**Impact of unresolved neutropenia in patients with neutropenia and invasive aspergillosis: a post hoc analysis of the SECURE trial**

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Running title: IA treatment and persistent neutropenia(40 characters with spaces)

**Abstract**

**Background:** Historically, baseline neutropenia and lack of neutrophil recovery have been associated with poor outcomes in invasive aspergillosis (IA). It is unclear how treatment with the new *Aspergillus*-active triazoles isavuconazole and voriconazole affects outcomes in neutropenic patients with IA.

**Methods:** A *post hoc* analysis of the phase 3 SECURE trial assessed patients with neutropenia (neutrophil count <0.5 x 109/L for >10 days at baseline) with IA (proven/probable) who had received either isavuconazole or voriconazole. The primary endpoint was all-cause mortality (ACM) through day 42. ACM in patients with resolved, versus unresolved, neutropenia at day 7 and overall success at end-of-treatment (EOT) was also assessed.

**Results:** 142 patients with neutropenia with IA were included (isavuconazole n = 78, voriconazole n = 64). ACM through day 42 (primary endpoint), day 7, and EOT was higher for patients with unresolved, versus resolved, neutropenia at each timepoint (day 42, unresolved: 45.0% isavuconazole, 45.2% voriconazole; resolved: 5.0% isavuconazole, 5.9% voriconazole; day 7, unresolved: 31.0% isavuconazole, 29.8% voriconazole; resolved: 5.0% isavuconazole, 5.9% voriconazole; EOT, unresolved: 48.6% isavuconazole, 36.4% voriconazole; resolved: 5.0% isavuconazole, 14.3% voriconazole). ACM was significantly higher for isavuconazole-treated patients with unresolved, versus resolved, neutropenia (day 7, *P* = 0.031; day 42, *P* < 0.001; EOT *P* < 0.001). In voriconazole-treated patients, ACM was significantly higher among patients with unresolved versus resolved neutropenia at day 42 (*P* = 0.002) and numerically higher at day 7 and EOT (*P* > 0.05 for both).

**Conclusions:** Isavuconazole had comparable efficacy and safety to voriconazole in neutropenic patients with IA. Resolution of neutropenia was associated with improved outcomes.

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**Introduction**

Invasive aspergillosis (IA) has become the predominant mycosis in patients with haematological cancer and prolonged neutropenia.[1](#_ENREF_1) Historically, prolonged neutropenia was associated with a failure to respond to antifungal therapy as well as increased mortality in patients with haematological malignancies, although the data come mostly from older, single-institution, retrospective studies that relied on culture- or histopathology-proven IA cases in which the outcomes were poor.[1-3](#_ENREF_1) Pivotal randomized studies for the treatment of IA in the last two decades showed improvement of responses with triazoles,[3-5](#_ENREF_3) yet they do not provide an in-depth evaluation on the impact of neutropenia in IA outcomes. The importance of persistent neutropenia for outcomes in IA is a timely question in the era of high potency new anti-*Aspergillus* triazoles, such as isavuconazole and voriconazole, and revised guidelines for the diagnosis of probable IA that heavily rely on *Aspergillus* galactomannan (GM) detection. Specifically, a potential confounder for improved outcome in the latest studies might have been the introduction of *Aspergillus* GM in serum or broncholalveolar lavage samples, which is an important step in the early diagnosis of IA.[6](#_ENREF_6)

The SECURE trial demonstrated the non-inferiority of isavuconazole compared with voriconazole for the treatment of IA and other filamentous fungi.[5](#_ENREF_5) In this *post hoc* analysis of the SECURE trial, we compared the efficacy and safety outcomes in the subset of patients with baseline neutropenia and IA in order to assess the impact of persistent neutropenia on mortality and outcomes in each treatment group. We also examined the impact of baseline GM on outcomes for each treatment arm.

**Methods**

***Study design***

The SECURE trial (ClinicalTrials.gov, NCT00412893) was a global, phase 3, randomized, multicenter, double-blind, comparative-group, non-inferiority trial of isavuconazole versus voriconazole.[5](#_ENREF_5) The primary findings of this trial together with methodology and patient eligibility criteria have been reported elsewhere.[5](#_ENREF_5) Briefly, patients aged ≥18 years with proven, probable, or possible invasive fungal infections, defined according to the criteria of 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,[7](#_ENREF_7) were randomized 1:1 to receive isavuconazole or voriconazole. Patients assigned to isavuconazole received a loading dose of treatment of isavuconazonium sulfate prodrug 372 mg, equivalent to 200 mg of isavuconazole, three times daily intravenously (IV) for the first 2 days, followed by a maintenance once-daily IV or oral (PO) dose of 200 mg of isavuconazole from day 3 to end of treatment (EOT). Patients assigned to voriconazole received a loading dose of 6 mg/kg every 12 hours IV on study day 1, followed by a maintenance dose of 4 mg/kg every 12 hours IV or 200 mg every 12 hours PO from day 2 to EOT.

Patients were treated up to a maximum of 84 days. The final follow-up visit was scheduled at 4 weeks ± 7 days after the last dose of study drug that may have occurred before or after day 42 and/or day 84.

The primary endpoint of this *post hoc* analysis was all-cause mortality (ACM) through day 42 following primary treatment with isavuconazole compared with voriconazole in patients with neutropenia and IA. Differences in the primary outcome by neutropenic status and treatment assignment, for patients with neutropenia at baseline that had resolved or remained at day 7, day 42, and EOT, were also assessed. Overall success at EOT was a key secondary endpoint and was based on clinical, mycological, and radiological responses as described previously.[5](#_ENREF_5) The impact of baseline GM on outcomes in each treatment arm was evaluated.

***Assessments***

Mycological assessments were performed locally according to best practice and included samples for fungal culture and isolation and biopsy/biological fluid samples from the infected site for histology/cytology. Serum samples were assessed for *Aspergillus* infection by GM antigen assay, with a single value ≥0.7 or two consecutive values ≥0.5 by Bio-Rad Platelia™ (Bio-Rad, Hercules, California, USA) considered a positive result.

An independent data review committee (DRC) assessed proven or probable IA status and evaluated clinical, mycological and overall response at EOT based on consensus criteria.[8](#_ENREF_8) Specifically, complete or partial clinical success was defined as the complete resolution or partial resolution, respectively, of attributable clinical symptoms and physical findings. Clinical failure was defined as no resolution of any attributable clinical symptoms and physical findings and/or worsening of symptoms or results not available. Mycological success was defined as eradication, or presumed eradication, of infection, or as failure in cases of persistence or presumed persistence of infection.

Neutropenic status was determined at baseline, day 7, day 42 and EOT. Neutropenia was defined as an absolute neutrophil count (ANC) <0.5 x 109/L for >10 days at baseline. For measurements on or before day 7, unresolved neutropenia was defined as no ANC measurement available or at least one ANC <0.5 x 109/L measurement. For day 42 and EOT measurements, unresolved neutropenia was defined as no ANC measurement in patients whose previously available ANC indicated neutropenia, or at least one ANC <0.5 x 109/L measurement from days 35 to 49, or from 3 days before to 3 days after last treatment dose, respectively.

Patients whose neutropenia had resolved were compared with those who remained neutropenic (unresolved neutropenia). A comparison of the efficacy and safety of isavuconazole compared with voriconazole was also carried out for these patient groups.

The incidence, nature, and severity of treatment-emergent adverse events (TEAEs) were monitored and assessed throughout the study for all patients who received ≥1 dose of study drug.

***Analysis populations***

This analysis was performed using the mycological intent-to-treat (myITT) population, which included all patients with neutropenia and with proven or probable IA, as assessed by the DRC, and who had received at least one dose of study drug.

***Statistical analyses***

Demographic and baseline characteristics were summarized for the myITT population. The primary efficacy endpoint of crude ACM through day 42 was assessed from the myITT population, with the between-group treatment difference obtained by subtracting the voriconazole rate from isavuconazole rate. Fisher’s exact test (two-tailed) (R software, University of Aix-Marseille, France) was used to assess differences between treatment groups and between groups with resolved, versus unresolved, neutropenia and *P* < 0.05 was considered significant.

**Results**

***Patient demographics and baseline characteristics***

Overall, 142 patients with neutropenia received ≥1 dose of study drug and had either proven or probable IA, and thus constituted the myITT population. The treatment subgroups were mostly well balanced with respect to age and other baseline characteristics (**Table 1**). The percentage of males was lower among those assigned to isavuconazole group, compared with those assigned to voriconazole group. Nearly all patients had underlying haematological malignancy disease with acute leukemia accounting for >50% cases in each treatment groups (**Table 1**). Most patients had active malignancy at the diagnosis of IA (83.3% and 89.1% in isavuconazole and voriconazole groups, respectively). The majority of patients only had invasive pulmonary aspergillosis (91.0% in isavuconazole group and 96.9% in voriconazole group). More patients in the isacuconazole group (2/78) had disseminated IA compared with the voriconazole group (0/64, *P* = NS, **Table 1**).

Most aspergillosis diagnoses were based only on positive serum GM (74.4% isavuconazole group, 82.8% voriconazole group) versus isolation of *Aspergillus* spp. (25.6% isavuconazole group, 17.2% voriconazole group; **Table 2**). Among those patients with a pathogen identified at baseline, the predominant pathogens causing IA as assessed by the DRC were *A. fumigatus* and *A. flavus* (**Table 2**), which accounted for 15.4% of cases in the isavuconazole group and 17.2% of cases in the voriconazole group.

***Efficacy outcomes***

In the isavuconazole group, neutropenia persisted in 58/78 (74.4%) patients at day 7, 40/78 (51.3%) patients at day 42 and 37/78 (47.4%) patients at EOT. In the voriconazole group, neutropenia persisted in 47/64 (73.4%) patients at day 7, 31/64 (48.4%) patients at day 42 and 33/64 (51.6%) patients at EOT. How the diagnosis of neutropenia was made is shown in **Supplementary Table 1**. Patients who had resolved their neutropenia at day 7 but subsequently relapsed are shown in **Supplementary Table 2**. Overall, 10/20 (50.0%) and 11/17 (64.7%) patients in the isavuconazole and voriconazole groups, respectively, who had resolved neutropenia at day 7 subsequently were diagnosed with unresolved neutropenia at day 42. Similarly, 8/20 (40.0%) and 7/17 (41.0%) patients in the isavuconazole and voriconazole groups, respectively, who had resolved neutropenia at day 7 subsequently were diagnosed with unresolved neutropenia at EOT. The relapse in neutropenia was predominantly due to the lack of availability of absolute neutrophil counts at these time points (**Supplementary Table 2**).

In patients who were neutropenic at baseline, overall ACM at day 42 occurred in 19/78 (24.4%) patients [18/58 patients with unresolved neutropenia at day 7 and 1/20 patients with resolved neutropenia at day 7] in the isavuconazole group and 15/64 (23.4%) patients [14/47 patients with unresolved neutropenia at day 7 and 1/17 patients with resolved neutropenia at day 7] in the voriconazole group (**Table 3**). Irrespective of treatment assignment, ACM was higher for patients who remained neutropenic at each time point (day 7, 32/105 [30.5%]; day 42, 32/71 [45.1%]; EOT, 30/70 [42.9%]) compared with patients whose neutropenia had resolved at that time point (day 7, 2/37 [5.4%]; day 42 0/32; EOT 2/35 [5.7%]), regardless of whether the diagnosis of IA was by culture plus GM or just GM positivity (culture negative) (**Table 3**). A separate analysis of the data showed that 5/142 [3.5%] patients died before day 7 (4/78 [5.1%] in the isavuconazole group and 1/64 [1.6%] in the voriconazole group), 28/142 [19.7%] patients died between day 7 and 42 (15/78 [19.2%] in the isavuconazole group and 13/64 [20.3%] in the voriconazole group) and 14/142 [9.9%] patients died between day 43 and day 84 (7/78 [9.0%] in the isavuconazole group and 7/64 [10.9%] voriconazole group).

In analyses by treatment group (**Table 3**), ACM was comparable in both the isavuconazole and voriconazole groups who remained neutropenic at day 7 (18/58 [31.0%] and 14/47 [29.8%], respectively), day 42 (18/40 [45.0%] and 14/31 [45.2%], respectively) and EOT (18/37 [48.6%] and 12/33 [36.4%], respectively). ACM was statistically significantly lower in isavuconazole-treated patients whose neutropenia had resolved compared with isavuconazole-treated patients with unresolved neutropenia at day 7 (1/20 [5.0%] compared with 18/58 [31.0%], *P* = 0.031), day 42 (0/18 compared with 18/40 [45.0%], *P* < 0.001) and EOT (0/21 compared with 18/37 [48.6%], *P* < 0.001). In voriconazole-treated patients, ACM was significantly lower for resolved, compared with unresolved, neutropenia at day 42 (0/16 compared with 14/31 [45.2%], *P* = 0.002) but not at day 7 (1/17 [5.9%] compared with 14/47 [29.8%], *P* = 0.053) or at EOT (2/14 [14.3%] compared with 12/33 [36.4%], *P* = 0.175) (**Table 3**).

Although the numbers were small, ACM was slightly higher in patients with unresolved neutropenia regardless of treatment arm at day 7 and day 42 when diagnosis was based upon culture plus GM positivity, compared with culture negative GM positivity (day 7, 8/22 versus 24/83; day 42, 8/17 versus 24/54, respectively, **Table 3**). There was a statistically significant association between baseline GM values and the risk of mortality in the isavuconazole group at day 42, with 0/12 patients in the ≥0.5 to ≤1.0 group, compared with 15/44 [34.1%] (*P* = 0.024) in the >1.0 group, and at EOT with 0/12 patients in the ≥0.5 to ≤1.0 group, compared with 18/44 [40.9%] (*P* = 0.006) in the >1.0 group, progressing to death (**Table 4**). In contrast, no significant link was observed in the voriconazole group.

In line with the ACM results, the finding of DRC-assessed treatment success at EOT was greater in patients with resolved, compared to those with unresolved, neutropenia at all time points, regardless of treatment group. Isavuconazole achieved similar rates of success as voriconazole in those stratified according to unresolved or resolved neutropenia status at day 7 and at day 42 but not at EOT (**Table 5**). At EOT, voriconazole appeared to have a greater success rate among those with unresolved neutropenia while isavuconazole appeared to have a greater success rate in those with resolved neutropenia. Overall, there were no differences between treatment groups at EOT (success in the isavuconazole group 19/58 [32.8%] versus voriconazole 16/47 [34.0%]).

**Discussion**

Using a *post hoc* analysis of the large phase 3 SECURE trial, we report the largest contemporary dataset to date assessing the impact of neutropenia resolution on outcomes in patients with IA treated by modern triazoles, isavuconazole and voriconazole, that are endorsed by guidelines as the preferred first line agents.[1](#_ENREF_1) Failure to resolve neutropenia was a major factor for ACM regardless of the treatment group and is a major finding of our study. We also found that isavuconazole had similar efficacy to voriconazole in patients with baseline neutropenia, irrespective of whether neutropenia had resolved or remained at day 7, day 42 or EOT. However, poorer outcomes were observed for both drugs in the setting of persistent neutropenia. This suggests that neutropenia continues to be a predictor of poor outcomes, and that persistence of neutropenia could potentially influence outcomes in clinical trials.

A number of studies have identified neutropenia as a risk factor for mortality and response to therapy in IA.[9-14](#_ENREF_9) Neutrophils are crucial for host protection against aspergillosis as they have a direct role in the destruction of hyphae and prevent germination of conidia.[15](#_ENREF_15),[16](#_ENREF_16) Delayed engraftment post stem cell transplantation and prolonged neutropenia are strong predictors for both IA and poor outcome.[17](#_ENREF_17) In a study in patients with haematological malignancies, Reuter *et al*. found that patients with neutropenia of ≤5 days had a 12-month survival rate of 92%, compared with 58% in those with persistent neutropenia of >10 days.[18](#_ENREF_18) Our study emphasizes the importance of resolving neutropenia in patients with IA, even in the era of early GM-based diagnosis of IA and the use of potent triazoles. Indeed, there was no further ACM at day 42 in patients whose neutrophil counts recovered. Therefore, early restoration of neutrophil count is an important consideration in the management of patients with IA. Whether the inferior outcomes of neutropenia reflect the fact that voriconazole and isavuconazole are static drugs in the currently used doses against *Aspergillus* spp. is a theoretical, yet tenable hypothesis.[19-21](#_ENREF_19)

In our analysis of patients who were neutropenic at baseline, the overall day 42 ACM rates of 24.4% (isavuconazole) and 23.4% (voriconazole). These rates were slightly lower than previous studies that reported 6- and 12-week mortality data in the order of 27%–30% when voriconazole was used as primary monotherapy treatment of IA in patients with haematological diseases and haematopoietic stem cell transplantation,[3](#_ENREF_3),[4](#_ENREF_4),[22](#_ENREF_22) although not all patients in these older studies had neutropenia. In the current study, similar overall treatment success rates at EOT were observed between isavuconazole- and voriconazole-treated patients with neutropenia. At EOT, success was greater in those with resolved, versus persistent, neutropenia. Although the numbers were small, intriguingly voriconazole appeared to have a better success rate among those with unresolved neutropenia while isavuconazole appeared to have a greater success rate in those with resolved neutropenia. Whether there are differences in intracellular concentration of each azole in neutrophils and its immunomodulatory effect (favouring isavuconazole) or more inherent fungicidal effect of voriconazole in the absence of neutrophils (favouring voriconazole) is a complex question that requires careful experimental testing. Alternatively, this might reflect some imbalances in the population. For example, disseminated IA was more common in the isavuconazole group, compared with the voriconazole group, and may have been imbalanced between the resolved and unresolved neutropenia groups.

Not surprisingly, most of the patients in our study had haematological cancer and had a diagnosis of probable IA, on the basis of a positive GM in serum and/or bronchoalveolar lavage. A number of studies have shown that GM values may be a surrogate marker for mortality from IA, with high GM values being a predictor of mortality in patients with neutropenia.[6](#_ENREF_6),[23-26](#_ENREF_23) Furthermore, a diagnosis based on a positive culture together with GM positivity has been shown in a multivariate analysis to be independently associated with an increased risk of death.[27](#_ENREF_27) Our study did not show any significant differences in the risk of death between culture positive and GM alone diagnosis.

In our study, irrespective of neutropenia status, there was a link between baseline GM values and ACM in patients receiving isavuconazole, but not in patients who received voriconazole. Furthermore, others have shown that patients with IA regardless of neutropenia status whose GM values normalize after initiation of antifungal therapy, including isavuconazole, have significantly better outcomes compared with patients with persistently positive GM values.[6](#_ENREF_6),[23-26](#_ENREF_23),[28](#_ENREF_28) Future clinical trials on IA should consider sequential GM values during treatment as a possible surrogate marker for success.

As a *post hoc* analysis, it has inherent limitations, including a limited analysis population that may have resulted in sampling bias and/or introduced imbalances and a lack of powering to support firm conclusions. In addition, as the study enrolment criteria excluded patients who were severely ill, and with comorbidities such as renal or hepatic dysfunction, there might be limitations in the generalizability of our findings.

In conclusion, the findings of this *post hoc* analysis of the phase 3 SECURE trial suggest that isavuconazole has comparable efficacy to voriconazole in the primary treatment of IA in patients with either resolved or unresolved neutropenia. These data confirm the durable influence of resolving neutropenia on improving antifungal treatment success and outcomes in patients with haematological cancer and IA. Similar observations on the profound influence of neutrophil recovery on outcome have been made for the other clinically important, yet less common non-*Aspergillus* moulds that cause invasive fungal infections in this patient population.[29-31](#_ENREF_29) Future studies should carefully analyze and report outcomes of agents by taking the issue of persistent neutropenia into account. Finally, whether there are meaningful differences in activity of voriconazole compared with isavuconazole in patients with IA and unresolved neutropenia would require further study.

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**Conflict of interest**

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**Table 1.** Demographics and baseline characteristics of patients with neutropenia and invasive aspergillosis (myITT population)a

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| --- | --- | --- |
| Parameter | Isavuconazole  (*n* = 78) | Voriconazole  (*n* = 64) |
| Age, years, mean (SD) | 51.6 (15.2) | 50.0 (15.1) |
| Male, *n* (%) | 38 (48.7) | 39 (60.9) |
| Race, *n* (%) |  |  |
| White | 62 (79.5) | 45 (70.3) |
| Asian | 15 (19.2) | 19 (29.7) |
| Other | 1 (1.3) | 0 |
| Baseline condition, *n* (%) |  |  |
| Primary underlying disease  Acute myeloid leukemia  Acute lymphocytic leukemia  Refractory anemia with excess of blasts  Myelodysplastc syndrome  Non-Hodgkin’s lymphoma  Chronic lymphocytic leukemia  Chronic myeloid leukemia  T-cell lymphoma  Aplastic anemia  Otherc | 78 (100.0)  37 (47.4)  14 (17.9)  6 (7.7)  2 (2.6)  6 (7.7)  1 (1.3)  2 (2.6)  1 (1.3)  1 (1.3)  17 (21.8) | 64 (100.0)  38 (59.4)  7 (10.9)  1 (1.6)  4 (6.3)  0  3 (4.7)  2 (3.1)  2 (3.1)  2 (3.1)  12 (18.8) |
| Active malignancy | 65 (83.3) | 57 (89.1) |
| T-cell immunosuppressant | 27 (34.6) | 26 (40.6) |
| Allogeneic BMT | 17 (21.8) | 7 (10.9) |
| Corticosteroid use | 10 (12.8) | 9 (14.1) |
| Location of aspergillosis, *n* (%)  LRTD only  LRTD + other organ  Non LRTD only | 71 (91.0)  4 (5.1)  3 (3.8) | 62 (96.9)  0  2 (3.1) |
| Non-LRTD location  Disseminated  Brain  Sinus  Skin  Other | 7 (9.0)  2 (2.6)  1 (1.3)  5 (6.4)  1 (1.3)  1 (1.3) | 2 (3.1)  0  0  2 (3.1)  0  0 |

amyITT, mycological intent-to-treat population: all randomized patients who received ≥1 dose of study drug and were diagnosed with invasive aspergillosis.

bNeutropenia: ANC <0.5 x 109/L for >10 days at baseline.  
cOther occurring in a single patient from each or either treatment group: Hodgkin’s disease, acute biphenotypic leukemia, acute monocytic leukemia,acute promyelocytic leukemia, B-cell lymphoma, Burkitt’s leukemia, Chloroma, Hairy cell leukemia, leukemia, lymphoplasmacytoid lymphoma/ immunocytoma stage IV, multiple myeloma.

ANC, absolute neutrophil count; BMT, bone marrow transplantation; LRTD, lower respiratory tract disease.

**Table 2.** Baseline pathogens causing invasive aspergillosis in patients with neutropeniaa

|  |  |  |
| --- | --- | --- |
| Pathogen causing IAc | Isavuconazole (*n* = 78) | Voriconazole (*n* = 64) |
| *Aspergillus* spp. only, *n* (%) | 17 (21.8) | 11 (17.2) |
| *A. fumigatus* | 8 (10.3) | 6 (9.4) |
| *A. flavus* | 4 (5.1) | 5 (7.8) |
| *A. niger* | 4 (5.1) | 0 |
| *A. terreus* | 1 (1.3) | 0 |
| *A. sydowi* | 1 (1.3) | 0 |
| *Aspergillus* spp. plus other filamentous fungi, *n* (%) | 3 (3.8) | 0 |
| Positive serum galactomannand, *n* (%) | 58 (74.4) | 53 (82.8) |

aMycological intent-to-treat population: all randomized patients who received ≥1 dose of study drug with proven or probable invasive aspergillosis.

bNeutropenia: ANC <0.5 x 109/L for >10 days at baseline.

cAs assessed by the DRC.

dSerum galactomannan single value ≥0.7 or two consecutive serum sample values of ≥0.5 — <0.7.

ANC, absolute neutrophil count; DRC, data review committee; IA, invasive aspergillosis; myITT, mycological intent-to-treat.

**Table 3.** All-cause mortality at day 42 in patients with unresolved versus resolved neutropenia dependent on day of resolution of neutropenia and diagnosis by culture and galactomannan or by galactomannan alone

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Culture based + galactomannan IAa | | Galactomannan alone IAb | | Total | |
| Neutropeniac status  Deaths, *n/N* (%) | Isavuconazole | Voriconazole | Isavuconazole | Voriconazole | Isavuconazole | Voriconazole |
|  |  | Day 7d | | | |  |
| Unresolved | 6/16 (37.5) | 2/6 (33.3) | 12/42 (28.6) | 12/41 (29.3) | 18/58 (31.0) | 14/47 (29.8) |
|  |  |  |  |  |  |  |
| Resolved  *P\** | 0/4  0.267 | 1/5 (20.0)  1.000 | 1/16 (6.3)  0.087 | 0/12  0.048 | 1/20 (5.0)  0.031 | 1/17 (5.9)  0.053 |
|  |  | Day 42e | | | |  |
|  |  |  | |  |  |  |
| Unresolved | 6/13 (46.2) | 2/4 (50.0) | 12/27 (44.4) | 12/27 (44.4) | 18/40 (45.0) | 14/31 (45.2) |
|  |  |  |  |  |  |  |
| Resolved  *P\** | 0/3  0.250 | 0/2  0.467 | 0/15  0.003 | 0/14  0.003 | 0/18  <0.001 | 0/16  0.002 |
|  |  | EOTf | | | |  |
| Unresolved | 6/8 (75.0) | 0/3 | 12/29 (41.4) | 12/30 (40.0) | 18/37 (48.6) | 12/33 (36.4) |
|  |  |  |  |  |  |  |
| Resolved  *P\** | 0/8  0.007 | 2/3 (66.7)  0.400 | 0/13  0.008 | 0/11  0.018 | 0/21  <0.001 | 2/14 (14.3)  0.175 |

aDiagnosis of IA culture positive and galactomannan positive.   
bDiagnosis of IA culture negative but galactomannan positive.

cNeutropenia: ANC <0.5 x 109/L for >10 days at baseline.

dUnresolved neutropenia: no ANC measurement available or ≥1 ANC <0.5 x 109/L measurement from days 2–7.

eUnresolved neutropenia at day 42 defined as: no ANC measurement available or ≥1 ANC <0.5 x 109/L measurement from days 35–49.

fUnresolved neutropenia at EOT defined as: no ANC measurement available or ≥1 ANC <0.5 x 109/L measurement from 3 days before last dose to 3 days after last dose.

ANC, absolute neutrophil count; EOT, end of treatment; IA, invasive aspergillosis.

*\*P*, Fisher’s two-tailed exact test for unresolved versus resolved neutropenia.

**Table 4.** Analysis of all-cause mortality at day 42 and EOT by baseline galactomannan values (myITT population)

|  |  |  |
| --- | --- | --- |
| Serum galactomannan values  n/N (%) deaths | Isavuconazole  (*n* = 78) | Voriconazole  (*n* = 64) |
|  | Day 42 | |
| Two consecutive values ≥0.5 but ≤1.0 | 0/12 | 4/15 (26.7) |
| At least one value of ≥0.7 but <1.0 | 2/9 (22.2) *P* = 0.171b | 2/6 (33.3) *P* = 1.000b |
| At least one value ≥1.0 | 15/44 (34.1) *P* = 0.024b | 8/38 (21.1) *P* = 0.722b |
| No serum galactomannan values checkeda | 2/13 (15.4) | 1/5 (20.0) |
|  | EOT | |
| Two consecutive values ≥0.5 but ≤1.0 | 0/12 | 5/15 (33.3) |
| At least one value of ≥0.7 but <1.0 | 4/9 (44.4) *P* = 0.021b | 4/6 (66.7) *P* = 0.331b |
| At least one value ≥1.0 | 18/44 (40.9) *P* = 0.006b | 12/38 (31.6) *P* = 1.000b |
| No serum galactomannan values checkeda | 4/13 (30.8) | 1/5 (20.0) |

aGalactomannan positive result but no titre data available.

b*P*, versus two consecutive values ≥0.5 but ≤1.0 (Fisher’s two-tailed exact test).

EOT, end of treatment; myITT, mycological intent-to-treat.

**Table 5.** DRC-assessed overall success at EOT (myITT population)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Culture + galactomannan IAa | | Galactomannan only IAb | | Total | |
| Neutropeniac status  Success, *n/N* (%) | Isavuconazole | Voriconazole | Isavuconazole | Voriconazole | Isavuconazole | Voriconazole |
|  |  | | Day 7d | |  | |
| Unresolved | 5/16 (31.3) | 1/6 (16.7) | 14/42 (33.3) | 15/41 (36.6) | 19/58 (32.8) | 16/47 (34.0) |
|  |  |  |  |  |  |  |
| Resolved | 4/4 (100.0) | 3/5 (60.0) | 7/16 (43.8) | 7/12 (58.3) | 11/20 (55.0) | 10/17 (58.8) |
| *P*\* | 0.026 | 0.242 | 0.546 | 0.202 | 0.110 | 0.091 |
|  |  | | Day 42e | |  | |
| Unresolved | 3/13 (23.1) | 0/4 | 4/27 (14.8) | 6/27 (22.2) | 7/40 (17.5) | 6/31 (19.4) |
|  |  |  |  |  |  |  |
| Resolved  *P*\* | 2/3 (66.7)  0.214 | 1/2 (50.0)  0.400 | 10/15 (66.7)  0.001 | 9/14 (64.3)  0.015 | 12/18 (66.7)  0.001 | 10/16 (62.5)  0.008 |
|  |  | | EOTf | |  | |
| Unresolved | 0/8 | 1/3 (33.3) | 4/29 (13.8) | 10/30 (33.3) | 4/37 (10.8) | 11/33 (33.3) |
|  |  |  |  |  |  |  |
| Resolved  *P*\* | 5/8 (62.5)  0.026 | 0/3  1.000 | 10/13 (76.9)  <0.001 | 5/11 (45.5)  0.491 | 15/21 (71.4)  <0.001 | 5/14 (35.7)  1.000 |

aDiagnosis of IA culture positive and galactomannan positive.   
bDiagnosis of IA culture negative but galactomannan positive.

cNeutropenia: ANC <0.5 x 109/L for >10 days at baseline.

dUnresolved neutropenia: no ANC measurement available or ≥1 ANC <0.5 x 109/L measurement from days 2–7.

eUnresolved neutropenia at day 42 defined as: no ANC measurement available or ≥1 ANC <0.5 x 109/L measurement from days 35–49.

fUnresolved neutropenia at EOT defined as: no ANC measurement available or ≥1 ANC <0.5 x 109/L measurement from 3 days before last dose to 3 days after last dose.

ANC, absolute neutrophil count; EOT, end of treatment; IA, invasive aspergillosis; myITT, mycological intent-to-treat.

\**P*, Fisher’s two-tailed exact test for unresolved versus resolved neutropenia.