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

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Summary

Background **Isavuconazole is a novel triazole with broad-spectrum antifungal activity. The SECURE trial assessed efficacy and safety of isavuconazole versus voriconazole in patients with invasive mould disease.**

Methods **This was a phase 3, double-blind, global multicentre, comparative-group study. Patients with suspected invasive mould disease were randomised in a 1:1 ratio using an interactive voice–web response system, stratified by geographical region, allogeneic haemopoietic stem cell transplantation, and active malignant disease at baseline, to receive isavuconazonium sulfate 372 mg (prodrug; equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily) or voriconazole (6 mg/kg intravenously twice daily on day 1, 4 mg/kg intravenously twice daily on day 2, then intravenously 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onwards). We tested non-inferiority of the primary efficacy endpoint of all-cause mortality from first dose of study drug to day 42 in patients who received at least one dose of the study drug (intention-to-treat [ITT] population) using a 10% non-inferiority margin. Safety was assessed in patients who received the first dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00412893.**

Findings **527 adult patients were randomly assigned (258 received study medication per group) between March 7, 2007, and March 28, 2013. All-cause mortality from first dose of study drug to day 42 for the ITT population was 19% with isavuconazole (48 patients) and 20% with voriconazole (52 patients), with an adjusted treatment difference of –1·0% (95% CI –7·8 to 5·7). Because the upper bound of the 95% CI (5·7%) did not exceed 10%, non-inferiority was shown. Most patients (247 [96%] receiving isavuconazole and 255 [98%] receiving voriconazole) had treatment-emergent adverse events (p=0·122); the most common were gastrointestinal disorders (174 [68%] *vs* 180 [69%]) and infections and infestations (152 [59%] *vs* 158 [61%]). Proportions of patients with treatment-emergent adverse events by system organ class were similar overall. However, isavuconazole-treated patients had a lower frequency of hepatobiliary disorders (23 [9%] *vs* 42 [16%]; p=0·016), eye disorders (39 [15%] *vs* 69 [27%]; p=0·002), and skin or subcutaneous tissue disorders (86 [33%] *vs* 110 [42%]; p=0·037). Drug-related adverse events were reported in 109 (42%) patients receiving isavuconazole and 155 (60%) receiving voriconazole (p<0·001).**

Interpretation **Isavuconazole was non-inferior to voriconazole for the primary treatment of suspected invasive mould disease. Isavuconazole was well tolerated compared with voriconazole, with fewer study-drug-related adverse events. Our results support the use of isavuconazole for the primary treatment of patients with invasive mould disease.**

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Introduction

Invasive mould disease represents a challenge, especially in patients with haematological malignant disease and haemopoietic stem cell transplantation, solid organ transplant recipients, and patients in intensive-care units.[1] Invasive mould disease still accounts for substantial mortality in these patients.[1,2]

The available range of antifungal drugs that are active against mould disease has shortcomings. Polyenes, once the mainstay of anti-mould therapy, now have a limited role because of toxicity concerns and the requirement for intravenous administration.[3] Echinocandins have an excellent safety profile; however, there is relatively little experience in their use for the primary treatment of invasive mould disease.[4,5] Posaconazole is licensed for the salvage treatment of invasive mould disease,[6] but data to support its first-line use are lacking. Voriconazole has been endorsed by international guidelines as primary treatment for invasive aspergillosis,[2,7,8] as well as some other mould infections.[9] However, drug interactions, pharmacokinetic variability, short-term acute toxicities (including photopsia, visual

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Research in context

Evidence before this study

We searched PubMed without time or language limitation with the search criteria ("invasive"[All Fields] AND ("aspergillosis"[MeSH Terms] OR "aspergillosis"[All Fields])) AND (("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) AND (("registries"[MeSH Terms] OR "registries"[All Fields] OR "trial"[All Fields])), up to October, 2015. 55 references were found, of which 36 were categorised as clinical trials. By excluding prevention trials and studies in patients with *Candida* infections only, 15 clinical trials or cohorts or registries were identified, with nine studies before 2003. Mortality in all trials was similarly high. Only one study was well powered, prospective, and randomised-controlled prior to the beginning of the trial. Overall 10 studies were non-randomised or uncontrolled in nature; four studies were identified in patients refractory or intolerant to therapy; three trials included only patients with non-haematological disease (mainly solid organ transplant recipients). The only study published before 2003 was that by Herbrecht and colleagues (2002), which showed significantly improved outcomes, including survival advantage of voriconazole compared with conventional amphotericin B.

Added value of this study

SECURE is a prospective, double-blind, randomised, global trial demonstrating that the novel triazole isavuconazole is non-inferior to voriconazole for the primary treatment of invasive aspergillosis and disease caused by other moulds. Additionally, isavuconazole was well tolerated compared with voriconazole, with significantly fewer study drug-related adverse events and adverse events of the skin, eye, and hepatobiliary systems.

Implications of all the available evidence

Voriconazole is the current gold standard for treatment of invasive aspergillosis but is limited by drug–drug interactions and safety concerns. Moreover, many non-*Aspergillus* moulds, such as the agents of mucormycosis, are often resistant to voriconazole. This trial offers strong evidence that isavuconazole is an appropriate alternative to voriconazole for the primary treatment of invasive aspergillosis and other mould disease.

hallucinations, and abnormalities in liver function), long-term toxicities (such as skin carcinogenesis and fluorosis), concerns about β-cyclodextrin administration in the setting of impaired renal function, and recommendations for therapeutic drug monitoring have been problematic for patients.[10]

The water-soluble prodrug isavuconazonium sulfate was developed to facilitate intravenous administration without the need for potentially nephrotoxic excipients such as β-cyclodextrin. Isavuconazole, the active moiety, displays excellent bioavailability (roughly 98%)[11] after oral administration without any clinically relevant food effects. Isavuconazole is a broad-spectrum triazole that has demonstrated potent activity in animal models of invasive aspergillosis,[12] mucormycosis,[13] invasive candidiasis,[14] and cryptococcosis.[15] Isavuconazonium sulfate was approved in 2015 by the US Food and Drug Administration (FDA) for the treatment of invasive aspergillosis and invasive mucormycosis,[16] and by the European Medicines Agency for the treatment of invasive aspergillosis and of mucormycosis when amphotericin B is inappropriate.[17]

We conducted a phase 3, double-blind trial to compare the efficacy and safety of intravenous and oral formulations of isavuconazole to voriconazole for the primary treatment of invasive mould disease caused by *Aspergillus* spp or other filamentous fungi (the SECURE trial).

Methods

Study design and participants

This was a phase 3, randomised, double-blind, international, multicentre, non-inferiority study of isavuconazole versus voriconazole for the primary treatment of invasive mould disease, conducted from 2007 to 2013. Enrolment was suspended from January, 2009, to March, 2011, to allow for completion of non-clinical toxicity studies and licensing activities.

Patients 18 years or older were eligible if they were considered to have invasive mould disease by meeting the criteria for proven, probable, or possible invasive mould disease caused by *Aspergillus* spp or other filamentous fungi.[18] Key exclusion criteria were hepatic dysfunction (bilirubin ≥3×upper limit of normal [ULN], alanine transaminase or aspartate transaminase ≥5×ULN, cirrhosis or chronic hepatic failure), or moderate to severe renal dysfunction (calculated creatinine clearance <50 mL/min). Mycological criteria for diagnosis of invasive mould disease included detection by cytology or direct microscopy of fungal elements indicating a mould, or by culture. A positive serum galactomannan test (single optical density index value ≥0·7 or two consecutive values ≥0·5) was regarded as mycological evidence for aspergillosis, except in patients receiving concomitant amoxicillin-clavulanate, piperacillin-tazobactam, or gluconate-containing plasma expanders. Galactomannan detection in broncho-alveolar lavage fluid was not accepted as a mycological criterion for probable aspergillosis because the galactomannan assay in fluid had not yet been approved by the US FDA. After the protocol was drafted, but before unblinding of the locked database, the FDA provided revised galactomannan criteria for probable disease. Subsequently, a prespecified analysis was performed using these criteria (appendix).[19] Full inclusion and exclusion criteria are detailed in the appendix.

Independent ethics committees or institutional review boards at participating sites approved the protocol and all

amendments. The study was conducted in accordance with the Declaration of Helsinki (2000) and the International Conference on Harmonisation Guidelines for Good Clinical Practice. For all sites, approval of the protocol was obtained from the governmental authorities. Written informed consent was obtained from patients or their legally authorised representatives before initiation of any trial procedures.

Randomisation and masking

Patients were centrally randomised using a third-party interactive response computer system to assign them to receive isavuconazole or voriconazole in a 1:1 allocation. Randomisation was performed using a block size of four and was stratified by geographical region, allogeneic haemopoietic stem cell transplantation, and active malignancy at study entry. All trial site personnel involved in patient care and non-site personnel were blinded to treatment assignment, except pharmacy personnel responsible for medication preparation. Placebo was used to maintain blinding by matching the frequency of daily dosing. Blinding codes and randomisation lists were prepared by the study funder's designee.

Procedures

Patients assigned to isavuconazole received isavuconazonium sulfate 372 mg (equivalent to isavuconazole 200 mg) intravenously three times a day on days 1 and 2, followed by either intravenous or oral isavuconazole 200 mg once daily, followed in 12 h by a corresponding placebo (excipient only) from day 3 onwards. Patients allocated to voriconazole received the labelled dose: 6 mg/kg intravenously twice daily on day 1, followed by 4 mg/kg intravenously twice daily on day 2. Voriconazole was given either intravenously (4 mg/kg twice daily) or orally (200 mg twice daily) from day 3 onwards. The protocol did not allow therapeutic drug monitoring (to maintain study blinding) and stipulated that the maximum treatment duration was to be 84 days.

Assessment of clinical symptoms and physical findings was conducted at screening and at all visits after day 3, including days 7, 14, 28, 42, 63, 84, end of treatment (if before day 84), and 4 weeks after end of treatment. Radiological and mycological assessments were performed between screening and day 7, on days 42 and 84, and at end of treatment. Additional radiological and mycological assessments were performed during treatment and follow-up if clinically indicated.

An independent data review committee, consisting of infectious disease experts who were masked to treatment allocation, was established to independently adjudicate the diagnosis of invasive mould disease at enrolment (including data up to day 7 as relevant). They also assessed clinical, mycological, radiological, and overall responses, at end of treatment, day 42, and day 84 (appendix). Consensus of three members of the data review committee per case was required for adjudication. A central radiologist, masked to treatment allocation, initially determined radiological responses at prespecified timepoints. Patients with radiological evidence at baseline but without post-baseline radiological follow-up were assumed not to have achieved treatment success.

Outcomes

The intention-to-treat (ITT) population, the primary efficacy population, included all patients who were enrolled, randomly assigned, and received at least one dose of medication. The modified intention-to-treat (mITT) population consisted of ITT patients with proven or probable invasive mould disease, as determined by the data review committee. The mycological intention-to-treat (myITT) population was a subset of the mITT population with proven or probable invasive aspergillosis (as assessed by the data review committee). The safety population included all enrolled patients who received their first dose of study drug, and is analysed by drug received (irrespective of study group assignment). We also assessed the primary outcome in a per-protocol population, excluding patients who met prespecified classification criteria (eg, met key exclusionary criteria, received at least three consecutive days of prohibited concomitant medications, or received less than 7 days of study drug). Additionally, we assessed the primary endpoint in a strictly defined intention-to-treat population (including all patients who were enrolled and randomly assigned, irrespective of whether they received any study drug) in a post-hoc analysis.

The primary efficacy endpoint was all-cause mortality from first dose of study drug to day 42 in the ITT population. The ITT population was chosen because it is representative of a population of patients requiring antifungal therapy in a real-world setting. Patients with unknown survival status were counted as deaths, defined by the date of last known follow-up; this approach was approved by the FDA. The key secondary endpoint was overall response (as assessed by the data review committee) at end of treatment in the mITT population (appendix). Other secondary endpoints included all-cause mortality from first dose of study drug to day 84, overall, clinical, mycological, and radiological responses (as assessed by the data review committee) on day 42, day 84, and end of treatment, as well as safety and tolerability.

Investigators evaluated safety and tolerability by monitoring adverse events and findings from physical examinations, vital signs, laboratory tests, electrocardiogram, and concomitant medication or surgery. Treatment-emergent adverse events were defined as an adverse event starting or worsening after first study drug administration until 28 days after the last dose. Study-drug-related adverse events included those reported as remotely, possibly, or probably related to the study drug by the blinded investigator.

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See **Online** for appendix

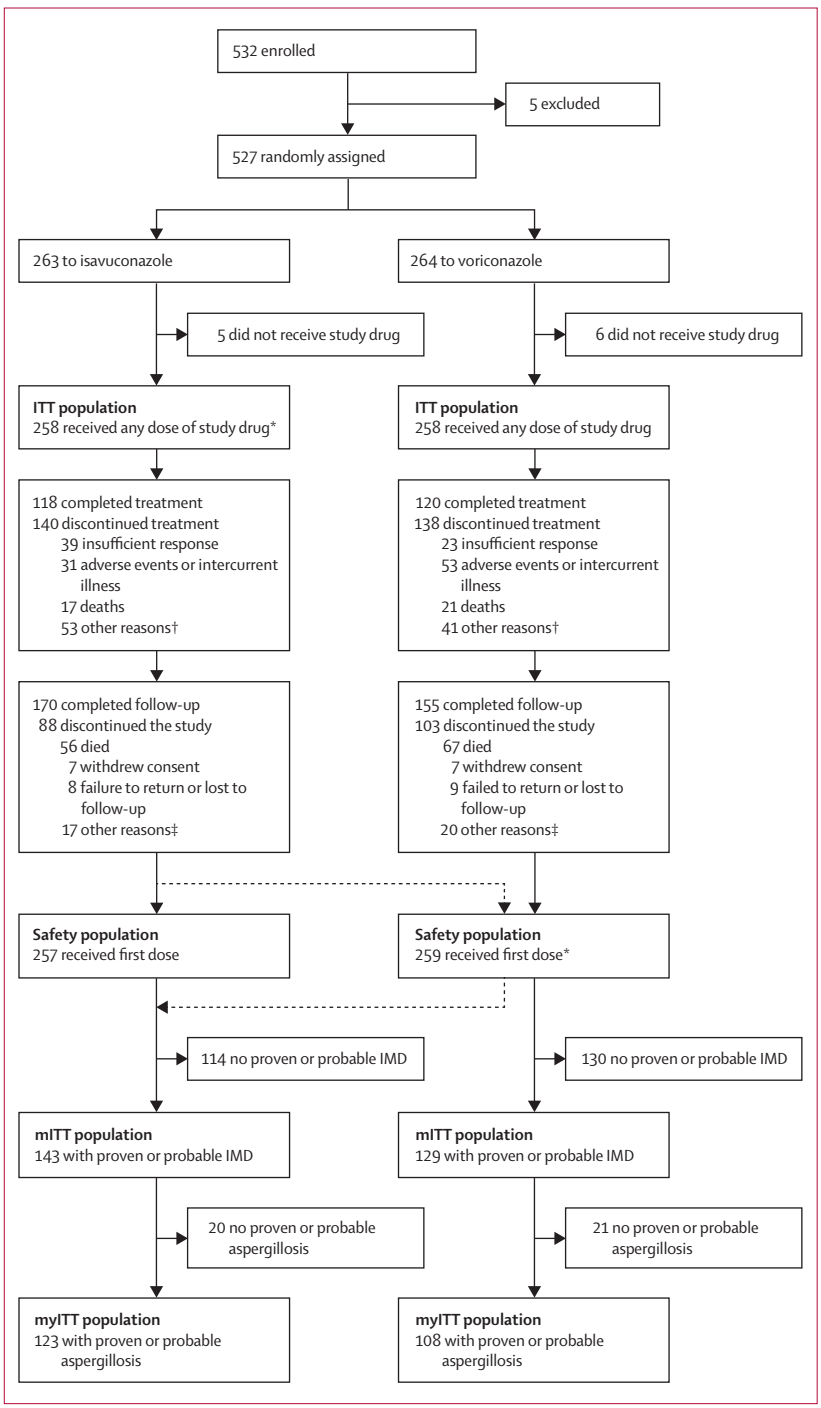

Figure 1: **Trial profile**
Enrolled refers to patients who provided written informed consent. IMD=invasive mould disease. ITT=intention to treat; all randomised patients who received study drug. mITT=modified intention to treat; ITT patients with proven or probable invasive mould disease. myITT=mycological intention to treat; mITT patients with proven or probable invasive aspergillosis. *Including one patient assigned to isavuconazole who received voriconazole for 7 days followed by isavuconazole oral study drug; this patient is included in the isavuconazole efficacy analysis and the voriconazole safety analysis. †Including failure to return or loss to follow-up, violation of selection at entry, other protocol deviation, did not cooperate, refused treatment, withdrew consent, and administrative or other. ‡Including adverse events or intercurrent illness and administrative or other.

Statistical analyses

Our sample size calculation was based on the primary efficacy endpoint, all-cause mortality in the ITT population from first dose of study drug to day 42. Roughly 255 patients per group were required for an 80% power to demonstrate that the upper limit of the 95% CI for a treatment difference was 10% or less (prespecified non-inferiority margin for this endpoint). This calculation was based on a one-sided, large-sample, normal-approximation and non-inferiority test at a 2·5% significance level. A 20% mortality rate was assumed for both drugs in the primary efficacy population.

To evaluate the efficacy (mortality endpoint) of amphotericin B over placebo in patients with invasive fungal disease caused by *Aspergillus* spp, the funder conducted a meta-analysis using historical individual patient data from 90 articles dating from 1952 to 2006. A 10% non-inferiority margin was established for the all-cause mortality rate from first dose of study drug to day 42 in untreated patients (ie, placebo) of 84·8% (95% CI 75·1 to 94·5). This estimation was further supported by a mortality rate of 100% in untreated patients reported by Denning.[20] The historical all-cause mortality rate from first dose of study drug to day 42 for voriconazole was 18·8% (95% CI 12·4 to 25·1), on the basis of a randomised comparative study assessing voriconazole and amphotericin B.[21] A conservative estimate of effect size for voriconazole compared with untreated (placebo) patients with invasive aspergillosis for all-cause mortality from first dose of study drug to day 42 was 50% (lower bound of placebo 95% CI minus upper bound of voriconazole 95% CI). Therefore, a 10% non-inferiority margin would provide statistical evidence that isavuconazole is superior to placebo, preserving more than 80% of the estimated voriconazole treatment effect. In a 2009 workshop on hospital-acquired and ventilator-associated pneumonia sponsored by the FDA, the Infectious Diseases Society of America, the American Thoracic Society, the Society of Critical Care Medicine, and the American College of Chest Physicians, it was proposed that a 10% non-inferiority margin for all-cause mortality in serious infections would be clinically acceptable.[22]

Adjusted treatment difference was calculated by a stratified Cochran-Mantel-Haenszel method with the randomisation strata of geographical region, allogeneic haemopoietic stem cell transplantation status, and active malignancy status. The 95% CI for the adjusted treatment difference was calculated on the basis of a normal approximation. Treatment-by-subgroup interaction (age, sex, race, ethnic origin, baseline neutropenic status, body-mass index, glomerular filtration rate, and enrolment period) was evaluated using a logistic regression according to the prespecified statistical significance value of $p<0·15$. For assessment of treatment-emergent adverse events, we did a prespecified comparison between the proportions of treatment-emergent adverse events reported in each system organ class between treatment groups, based on Fisher's exact

	Isavuconazole	Voriconazole
ITT population		
Number of patients	258	258
Age, years	51·1 (16·2)	51·2 (15·9)
Sex		
Men	145 (56%)	163 (63%)
Women	113 (44%)	95 (37%)
Geographical region		
North America	30 (12%)	28 (11%)
Western Europe, Australia, and New Zealand	105 (41%)	107 (41%)
Other*	123 (48%)	123 (48%)
Mean body-mass index, kg/m²	24·2	23·7
Risk factor		
Haematological malignancy	211 (82%)	222 (86%)
Allogeneic BMT/HSCT	54 (21%)	51 (20%)
Active malignancy at study entry	173 (67%)	187 (72%)
Absolute neutrophil count <500/mm³	163 (63%)	175 (68%)
Use of T-cell immunosuppressants	111 (43%)	109 (42%)
Use of corticosteroids	48 (19%)	39 (15%)
eGFR-MDRD		
<60 mL/min per 1·73 m²	20 (8%)	33 (13%)
≥60 mL/min per 1·73 m²	231 (92%)	217 (87%)
Missing	7	8
Primary underlying disease†		
Acute myeloid leukaemia	99 (38%)	126 (49%)
Acute lymphoblastic leukaemia	30 (12%)	24 (9%)
Lymphoma	33 (13%)	24 (9%)
Myelodysplastic syndrome	23 (9%)	14 (5%)
Chronic lymphocytic leukaemia	10 (4%)	13 (5%)
Aplastic anaemia	9 (3%)	7 (3%)
Chronic myeloid leukaemia	5 (2%)	8 (3%)
Multiple myeloma	5 (2%)	7 (3%)
Chronic obstructive pulmonary disease	5 (2%)	3 (1%)
Hodgkin's disease	2 (1%)	3 (1%)
Diabetes mellitus	4 (2%)	0
Certainty of diagnosis‡		
Proven invasive mould disease	29 (11%)	36 (14%)
Probable invasive mould disease	114 (44%)	93 (36%)
Possible invasive mould disease	88 (34%)	108 (42%)
No invasive mould disease	27 (10%)	21 (8%)
Mycological criteria		
No mycological evidence available§	92 (36%)	113 (44%)
Serum galactomannan positive	91 (35%)	94 (36%)
Non-sterile cytology, direct microscopy, or culture evidence of invasive mould disease	59 (23%)	39 (15%)
Sterile-site cytology, histopathology, or culture evidence of invasive mould disease	30 (12%)	34 (13%)
Autopsy	1 (<1%)	7 (3%)
mITT population		
Number of patients	143	129
Pathogen causing disease		
Aspergillus spp only	49 (34%)	39 (30%)
A fumigatus	32 (22%)	21 (16%)
A flavus	10 (7%)	12 (9%)
A niger	6 (4%)	2 (2%)
A terreus	4 (3%)	2 (2%)
A usti	0	1 (1%)
Aspergillus spp¶	1 (1%)	3 (2%)
A sydowi	1 (1%)	0
Aspergillus plus other filamentous fungi	3 (2%)	1 (1%)
A fumigatus	0	1 (1%)
A flavus	1 (1%)	0
A terreus	1 (1%)	0
Aspergillus spp¶	1 (1%)	0
Lichtheimia corymbifera	1 (1%)	0
Lichtheimia spp¶	1 (1%)	0
Scedosporium spp¶	1 (1%)	1 (1%)
Non-*Aspergillus* spp only	5 (3%)	6 (5%)
Rhizopus spp¶	1 (1%)	0
Mucor spp¶	0	1 (1%)
Fusarium solani	2 (1%)	0
Fusarium spp¶	1 (1%)	3 (2%)
Exserohilum rostratum	0	1 (1%)
Talaromyces marnefei	0	1 (1%)
Talaromyces spp¶	0	1 (1%)
Trichosporon inkin	1 (1%)	0
Filamentous fungi (no species identified)	14 (10%)	15 (12%)
Galactomannan positive only‖	72 (50%)	68 (53%)
Location of disease		
LRTD only	116 (81%)	107 (83%)
LRTD plus other organ	12 (8%)	15 (12%)
Non-LRTD only	15 (10%)	7 (5%)

(Table 1 continues in next column)

(Continued from previous column)

Data are n, n (%), or mean (SD), unless otherwise indicated. ITT=intention to treat; all randomised patients who received study drug. BMT=bone marrow transplantation. HSCT=haemopoietic stem cell transplantation. eGFR-MDRD=estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula. mITT=modified intention to treat; ITT patients with proven or probable invasive mould disease. LRTD=lower respiratory tract disease. *Other regions consist of Argentina, Brazil, Chile, China, Egypt, Hungary, India, Israel, Malaysia, Mexico, Poland, Russia, South Korea, Thailand, and Turkey. †Primary underlying disease in ≥1% of patients. ‡As assessed by the data review committee. §Fungal species were isolated from some patients in this group but these organisms were considered as colonisers. No mycological evidence does not include patients with possible invasive mould disease. ¶No further information. ‖Two consecutive serum galactomannan values ≥0·5 or at least one serum galactomannan value ≥0·7, as defined in the trial protocol.

Table 1: **Demographics and baseline characteristics**

test. Continuous data were summarised descriptively. Categorical data were summarised by number and percentage of patients within each category. All data analyses were done with SAS version 9.3.

This trial is registered with ClinicalTrials.gov, number NCT00412893.

	Isavuconazole	Voriconazole	Adjusted treatment difference (95% CI)*
All-cause mortality			
ITT population	258	258	
Day 42 all-cause mortality	48 (19%)	52 (20%)	−1·0% (−7·8 to 5·7)
Deaths	45 (17%)	50 (19%)	..
Unknown survival status†	3 (1%)	2 (1%)	..
Day 84 all-cause mortality	75 (29%)	80 (31%)	−1·4% (−9·2 to 6·3)
Deaths	72 (28%)	75 (29%)	..
Unknown survival status†	3 (1%)	5 (2%)	..
mITT population	143	129	
Day 42 all-cause mortality	28 (20%)	30 (23%)	−2·6% (−12·2 to 6·9)
Day 84 all-cause mortality	43 (30%)	48 (37%)	−5·5% (−16·1 to 5·1)
myITT population	123	108	
Day 42 all-cause mortality	23 (19%)	24 (22%)	−2·7% (−12·9 to 7·5)
Day 84 all-cause mortality	35 (28%)	39 (36%)	−5·7% (−17·1 to 5·6)
Possible invasive mould disease	88	108	
Day 42 all-cause mortality	15 (17%)	19 (18%)	−0·5% (−12·3 to 11·2)‡
Day 84 all-cause mortality	24 (27%)	27 (25%)	2·3% (−11·2 to 15·8)‡
DRC-assessed response (mITT population)			
Overall response at EOT§	143	129	
Success	50 (35%)	47 (36%)	1·6% (−9·3 to 12·6)
Complete	17 (12%)	13 (10%)	..
Partial	33 (23%)	34 (26%)	..
Failure¶	93 (65%)	82 (64%)	..
Stable	42 (29%)	33 (26%)	..
Progression	51 (36%)	49 (38%)	..
Clinical response at EOT§	85/137 (62%)	73/121 (60%)	0·4% (−10·6 to 11·5)
Mycological response at EOT§	54/143 (38%)	53/129 (41%)	3·8% (−7·4 to 15·1)
Radiological response at EOT§	41/141 (29%)	42/127 (33%)	5·7% (−4·9 to 16·3)

Data are n, n (%), or n/N (%).The non-inferiority margin was 10% for adjusted treatment differences between isavuconazole and voriconazole; an upper 95% CI less than 10% suggests that isavuconazole is non-inferior to voriconazole. ITT=intention to treat; all randomised patients who received study drug. mITT=modified intention to treat; ITT patients with proven or probable invasive mould disease. myITT=mycological intention to treat; mITT patients with proven or probable invasive aspergillosis. EOT=end of treatment. *Isavuconazole minus voriconazole for all-cause mortality; voriconazole–isavuconazole for overall, clinical, mycological, and radiological responses. †Patients with unknown survival status were counted as deaths. ‡Crude treatment difference (isavuconazole minus voriconazole) was calculated for possible invasive mould disease and its 95% CI was based on a normal approximation. §Assessed in the ITT population. Favourable mycological response was defined as eradication or presumed eradication. ¶Death or patients with missing information assumed not to have achieved treatment success.

Table 2: **Efficacy outcomes**

Role of funding source

The funders of the study, Astellas Pharma Global Development and Basilea Pharmaceutica International, were involved in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 7, 2007, and March 28, 2013, we recruited patients from 102 centres from 26 countries located across North and South America, Europe, the Middle East, southeast Asia, east Asia, and Pacific regions. 532 patients gave consent, of whom 527 were randomly assigned. 11 patients did not receive any study drug (five did not meet entry criteria, four withdrew consent, and two died), and were excluded from the ITT population, which included 516 patients (n=258 for each treatment group; figure 1). The mITT population consisted of 143 patients in the isavuconazole and 129 patients in the voriconazole group. The myITT population included 123 patients in the isavuconazole group and 108 patients in the voriconazole group.

Baseline demographics and underlying disorders in the ITT population are shown in table 1; there were fewer men in the isavuconazole group and more patients with acute myeloid leukaemia in the voriconazole group. The most common underlying disorder was haematological malignant disease (433 patients; 84%). 105 (20%) patients were recipients of allogeneic haemopoietic stem cell transplantation, and 338 (66%) had neutropenia. The mITT baseline characteristics were similar to those in the ITT population (data not shown).

At baseline, as assessed by the data review committee, 65 (13%) patients had proven invasive mould disease and 207 (40%) had probable invasive mould disease. Possible invasive mould disease was diagnosed in 196 (38%) patients; 48 (9%) had no evidence of invasive mould disease. When *Aspergillus* was cultured as the only mould at baseline, *A fumigatus* (n=53), *A flavus* (n=22), *A niger* (n=8), and *A terreus* (n=6) were the most commonly identified species.

Total treatment duration for the safety population was similar to that of the ITT population. The median durations of total dosing for isavuconazole were 45 days (IQR 13–83; five intravenous, 60 oral) and for voriconazole were 47 days (IQR 13–83; five intravenous, 53 oral). 400 (78%) patients switched from intravenous to oral dosing (194 for isavuconazole and 206 for voriconazole). At day 14, isavuconazole trough plasma concentrations ranged from 813·1 ng/mL to 9952·5 ng/mL, with a mean of 3354 ng/mL (SD 1816 ng/mL) (appendix).

Of 258 patients who received isavuconazole, 118 completed treatment and 140 discontinued treatment. 170 completed follow-up (28 days after end of treatment), and 88 discontinued the study. Of 258 patients who received voriconazole, 120 completed treatment and 138 discontinued treatment. 155 patients completed follow-up and 103 discontinued the study.

For the primary efficacy endpoint, all-cause mortality from first dose of study drug to day 42 in the ITT population was 19% (48 patients) for isavuconazole and 20% (52 patients) for voriconazole (adjusted treatment difference –1·0%, 95% CI –7·8 to 5·7; table 2). The study met the primary objective of demonstrating non-inferiority of isavuconazole versus voriconazole, because the upper limit of the 95% CI (5·7%) was lower than the prespecified 10% non-inferiority margin. All-cause mortality from first dose of study drug to day 42 across the mITT and myITT subpopulations supported this

conclusion (table 2). No treatment-by-subgroup factor interaction was noted according to the prespecified significance value of p<0·15.

For the per-protocol analysis, all-cause mortality from first dose of study drug to day 42 was 15% (26 of 172 patients) for isavuconazole and 18% (31 of 175 patients) for voriconazole (adjusted treatment difference –2·6%, 95% CI –10·3 to 5·1).

For the key secondary efficacy endpoint, overall response at end of treatment (as assessed by the data review committee) in the mITT population was similar for isavuconazole and voriconazole (complete response in 35% [50/143] patients *vs* 36% [47/129]; table 2). Clinical, mycological, and radiological responses at end of treatment, as assessed by the data review committee, were similar in the mITT population (table 2). 31 patients in the isavuconazole group and 29 patients in the voriconazole group were assumed to have not achieved treatment success because they had no imaging after baseline.

Mortality from first dose of study drug to day 84 using the Kaplan-Meier method was similar between treatment groups in both the ITT population (treatment difference –1·1%, 95% CI –8·9 to 6·7; figure 2) and the mITT population (–5·7%, 95% CI –16·9 to 5·5; appendix). An analysis of mortality using the revised galactomannan criteria is provided in the appendix.

Nearly all patients in the safety population had at least one treatment-emergent adverse event (247 [96%] receiving isavuconazole and 255 [98%] receiving voriconazole; p=0·122). The five most common events that occurred in at least 5% of patients in either group were nausea, vomiting, diarrhoea, pyrexia, and hypokalaemia (appendix).

Proportions of patients with treatment-emergent adverse events by system organ classes were similar for most categories (table 3), although isavuconazole-treated patients had a significantly lower frequency of hepatobiliary disorders, eye disorders, and skin or subcutaneous tissue disorders. The proportion of patients with serious treatment-emergent adverse events was similar between treatment groups.

Significantly fewer patients reported events considered drug-related by the investigator for isavuconazole than for voriconazole (109 [42%] *vs* 155 [60%]; p<0·001). Additionally, fewer isavuconazole-treated patients experienced drug-related treatment-emergent adverse events within the following system organ classes: hepatobiliary disorders, laboratory investigations, eye disorders, and psychiatric disorders. Permanent drug discontinuation due to treatment-emergent adverse events were less common with isavuconazole (37 [14%] *vs* 59 [23%]). Permanent drug discontinuation due to drug-related adverse events was lower for isavuconazole than for voriconazole (21 [8%] *vs* 35 [14%]).

Differences between isavuconazole and voriconazole for the overall analysis of treatment-emergent adverse events and serious treatment-emergent adverse events were consistent with those of the subgroup analysis by age, sex, race, ethnic origin, geographical region, allogeneic transplantation, active malignancy status, and neutropenia (data not shown). Analyses of other safety parameters, including laboratory parameters and ECG, revealed no clinically relevant trends (data not shown).

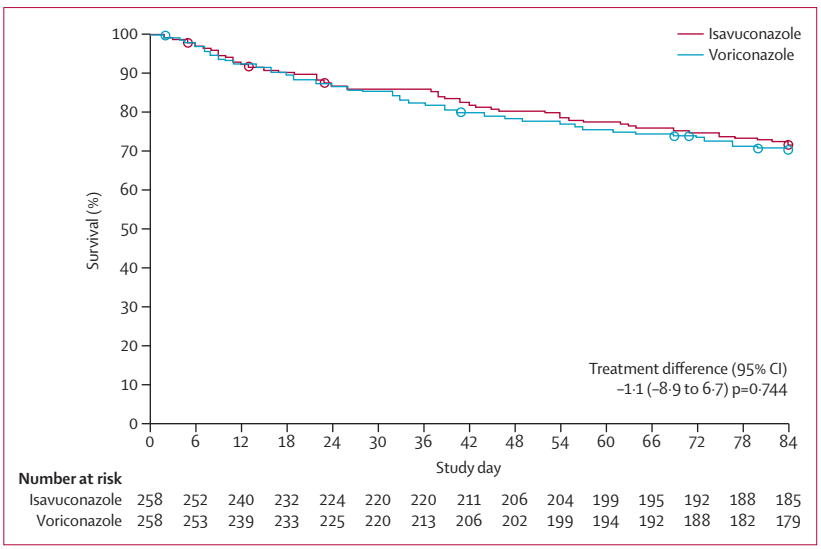

Figure 2: **Survival from first dose of study drug to day 84**
Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

In a post-hoc analysis of the strictly defined intention-to-treat population (all patients randomly assigned, irrespective of whether they received the study drug), all-cause mortality from first dose of study drug to day 42 was 20% (53 of 263 patients) for isavuconazole and 22% (57 of 264 patients) for voriconazole (adjusted treatment difference –1·1%, 95% CI –7·9 to 5·7).

Discussion

In this double-blind, randomised trial, we compared the efficacy and safety of intravenous and oral formulations of two mould-active azoles for the treatment of invasive aspergillosis and other mould infections. Our study demonstrates that isavuconazole is non-inferior to voriconazole in patients suspected of having invasive mould disease, but showed significantly fewer drug-related adverse events and fewer drug discontinuations.

Our primary analysis, 42-day mortality in the ITT population, met the prespecified non-inferiority margin of 10% (adjusted treatment difference –1·0%, 95% CI –7·8 to 5·7). The equivalent analysis in the mITT population, consisting of patients with proven or probable invasive mould disease, was –2·6% (95% CI –12·2 to 6·9); because the upper 95% CI was less than 10%, this finding also supports non-inferiority of isavuconazole versus voriconazole in this population. However, the study was powered to show a non-inferiority margin for the primary endpoint only; the denominator

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0·122
Gastrointestinal disorders	174 (68%)	180 (69%)	0·705
Infections and infestations	152 (59%)	158 (61%)	0·719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0·658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0·859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0·289
Nervous system disorders	95 (37%)	89 (34%)	0·582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0·037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0·357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0·703
Psychiatric disorders†	70 (27%)	86 (33%)	0·151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0·495
Vascular disorders	67 (26%)	77 (30%)	0·378
Renal and urinary disorders	55 (21%)	58 (22%)	0·832
Cardiac disorders	43 (17%)	57 (22%)	0·148
Eye disorders‡	39 (15%)	69 (27%)	0·002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0·526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0·016¶
Immune system disorders	20 (8%)	25 (10%)	0·533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0·101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0·846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0·373
Endocrine disorders	5 (2%)	3 (1%)	0·503
Congenital, familial, and genetic disorders	3 (1%)	2 (1%)	0·685
Social circumstances	0	1 (<1%)	>0·999

Coded in MedDRA 12.1. Adverse events (preferred terms) reported in safety population (all patients who received first dose of study drug). *Rash, 17/257 (7%) *vs* 28/259 (11%); erythema, 9/257 (4%) *vs* 15/259 (6%); skin lesion, 4/257 (2%) *vs* 8/259 (3%); and drug eruption, 3/257 (1%) *vs* 11/259 (4%). †Hallucinations, 6/257 (2%) *vs* 11/259 (4%); visual hallucinations, 3/257 (1%) *vs* 11/259 (4%); and agitation, 2/257 (1%) *vs* 7/259 (3%). ‡Visual impairment, 4/257 (2%) *vs* 19/259 (7%); photophobia, 2/257 (1%) *vs* 6/259 (2%); reduced visual acuity, 1/257 (<1%) *vs* 6/259 (2%); and retinal haemorrhage 0/257 (0%) *vs* 5/259 (2%). §Hyperbilirubinaemia, 5/257 (2%) *vs* 10/259 (4%); abnormal hepatic function, 4/257 (2%) *vs* 9/259 (3%); jaundice, 1/257 (<1%) *vs* 6/259 (2%); and cholestasis, 1/257 (<1%) *vs* 6/259 (2%). ¶Statistical significance at p≤0·05 (Fisher's exact test).

Table 3: **Treatment-emergent adverse events by system organ class**

was substantially smaller in the mITT population (n=272) than in the ITT population (n=516), which resulted in widened 95% CIs. Nevertheless, the upper 95% CI was also less than 10% for the mITT, myITT, per-protocol, and (post-hoc) strictly defined intention-to-treat populations, thereby providing strong support for the non-inferiority of isavuconazole versus voriconazole.

Voriconazole is currently recommended for the primary treatment of invasive aspergillosis on the basis of results from a study in which voriconazole significantly improved survival compared with amphotericin B deoxycholate.[21] In real-life registries, the first-line use of voriconazole has been consistently associated with improved response and decreased mortality attributable to invasive aspergillosis compared with other mould-active agents.[2,23] Voriconazole is also recommended for the primary treatment of some rare mould infections, but is not active against Mucorales.[9] It displays highly variable non-linear pharmacokinetics in adults, which has triggered recommendations for therapeutic drug monitoring.[10,24] By contrast, isavuconazole, which has activity against Mucorales,[13] demonstrates predictable and linear pharmacokinetics with low interpatient variability, making it an attractive alternative.[25]

Similar to a recent study in invasive aspergillosis, we used all-cause mortality at 6 weeks as the primary outcome measure.[26] This outcome was chosen because it provides the most objective and reproducible effect of therapy, and approximates best the attributable mortality, because deaths due to competing causes occur increasingly after 6 weeks.[27]

Overall response, our secondary endpoint, is traditionally used as the primary endpoint, but is less rigorous and more subjective. When analysing individual components of the data review committee-assessed overall response in our study, an inconsistency was noted between clinical response and radiological response rates. Indeed, as described previously,[28] radiographic evidence of response, the key driver of overall response, lagged behind clinical improvement. Mycological and radiological responses for patients with missing data were counted as failures, thereby ensuring any bias that was introduced was conservative.

In a large phase 3 trial of voriconazole, the overall response at week 12 was 53% (76/144) in the voriconazole group (median treatment duration for voriconazole 77 days [range 2–84]).[21] The overall response at end of treatment in our study was 36% (47/129) for voriconazole (median treatment duration 50 days [range 1–88]). This difference could be accounted for by different definitions of neutropenia (at baseline), inclusion of possible cases in the previous study, and by the more stringent response criteria of the SECURE trial.[29] It should be noted that the all-cause mortality rates in both studies were similar.[21]

As in previous studies,[26,30] patients with possible invasive mould disease were enrolled to include early diagnoses and provide early therapy. However, confirmation of invasive mould disease can take up to a week or may not be possible at all. With all available diagnostic data from the first study week, the data review committee confirmed that 53% of the ITT population had proven or probable invasive mould disease and could be included in the mITT analysis. Importantly, as per our protocol but contrary to current international consensus definitions[18] and studies mentioned previously,[26,30] galactomannan positivity of broncho-alveolar fluid alone was not accepted to upgrade possible cases to probable disease. Many ITT patients could not be included in the mITT population, which, similar to previous trials, might have increased the probability of meeting the non-inferiority margin. However, examination of the mITT population suggests that the non-inferiority margin would have been met in that population. Nevertheless, enrolment of patients with possible invasive mould disease at study entry reflects the real-life strategy of early initiation of antifungal treatment.

The most important differentiating feature between isavuconazole and voriconazole in the current study was the tolerability and safety profile of isavuconazole, which could allow safer therapy. Voriconazole therapy is characterised by a narrow therapeutic window and an established association between elevated concentrations and neurotoxic,[31] hepatic, and visual adverse events.[32] These adverse events, although usually reversible, often lead to premature discontinuation of the drug. Of the drug-related hepatobiliary adverse events reported in our study, 26 (10%) were noted in the voriconazole group compared with five (2%) in the isavuconazole group. In this study, key adverse events known to be related to voriconazole (including eye, hepatic, and skin disorders) and discontinuations due to adverse events were significantly less common among isavuconazole-treated patients. Given the double-blind nature of the study, this suggests a true difference in the safety features of the two azoles. Whether the higher proportion of adverse events with voriconazole was due to supratherapeutic drug exposure cannot be excluded without therapeutic drug monitoring; however, the effect of therapeutic drug monitoring on the incidence of these adverse events remains speculative.

The generalisability of our study is limited because of the exclusion of patients with AIDS, abnormal liver or renal function, and those receiving antifungal prophylaxis with a mould-active azole. Additionally, few patients with rare disorders for invasive mould disease were enrolled in the study.

During the conduct of this study, therapeutic drug monitoring for voriconazole—aimed at improving response by individualising dosage regimens, preventing drug-related adverse events, and early discontinuation—became the standard of care in some institutions. This study used the labelled dose of voriconazole and did not address the comparative efficacy of isavuconazole versus voriconazole administered at higher oral doses or with therapeutic drug monitoring. However, on the basis of the predictable and linear pharmacokinetics,[11] no evidence seems to suggest that therapeutic drug monitoring is required for isavuconazole.

We conclude that isavuconazole is non-inferior to voriconazole for the primary treatment of suspected invasive mould disease, with substantially fewer drug-related adverse events and discontinuations.

Contributors

JAM, KAM, TFP, OAC, MA, RH, D-GL, RMM, A-HS-H, and AJU proposed the key elements of study design. KAM, TFP, DPK, OAC, DN, RH, D-GL, VAM, GRT, RMM, A-HS-H, BZ, and AJU provided critical review of draft protocol and made significant contributions to the design. KAM, TFP, DPK, OAC, EJB, DN, RH, D-GL, VAM, GRT, BZ, and AJU had an advisory role on the study and provided significant direction to study development and conduct. JAM was the principal coordinating investigator; other investigators on this study were IIR, OAC, GR, MA, JWB, MG, WJH, RH, MK, D-GL, OL, IO, DS, and GRT. ML was the statistical lead on the study who oversaw the analyses. TFP, DPK, EJB, WH, OL, VAM, SS, and AJU were members of the data review committee. All authors were involved in the interpretation of data, drafting the work or revising it critically for important intellectual content, approved the final version of the publication and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

JAM reports grants and personal fees from Bio-Rad, personal fees and non-financial support from Astellas and Basilea, and grants, personal fees and non-financial support from Gilead Sciences, Merck Sharp and Dohme, and Pfizer, Inc. during the conduct of the study. IIR participated in an International Speakers' Bureau for Pfizer, outside the submitted work. KAM reports personal fees from Astellas during the conduct of the study; personal fees from Chimerix, Cidara, Genentech and Merck, and grants and personal fees from Astellas, outside the submitted work. In addition, KAM has a patent (diagnostics for aspergillosis) licensed to MycoMed Technologies. TFP reports personal fees from Astellas during the conduct of the study; grants from Astellas, personal fees from Pfizer, Scynexis, Toyama, and Viamet, and grants and personal fees from Merck, outside the submitted work. OAC is supported by the German Federal Ministry of Research and Education, has received research grants from 3M, Actelion, Astellas, AstraZeneca, Basilea, Bayer, Celgene, Cubist/Optimer, Duke University (NIH UM1AI104681), Genzyme, Gilead, GSK, Leeds University, Merck/MSD, Miltenyi, Pfizer, Quintiles, Viropharma, is a consultant to Anacor, Astellas, Basilea, Cidara, Da Volterra, Daiichi Sankyo, F2G, Genentech, Gilead, Merck/MSD, Merck Serono, Pfizer, Sanofi Pasteur, Scynexis, Seres, Summit, Vical, Vifor, and received lecture honoraria from Astellas, Basilea, Gilead, Merck/MSD, and Pfizer. EJB was a member of the Data Review Committee for Astellas, after the conduct of the study; EJB also reports personal fees from Cidara, Gilead, GLY-Pharma, and Pfizer, outside the submitted work. GR reports grants from Astellas during the conduct of the study, and grants from Pfizer, MSD, Gilead, and AstraZeneca, outside the submitted work. DN reports personal fees from Astellas during the conduct of the study; personal fees from Astellas and Roche Molecular Diagnostics, outside the submitted work; DN is currently an employee of Roche Diagnostics. JWB reports personal fees from Astellas, Merck, and Pfizer, outside the submitted work. WJH reports personal fees from Astellas, Basilea, and Gilead Sciences, and grants and personal fees from MSD Sharp & Dohme/Merck, and Pfizer, outside the submitted work. RH reports personal fees from Astellas, Basilea, Gilead Sciences, MSD, and Schering-Plough, and grants and personal fees from Pfizer during the conduct of the study. WH reports grants and personal fees from Astellas, F2G, and Pfizer, outside the submitted work. MK reports participation on advisory boards for Astellas and Pfizer, outside the submitted work. D-GL reports grants and personal fees from Astellas, Gilead Sciences, MSD, Pfizer, and Yuhan, outside the submitted work. OL reports grants from Astellas during the conduct of the study, and personal fees from Gilead, Pfizer, and Merck, outside the submitted work. VAM was a member of the Data Review Committee for Astellas, after the conduct of the study. DS reports grants from Astellas during the conduct of the study; grants, personal fees and non-financial support from Pfizer, as well as personal fees and non-financial support from MSD, outside the submitted work. SS reports grants from Astellas during the conduct of the study; grants from Astellas, Chimerix, Merck, Pfizer, Scynexis, and Viropharma, and personal fees from the Mycoses Study Group Education and Research Consortium, outside the submitted work. GRT was a member of the Data Review Committee, after the conduct of the study; he reports grants from Pfizer and Merck, outside the submitted work. AJU received personal fees and fees for travel, speakers' bureau and consultancy from Basilea, and grants, personal fees, and fees for travel, speakers' bureau and consultancy from Astellas during the conduct of the study; grants, personal fees and fees for travel, speakers' bureau and consultancy from MSD, Gilead Sciences and Pfizer, and personal fees from Boehringer Ingelheim, outside the submitted work. ML, RMM, and BZ are employees of Astellas Pharma Global Development, Inc. A-HS-H is an employee of Basilea Pharmaceutica International Ltd. DPK, MA, MG, and IO declare no competing interests.

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References

1 Bitar D, Lortholary O, Le Strat Y, et al. Population-based analysis of invasive fungal infections, France, 2001-2010. *Emerg Infect Dis* 2014; **20:** 1149–55.

2 Lortholary O, Gangneux JP, Sitbon K, et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007). *Clin Microbiol Infect* 2011; **17:** 1882–89.

3 Lanternier F, Lortholary O. Liposomal amphotericin B: what is its role in 2008? *Clin Microbiol Infect* 2008; **14** (suppl 4)**:** 71–83.

4 Enoch DA, Idris SF, Aliyu SH, Micallef C, Sule O, Karas JA. Micafungin for the treatment of invasive aspergillosis. *J Infect* 2014; **68:** 507–26.

5 Herbrecht R, Maertens J, Baila L, et al. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: an European Organisation for Research and Treatment of Cancer study. *Bone Marrow Transplant* 2010; **45:** 1227–33.

6 Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007; **44:** 2–12.

7 Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46:** 327–60.

8 Maertens J, Marchetti O, Herbrecht R, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 update. *Bone Marrow Transplant* 2011; **46:** 709–18.

9 Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others. *Clin Microbiol Infect* 2014; **20** (suppl 3)**:** 27–46.

10 Mikulska M, Novelli A, Aversa F, et al. Voriconazole in clinical practice. *J Chemother* 2012; **24:** 311–27.

11 Schmitt-Hoffmann A, Roos B, Heep M, et al. Single-ascending-dose pharmacokinetics and safety of the novel broad-spectrum antifungal triazole BAL4815 after intravenous infusions (50, 100, and 200 milligrams) and oral administrations (100, 200, and 400 milligrams) of its prodrug, BAL8557, in healthy volunteers. *Antimicrob Agents Chemother* 2006; **50:** 279–85.

12 Lepak AJ, Marchillo K, Vanhecker J, Andes DR. Isavuconazole (BAL4815) pharmacodynamic target determination in an in vivo murine model of invasive pulmonary aspergillosis against wild-type and cyp51 mutant isolates of *Aspergillus fumigatus*. *Antimicrob Agents Chemother* 2013; **57:** 6284–89.

13 Luo G, Gebremariam T, Lee H, Edwards JE Jr, Kovanda L, Ibrahim AS. Isavuconazole therapy protects immunosuppressed mice from mucormycosis. *Antimicrob Agents Chemother* 2014; **58:** 2450–53.

14 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:** 5642–48.

15 Espinel-Ingroff A, Chowdhary A, Gonzalez GM, et al. Multicenter study of isavuconazole MIC distributions and epidemiological cutoff values for the *Cryptococcus neoformans-Cryptococcus gattii* species complex using the CLSI M27-A3 broth microdilution method. *Antimicrob Agents Chemother* 2015; **59:** 666–68.

16 Astellas Pharma US. Cresemba (isavuconazonium sulfate) prescribing information. 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207500Orig1s000lbl.pdf (accessed Oct 10, 2015).

17 European Medicines Agency. Cresemba (isavuconazole). 2015. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002734/human_med_001907.jsp&mid=WC0b01ac058001d124 (accessed Dec 2, 2015).

18 De Pauw B, Walsh TJ, Donnelly JP, et al. 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:** 1813–21.

19 US FDA. Draft guidance on qualification of biomarker—galactomannan in studies of treatments of invasive aspergillosis. 2014. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM420248.pdf (accessed June 16, 2015).

20 Denning DW. Therapeutic outcome in invasive aspergillosis. *Clin Infect Dis* 1996; **23:** 608–15.

21 Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347:** 408–15.

22 Spellberg B, Talbot G. Recommended design features of future clinical trials of antibacterial agents for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis* 2010; **51** (suppl 1)**:** S150–70.

23 Ramos ER, Jiang Y, Hachem R, Kassis C, Kontoyiannis DP, Raad I. Outcome analysis of invasive aspergillosis in hematologic malignancy and hematopoietic stem cell transplant patients: the role of novel antimold azoles. *Oncologist* 2011; **16:** 1049–60.

24 Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin Infect Dis* 2012; **55:** 1080–87.

25 Falci DR, Pasqualotto AC. Profile of isavuconazole and its potential in the treatment of severe invasive fungal infections. *Infect Drug Resist* 2013; **6:** 163–74.

26 Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Ann Intern Med* 2015; **162:** 81–89.

27 Wingard JR, Ribaud P, Schlamm HT, Herbrecht R. Changes in causes of death over time after treatment for invasive aspergillosis. *Cancer* 2008; **112:** 2309–12.

28 Miceli MH, Maertens J, Buve K, et al. Immune reconstitution inflammatory syndrome in cancer patients with pulmonary aspergillosis recovering from neutropenia: proof of principle, description, and clinical and research implications. *Cancer* 2007; **110:** 112–20.

29 Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. *Clin Infect Dis* 2008; **47:** 674–83.

30 Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis* 2007; **44:** 1289–97.

31 Pascual A, Csajka C, Buclin T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. *Clin Infect Dis* 2012; **55:** 381–90.

32 Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. *J Clin Pharmacol* 2006; **46:** 235–43.