–2.
22. Wang JF, Xue Y, Zhu XB, Fan H. Efficacy and safety of echinocandins versus triazoles for the prophylaxis and treatment of fungal infections: a meta-analysis of RCTs. Eur J Clin Microbiol Infect Dis **2015**; 34:651–9.