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Name of Finished Product: Isavuconazonium sulfate		
Name of Active Ingredient: Isavuconazole		

SYNOPSIS

Title of Study: A phase III, double-blind, randomized study to evaluate safety and efficacy of BAL8557 versus voriconazole for primary treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi (SECURE Study)

Investigators/Coordinating Investigator: [redacted], MD, PhD, [redacted]

Study Center(s): This multicenter study was conducted in 102 centers globally in North and South America, Europe, the Middle East, Africa, Southeast Asia, the Far East and Pacific regions.

Publication Based on the Study: No publications of the results of this study were submitted or published at the time of the approval of this clinical study report.

Study Period: 6 years

Study Initiation Date (Date of First Enrollment): March 7, 2007

Study Completion Date (Date of Last Evaluation): March 28, 2013

Phase of Development: phase 3

Objectives: The primary objective was to compare all-cause mortality through day 42 following primary treatment with isavuconazole versus voriconazole in patients with invasive fungal disease (IFD) caused by *Aspergillus* species or other filamentous fungi. The secondary objectives of the study were to characterize the safety and tolerability while assessing additional efficacy of treatment with isavuconazole versus voriconazole.

[redacted]

Methodology: This was a phase 3, randomized (1:1), multicenter, double-blind, noninferiority, comparative group study of isavuconazole versus voriconazole. Isavuconazole and voriconazole were administered using IV infusion for loading doses in the first 48 and 24 hours, respectively, and were administered either using IV infusion or oral capsules for maintenance doses from day 3 or day 2, respectively, to end of treatment (EOT). Loading doses were administered as 200 mg every 8 hours IV for isavuconazole and as 6 mg/kg every 12 hours IV for voriconazole. Maintenance doses were administered every 12 hours as 200 mg isavuconazole or placebo (IV or oral) and 4 mg/kg IV or 200 mg oral voriconazole.

An Independent Data and Safety Monitoring Board (IDSMB) monitored the data from this study on an ongoing basis to ensure the continuing safety of patients.

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A blinded Data Review Committee (DRC) consisting of experts in infectious diseases was established to adjudicate, independently from the Sponsor and the Investigator, the categorization of each patient's IFD at enrollment and to evaluate clinical, mycological, radiological and overall response, as well as to assess mortality attributable to IFD.

Efficacy endpoints included the assessment of all-cause mortality through day 42 (primary endpoint) and day 84; DRC-assessed overall response at EOT (key secondary analysis) and at days 42 and 84; DRC attribution of mortality to IFD, Investigator assessment of clinical, mycological and radiological response, impact of the use of potentially mould active systemic antifungal therapy (AFT), and the results of minimum inhibitory concentration (MIC) testing.

[redacted]

Number of Patients (Planned, Enrolled and Analyzed): Approximately 510 consenting adult patients were planned to be enrolled. A total of 532 patients were consented for the study. Of these, 527 patients were randomized, and 516 patients took at least 1 dose of study drug and were included in the Intent-to-treat (ITT) population.

Diagnosis and Main Criteria for Inclusion: Male and female patients ≥ 18 years of age, with proven, probable or possible IFD caused by *Aspergillus* species or other filamentous fungi were enrolled into the study. Patients with a known history of allergy, hypersensitivity or any serious reaction to the azole class of antifungals, for whom voriconazole was contra-indicated, at high risk for QT/QTc prolongation or with risk factors for Torsades de Pointes or use of concomitant medications that are known to prolong QT/QTc interval, with evidence of hepatic dysfunction or concomitant use of sirolimus, efavirenz, ritonavir, astemizole, cisapride, rifampin/rifampicin, rifabutin, ergot alkaloids, long acting barbiturates, carbamazepine, pimozide, quinidine, neostigmine, terfenadine, ketoconazole, valproic acid or St. John's Wort in the 5 days prior to first administration of study medication were excluded.

Other prohibited medications included Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (lovastatin, simvastatin and atorvastatin).

Test Product, Dose and Mode of Administration, Batch Numbers: Isavuconazole for IV administration was provided as lyophilized powder for IV infusion. Each vial contained 372.6 mg of isavuconazonium sulfate (BAL8557) corresponding to 200 mg of active isavuconazole (BAL4815) and included mannitol and sulfuric acid as excipients to be dissolved in 250 mL of a compatible infusion solution. Isavuconazole for oral administration was provided as capsules, each containing 186.3 mg of isavuconazonium sulfate (BAL8557) corresponding to 100 mg of active isavuconazole (BAL4815).

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Duration of Treatment: All patients receiving study drug were to undergo the assessments as scheduled and remain on therapy until they had reached a treatment endpoint or until they had received treatment for a maximum period of 84 days. The follow-up visit was to be performed 4 weeks (± 7 days) after the last dose of study drug and may have occurred before or after day 42 and/or day 84 (i.e., it was not necessarily the end of study visit for a given patient). Survival status at day 42 and day 84 were to be obtained for all patients who received a dose of study drug.

Reference Product, Dose and Mode of Administration, Batch Numbers: Voriconazole for IV administration was provided as a lyophilized powder. Each vial contained 200 mg voriconazole and sulfobutyl ether beta-cyclodextrin sodium supplied in single use 30 mL clear glass vials to be dissolved in 250 mL of a compatible infusion solution. VRC for oral administration was provided as capsules, each containing a 200 mg tablet of VRC.

Voriconazole was chosen as the active comparator for this study as it is the standard of care in the treatment of invasive aspergillosis and isavuconazole was shown to be at least as active as voriconazole in animal models of aspergillosis.

Criteria for Evaluation: The Investigator assessed clinical symptoms and physical findings of IFD at screening and at all subsequent visits from day 3 onward including EOT, day 42, day 84 and follow-up. Baseline mycological assessment (screening through day 7) of the patient's IFD status was performed according to best local practice using local laboratories, including suitable samples for fungal culture and isolation and/or biopsy/biological fluid samples from the infected site for histology/cytology. Mycological assessments were also performed at EOT, day 42 and day 84.

Serum galactomannan (GM) antigen was to be drawn at screening and on days 1, 2 and EOT for patients with *Aspergillus* only. In addition, serum samples obtained at screening, days 1, 2, 14, 28, 42, 84 and EOT for GM antigen assay (or collected any time while patients with probable, proven or possible *Aspergillus* were still receiving study drug) were shipped to a central laboratory. Bronchoalveolar lavage (BAL) specimens for GM could be processed locally, but an additional aliquot of serum or BAL fluid was collected for shipment to the central laboratory as well. A single serum GM value of ≥ 0.7 or two consecutive values each of ≥ 0.5 to < 0.7 (i.e., from two separate blood draws) by Bio-Rad Platelia™ were considered a positive result except in patients receiving concomitant amoxicillin-clavulanate, piperacillin-tazobactam or Plasma-Lyte™ (Baxter). Patients with two BAL GM (*Aspergillus* only) values of ≥ 1.0 (2 aliquots of the same sample) by Bio-Rad Platelia™ were allowed to enroll as possible IFD. Culture and histology/cytology were obtained from the same sample and serum GM must have been obtained per protocol requirements. Plasma-Lyte™ (Baxter) was not to be used as lavage fluid.

Baseline radiological assessments of IFD using computed tomography (CT), high resolution CT (HRCT), if available, magnetic resonance imaging (MRI) or X-ray in situations where no other assessment was available,

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were performed during the screening period. However, assessments performed up to 7 days after the first administration of study drug may have been used to confirm the diagnosis of IFD. Radiological assessments of IFD were to be performed at EOT and on study days 42 and 84 and additionally, on days 14, 28 and follow-up, if clinically indicated. EOT, day 42 and day 84 assessments were performed using the same radiologic methodology as baseline whenever possible. All radiological images and local reports pertaining to the IFD were forwarded to the central reading laboratory for independent review. The radiology experts also provided an overall impression of the images, as well as an overall outcome assessment of percent improvement from baseline at EOT, day 42 and day 84.

Survival status was recorded at EOT, day 42, day 84 and at the follow-up visits. Information on survival status on days 42 and 84 was to be collected for all patients, irrespective of when treatment was discontinued.

Neutropenic data was assessed within 4 weeks prior to screening and throughout the study period based on absolute neutrophil count (ANC). The presence or absence of neutropenia was defined as ANC $< 0.5 \times 10^9$/L ($< 500/mm^3$) and subsequent persistence (ongoing) or resolution was defined as 2 consecutive ANC values $> 0.5 \times 10^9$/L on 2 separate days.

[redacted]

The Investigator evaluated safety by monitoring treatment-emergent adverse events (TEAEs) and findings from physical examination (including eye exam), vital signs (systolic blood pressure and diastolic blood pressure, pulse rate [PR] and body temperature), laboratory tests, 12-lead ECG and concomitant medication/surgery. [redacted]

Samples for a full safety profile including hematology, biochemistry and urinalysis were collected at screening, at study visits on days 3 (chemistry only), 7, 14, 28, 42, EOT and at follow-up. Laboratory safety tests were only required while the patient was receiving study drug, with the exception of the screening and follow-up visits.

Twelve-lead ECG recordings were obtained at screening and were also performed on days 1, 14, 42, 84 and at the EOT visit. ECG was performed in the 15 minutes prior to the end of the first infusion of the day or approximately 3 hours after the oral dose, while the patient remained on study drug. Abnormal ECG findings, if not related to the underlying disease, were either confirmed as clinically not significant or were repeated until they returned to baseline levels. ECG recordings were also forwarded to the central reading laboratory for independent review. The central reading assessment included heart rate, PR interval, RR interval, QRS interval, QT interval, QT interval corrected for heart rate – Bazett's formula (QTcB), QT interval corrected for heart rate – Fridericia's formula (QTcF) and a qualitative ECG interpretation. [redacted]

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[redacted]

Vital signs were assessed at screening and on days 1, 2, 3, 7, 42, 84 and EOT and were to be measured after at least 3 minutes in the supine position.

Physical examinations were conducted at screening and on days 42, 84 and EOT. Physical exams were also performed throughout the study when clinically indicated as determined by the Investigator. An eye examination, consisting of visual acuity, confrontational visual field testing and color perception testing, was conducted at screening, day 14 and EOT. If the patient was continuing on study drug, an eye examination was also performed on days 28 and 42.

[redacted]

Statistical Methods: Continuous data were summarized descriptively including number of patients (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data were summarized by number and percentage of patients within the category.

Baseline was defined as the last observation on or prior to the first administration of study drug, unless otherwise specified.

The different analysis sets used in this study are described below:

- The ITT population consisted of all randomized patients who received at least one administration of study drug. For this population, data were analyzed by the treatment group that patients were randomized to even though they might not be compliant with the protocol or assigned treatment.
- The modified ITT (mITT) population consisted of ITT patients who had proven or probable IFD as determined by the DRC. Patients with appropriate host factor and clinical features were considered to have probable IFD based on the GM criteria (GMc) set forth in the protocol (i.e., 2 consecutive serum GM values ≥ 0.5 or at least 1 serum GM value ≥ 0.7).
- The safety analysis set (SAF) consisted of all randomized patients who received at least one dose of study drug. For the SAF, data were analyzed according to the study drug that patients received as the first dose even if it was different from what they were randomized to.
- The mITT-FDA population consisted of ITT patients who had proven or probable IFD. Patients with an appropriate host factor and clinical features were considered to have probable IFD based on the GM

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criteria (GMc) recommended by the FDA (i.e., 2 consecutive serum GM values ≥ 0.5 or at least 1 serum or BAL GM value ≥ 1.0) as determined by the DRC.

- The mycological ITT (myITT) population consisted of mITT patients with proven or probable invasive aspergillosis based on cytology, histology, culture or GMc set forth in the protocol and assessed by the DRC.
- The Per Protocol Set (PPS) was a subset of ITT (PPS-ITT) or a subset of mITT (PPS-mITT) patients who did not deviate from the prespecified Classification Criteria.
- [redacted]

Demographic and other baseline characteristics (age, gender, race [White, Black/African American, Asian and Other], ethnicity [Hispanic or Latino or non-Hispanic or Latino], height, weight, body mass index [BMI], age category 1 [≤ 45, > 45 to ≤ 65, > 65], age category 2 [≤ 65, > 65 to ≤ 75, > 75], BMI category [< 25, ≥ 25 to < 30, ≥ 30], geographical region [North America, Western Europe plus Australia and New Zealand, Other regions], hematologic malignancy status [yes, no], allogeneic BMT status [yes, no], uncontrolled malignancy status [yes, no], baseline neutropenic status [yes, no], T-cell immunosuppressant [yes, no], eGFR-MDRD [< 60, ≥ 60 mL/min/1.73 m^2], and study drug exposure were summarized descriptively by overall group and by treatment group for the ITT, mITT, PPS and SAF populations.

The primary efficacy endpoint was the crude rate of all-cause mortality from the first dose of study drug through day 42 and was analyzed in the ITT population. A patient with unknown survival status through day 42 with the last known survival status before day 42 or missing and the last assessment day before day 42, was treated as death. The treatment difference, subtracting voriconazole rate from isavuconazole rate, (ISA-VRC) and its 95% CI were calculated using a stratified Cochran-Mantel-Haenszel (CMH) method, where the 95% CI was calculated based on a normal approximation. The stratification factors were Geographical Region, Allogeneic BMT Status and Uncontrolled Malignancy Status. The upper bound of the 95% CI for the treatment difference was compared to the protocol prespecified noninferiority margin (NIM) value of 10%. If the upper bound was smaller than 10%, isavuconazole was declared as noninferior to voriconazole with respect to the primary efficacy endpoint.

A sensitivity analysis was conducted for the ITT population using a stratified minimum risk analysis including the same stratification factors as were used in the calculation of treatment group difference and 95% CIs.

The primary analysis was also performed on ITT patients excluding those who were assessed by the DRC as not having adequate evidence of proven, probable or possible IFD (ITT-excluding no IFD). Additional analyses of the primary efficacy endpoint included analyses in various populations (mITT, mITT-FDA, PPS-ITT, PPS-mITT and myITT), strata (Geographic Region, Allogeneic BMT Status and Uncontrolled Malignancy Status) and for subgroups (age categories, gender, race, ethnicity, baseline neutropenic status, BMI category and eGFR-MDRD). A Treatment-by-Subgroup interaction was evaluated using a logistic regression model with the

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following factors: Treatment Group, Geographical Region, Allogeneic BMT Status, Uncontrolled Malignancy Status, Subgroup Factor and Treatment-by-Subgroup interaction. The interaction was evaluated at the significance level of 0.15. If a subgroup with a level that had fewer than 10 patients within any treatment group, the level was excluded when the interaction was assessed.

All-cause mortality through day 84 was assessed using the same method as for the primary efficacy endpoint and in various populations. A time-to-event analysis was performed using Kaplan-Meier method that generated a survival function from day 1 through day 84. A patient without a reported death was censored on the patient's last assessment day.

DRC-assessed secondary efficacy outcomes included overall response at EOT, day 42 and day 84 in the mITT population. DRC-assessed overall response at EOT was also evaluated by sensitivity analyses, for various populations including subsets of the myITT population, for IFD by location (LRTD only, LRTD plus other organ and non-LRTD only), by strata and by subgroup. Additional efficacy assessments were DRC-assessed subcomponents of overall response (i.e., clinical, mycological and radiological response) and additional analyses for data where the DRC assessment was Not Done (last outcome carried forward and by including observed cases only).

Both all-cause mortality and DRC-assessed overall response endpoints were also evaluated by the status of potentially mould active systemic AFT concomitant use for treatment or empirical purposes.

In addition, the DRC assessed the attribution of death to the IFD for death up to day 42 and for death up to day 84, as either directly due to consequences of progressive IFD, associated with the evidence of residual or ongoing IFD, associated with no evidence of residual or ongoing IFD, indeterminate cause or no known death.

The MIC values for each antifungal agent for each pathogen species from central culture results were summarized descriptively for patients with appropriate data. The data summary will be given by organism and antifungal agent and will include the number of isolates, MIC value range, 50^{th} percentile and the 90^{th} percentile. The overall, clinical and mycological successes assessed by the DRC were presented by the baseline MIC values for the mITT population.

[redacted]

All TEAEs were tabulated and summarized (number and percentage) by SOC, higher level term (HLT) and preferred term (PT). Patient deaths after the first dose of study drug were summarized. Relationship to study drug were assessed by the Investigator.

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Events of interest (EOI) were evaluated in this study based on standardized MedDRA queries (SMQs) of TEAEs and on select HLTs or PTs and were grouped together into the following types of events: Acute pancreatitis (SMQ search of acute pancreatitis, narrow); Psychiatric events (select PTs from Psychiatric Disorders and Nervous System Disorders SOC); Potential hypersensitivity reactions including Infusion/Injection Site Reactions (HLT) and Anaphylaxes [SMQ, narrow] and severe cutaneous adverse reactions (SCAR) [SMQ, narrow]; Potential ocular toxicity (select PTs from the Eye Disorders, Skin and Subcutaneous Tissue Disorders and the Congenital, Familial and Genetic Disorders SOCs); and Torsade de pointes (SMQ, broad). Potential hepatotoxicity and nephrotoxicity were also considered EOI.

Clinical laboratory values (Hematology and Chemistry) from a central laboratory were summarized by treatment group for actual and change from baseline at baseline, day 3 (chemistry only), day 7, day 14, day 28, day 42, EOT and follow-up. A shift analysis was performed on select chemistry laboratory results by treatment group. Results were classified as low (L), normal (N), or high (H) at each visit according to the local or central laboratory-supplied reference ranges. Number and percentage of patients with shifts in laboratory results from baseline to postbaseline were summarized by treatment group.

Assessment of hepatotoxicity was determined based on categories consisting of increases (x-fold times the ULN) in liver chemistries (i.e., ALT, AST, ALP, total bilirubin) and increases in combinations of liver chemistries (i.e., ALT or AST and total bilirubin; ALT or AST and ALP and total bilirubin). Within this assessment, a patient may have been counted more than once as the categories were not mutually exclusive. The analysis included all postbaseline values up to 10 days after the last dose of study drug and values at the EOT visit.

Nephrotoxicity was assessed using serum creatinine and further analyzing the values by the following 3 categories: $\geq 25\%$, $\geq 50\%$, $\geq 100\%$ increase from baseline. A patient may have been counted in more than one category. The number and percentage of patients meeting the defined criteria were summarized by treatment group at EOT and using all postbaseline values.

Vital signs including SBP and DBP (mmHg), PR (bpm) and body temperature (°C) were descriptively summarized by treatment group for actual values and change from baseline to postbaseline time points. For the change values, patients with both values at baseline and each respective time point for calculating the change were included.

The number and percentage of patients who had treatment-emergent changes toward a worse category (normal, abnormal-clinically significant and abnormal-clinically not significant) in the ECG interpretations assessed by Investigators were summarized by treatment group. The central 12-lead ECG parameters (heart rate, PR interval, RR interval, QRS interval, QT interval, QTcB and QTcF) were summarized for actual and change from baseline to each visit by treatment group. The number and percentage of patients with QTcF meeting the

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criteria for change from baseline were summarized by treatment group in 2 ways: by taking greatest or smallest change from baseline and at EOT.

For the categories where actual values were evaluated, the most extreme value that was either highest or lowest depending on the direction of concern was used from all postbaseline assessments.

All computations were performed prior to rounding. All P values, where they were presented and the boundaries of 2-sided 95% CIs were rounded to 3 decimal places. The rounding of the 95% CIs occurred prior to comparison to the NIM.

Summary of Results/Conclusions:

Patient disposition and the primary reasons for discontinuation during treatment and follow-up periods for the ITT population as recorded on the Study Termination eCRF page can be found in [Table 1]. The number of patients randomized in each analysis set is presented in [Table 2].

The treatment groups were balanced for baseline characteristics in the ITT population as shown in [Table 3].

The total study drug duration was similar between the isavuconazole and voriconazole treatment groups. The median duration of study drug administration was 45 days for total dosing, 5 days for IV dosing and 56 days for oral dosing. A total of 400 patients (77.5%) switched from IV to oral study drug dosing.

Efficacy/[redacted] Results:

Efficacy Results: The all-cause mortality rate through day 42 in the ITT population was 18.6% and 20.2% in the isavuconazole and voriconazole treatment groups, respectively. This study met the primary objective of demonstrating noninferiority of isavuconazole relative to voriconazole since the upper bound of the 95% CI (5.683%) around the adjusted treatment difference (ISA-VRC: -1.0%) is lower than the prespecified NIM of 10% [Table 4]. A sensitivity analysis using a minimum risk method supported the results of the primary efficacy analysis. The 95% CI around the adjusted treatment difference (ISA-VRC: -1.1%) was (-7.842%, 5.624%).

All-cause mortality through day 42 numerically favored isavuconazole treatment across various populations with upper bounds of the 95% CI < 10% [Table 5].

All-cause mortality through day 42 was evaluated in several subgroups (age, gender, race, ethnicity, BMI, eGFR-MDRD category and neutropenia). Treatment-by-subgroup interaction was tested and, although certain subgroups showed different magnitude of treatment differences, no treatment-by-subgroup factor interaction was observed according to the prespecified statistical significance value of $P < 0.15$.

Results from a K-M survival analysis were consistent with the primary analysis. In the ITT population, all-cause mortality rates in the respective isavuconazole and voriconazole treatment groups were 17.6% and 19.5% through day 42 and 28.2% and 29.3% through day 84. The 95% CI around the treatment differences (-1.9% and

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-1.1%) were (-8.606%, 4.833%) through day 42 and (-8.944%, 6.739%) through day 84 in the ITT population. In the mITT population, all-cause mortality rates in the respective isavuconazole and voriconazole treatment groups were 19.6% and 22.5% through day 42 and 30.1% and 35.8% through day 84. The 95% CI around the treatment differences (-2.9% and -5.7%) were (-12.606%, 6.805%) through day 42 and (-16.925%, 5.462%) through day 84 in the mITT population.

All-cause mortality through day 84 for the ITT population was 29.1% in isavuconazole treated patients and 31.0% in voriconazole treated patients. Consistent results with those of the primary analysis were found when all-cause mortality was analyzed at day 84 across multiple prespecified populations and using different sensitivity analyses. All-cause mortality numerically favored isavuconazole treatment at day 84 in the ITT, mITT, mITT-FDA, PPS-ITT, PPS-mITT, ITT-excluding no IFD and myITT populations with upper bounds of the 95% CI < 10% in each of these populations [Table 5].

The key secondary efficacy endpoint of DRC-assessed overall response at EOT was analyzed for the mITT population and response rates for success were similar between treatment groups (ISA 35.0%, 50/143; VRC 36.4%, 47/129). The 95% CI around the adjusted treatment difference (VRC-ISA: 1.6%) was (-9.336%, 12.572%) [Table 6]. The results of a sensitivity analysis of DRC-assessed overall response at EOT using a minimum risk method were consistent with those of the DRC-assessed overall response at EOT in the mITT.

The DRC-assessed overall response at EOT, analyzed for various populations, showed that overall response rates were similar between the 2 treatment groups for the mITT–FDA and PPS-mITT populations [Table 7].

The results of analysis of DRC-assessed overall response at EOT by IFD location in the mITT population were similar between treatment groups for patients with LRTD only (ISA 37.1%, 43/116; VRC 35.5%, 38/107). The numbers of patients in the other location categories were small.

Success rates were also evaluated in several subgroups (age, gender, race, ethnicity, BMI, eGFR-MDRD category and neutropenia). Treatment-by-subgroup interaction was tested and no interaction was observed, except for race (P = 0.085; Wald-Chi-square test). The vast majorities of these patients were White and had similar success rates in both treatment groups (ISA 36.5%, 42/115; VRC 32.6%, 30/92). Asian patients had a numerically lower success rate in the isavuconazole group (25.9%, 7/27) than in the voriconazole treatment group (48.6%, 17/35). Of note, there were few patients in some of the subgroup categories, particularly for patients who were > 75 years of age, Black/African American and Other Race, and Hispanic or Latino.

A few patients in either treatment group (ISA: 3 patients and VRC: 1 patient in both the ITT and mITT populations) received potentially mould active systemic AFT (any reason for use) during study drug treatment (i.e., up to the EOT). In the ITT population, 92 isavuconazole treatment patients and 77 voriconazole treated patients received potentially mould active systemic AFT up to day 84. A posthoc analysis was conducted to evaluate the potential impact of the use of potentially mould active systemic AFT on the treatment effect on all-cause mortality and overall response at day 42 and day 84. The analyses of treatment-by-potentially mould

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active systemic AFT use through day 42 and 84 for all-cause mortality in the ITT and mITT populations as well as the analyses of the treatment-by-potentially mould active systemic AFT use for day 42 and 84 overall response in the mITT population showed no statistically significant interaction according to the preplanned significance level ($P < 0.15$).

Analyses of clinical fungal isolates from patients in the study with positive culture were tested for antifungal susceptibility according to Clinical and Laboratory Standards Institute (CLSI) and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) methodologies. Isavuconazole MIC values were similar to voriconazole MIC values for the clinical isolates tested. Of the small number of patients that had repeat cultures tested for susceptibility to isavuconazole and voriconazole, no increase in MIC suggestive of resistance during therapy was demonstrated. Successful outcomes were observed at MIC values up to 8 µg/mL. No trends were observed when comparing outcome by MIC overall or by individual species.

[redacted]

Safety Results: One or more TEAEs were reported by 96.1% of isavuconazole treated patients and 98.5% of voriconazole treated patients [Table 8]. The following important differences were seen between the respective isavuconazole and voriconazole treatment groups: study drug-related TEAEs (42.4% versus 59.8%), TEAEs leading to permanent discontinuation of study drug (14.4% versus 22.8%) and study drug-related TEAEs leading to permanent discontinuation of study drug (8.2% versus 13.5%). The proportions of patients with TEAEs in the remaining categories were similar between treatment groups.

In the analysis of TEAEs by SOC, the proportions of patients with TEAEs were similar between treatment groups for the majority of SOCs. Isavuconazole treated patients had a statistically significantly lower incidence of events than voriconazole treated patients in the Hepatobiliary Disorders, Eye Disorders and Skin and Subcutaneous Tissue Disorders SOCs. In addition, numerically lower event rates were observed for the Psychiatric Disorders (27.2% versus 33.2%) and Cardiac Disorders (16.7% versus 22.0%) SOC for patients in the isavuconazole treated group compared to the voriconazole treatment group.

The lower incidence in isavuconazole versus voriconazole treated patients was primarily influenced by the following TEAEs: tachycardia (12, 4.7% versus 21, 8.1%) and cardiac arrest (1, 0.4% versus 6, 2.3%); visual impairment (4, 1.6% versus 19, 7.3%), visual acuity reduced (1, 0.4% versus 6, 2.3%), retinal hemorrhage (0 versus 5, 1.9%) and photophobia (2, 0.8% versus 6, 2.3%); hyperbilirubinemia (5, 1.9% versus 10, 3.9%), hepatic function abnormal (4, 1.6% versus 9, 3.5%), jaundice (1, 0.4% versus 6, 2.3%) and cholestasis (1, 0.4% versus 6, 2.3%); hallucination (6, 2.3% versus 11, 4.2%), visual hallucination (3, 1.2% versus 11, 4.2%), agitation (2, 0.8% versus 7, 2.7%); rash (17, 6.6% versus 28, 10.8%), erythema (9, 3.5% versus 15, 5.8%), drug

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eruption (3, 1.2% versus 11. 4.2%) and skin lesion (4, 1.6% versus 8, 3.1%). The most common TEAEs by PT that occurred in ≥ 5% of patients in either of the respective isavuconazole or voriconazole treatment groups are shown in [Table 9].

Overall, fewer isavuconazole treated patients (42.4%) experienced study drug related TEAEs than voriconazole treated patients (59.8%). Particularly, fewer patients in the respective isavuconazole treatment group than the voriconazole treatment group experienced study drug-related TEAEs within the following 4 SOCs: Hepatobiliary Disorders (1.9% and 10.0%), Investigations (9.7% and 18.1%), Eye Disorders (3.1% and 10.8%) and Psychiatric Disorders (2.3% and 11.2%). A higher proportion of isavuconazole treated patients than voriconazole treated patients experienced study drug related TEAEs within the Respiratory, Thoracic and Mediastinal Disorders SOC (6.2% and 1.9%, respectively), which was influenced by differences for the PT of dyspnea (8, 3.1% versus 2, 0.8%). The proportions of patients with TEAEs in the remaining SOCs were similar between treatment groups.

The proportion of patient deaths from the first dose through 28 days after the last dose of study drug was similar between treatment groups (ISA: 24.1%, 62/257; VRC: 27.0%, 70/259). The overall pattern of TEAEs leading to death and the proportion of patients who had TEAEs leading to death was similar between treatment groups (ISA: 24.1%, 62/257; VRC: 27.8%, 72/259). Approximately one-fourth of TEAEs leading to death were experienced by more than one patient in either treatment group. The most common TEAEs leading to death by PT that occurred in ≥ 2% of either the respective isavuconazole or voriconazole treatment groups were septic shock (3.1% versus 1.5%), sepsis (2.7% versus 1.9%), respiratory failure (2.3% versus 2.3%), acute myeloid leukemia (1.2% versus 2.7%) and multi-organ failure (0.4% versus 2.3%).

Overall, more than half of patients experienced at least one serious TEAE (ISA: 52.1%; VRC: 57.5%). The overall pattern of serious TEAEs by SOC and the proportion of patients with serious TEAEs by SOC were similar between the respective isavuconazole and voriconazole treatment groups. The most common serious TEAEs that occurred in ≥ 1% of either isavuconazole or voriconazole treated patients are shown in [Table 10].

Overall, there were fewer isavuconazole than voriconazole treated patients (14.4% versus 22.8%, respectively) who had at least one TEAE leading to permanent discontinuation of study drug. The most common TEAEs leading to study drug discontinuation that were reported in ≥ 1.0% of either of the respective isavuconazole or voriconazole treatment groups were respiratory failure (0.8%, 2 patients versus 1.5%, 4 patients), sepsis (0.4%, 1 patient versus 1.2%, 3 patients), acute myeloid leukemia (0 patients versus 1.5%, 4 patients), rash (0 patients versus 1.5%, 4 patients), bacterial sepsis (0 patients versus 1.2%, 3 patients) and visual hallucination (0 patients versus 1.2%, 3 patients).

No TEAEs were reported in the Acute Pancreatitis SMQ.

Overall, a similar proportion of isavuconazole and voriconazole treated patients (28.4% and 30.5%, respectively) reported select TEAEs from the Psychiatric Disorders and Nervous System Disorders SOC. Of

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these, the most frequently reported TEAEs occurring in ≥ 5% of either the respective isavuconazole or voriconazole treatment groups were insomnia (8.9% versus 9.3%), anxiety (7.8% versus 6.6%) and confusional state (6.2% versus 7.7%). While the proportion of isavuconazole and voriconazole treated patients reporting individual TEAEs was generally similar, important differences were noted for hallucination-type events and agitation. Hallucinations (PT) were reported by 2.3% versus 4.2% of isavuconazole versus voriconazole treated patients, respectively. Visual hallucinations (PT) were reported by 1.2% versus 4.2% of isavuconazole versus voriconazole treated patients, respectively. Agitation was also reported in a numerically lower proportion of isavuconazole treated patients than in voriconazole treated patients (2, 0.8% versus 7, 2.7%, respectively). The vast majority of TEAEs in the Psychiatric EOI were of mild or moderate maximum intensity.

Infusion/injection site reactions were reported in a numerically higher proportion of isavuconazole than voriconazole treated patients (4.3%, 11 patients versus 1.5%, 4 patients, respectively). All TEAEs in the Infusion/Injection Site Reaction EOI were of mild or moderate maximum intensity with the exception of infusion site abscess (ISA: 1 patient with severe intensity; VRC: 1 patient with moderate intensity).

Overall, TEAEs in the anaphylaxis and SCAR SMQs were reported in the same proportion of isavuconazole and voriconazole treated patients (1.9%, 5 patients versus 1.9%, 5 patients, respectively). Two isavuconazole treated patients experienced erythema multiforme (1 mild and 1 moderate, both considered unrelated) and 2 voriconazole treated patients experienced an anaphylactic reaction (both moderate and considered unrelated). All other TEAEs in the Anaphylaxis and SCAR SMQs were seen in one patient each.

An important difference was observed in the number of isavuconazole and voriconazole treated patients reporting select TEAEs in the Potential Ocular Toxicity EOI (8.2% versus 16.6%, respectively). The difference between treatment groups in eye disorders was influenced by visual impairment and visual acuity reduced-type events. The most common TEAEs by PT in the Potential Ocular Toxicity EOI occurring in ≥ 1% of patients in either the respective isavuconazole or voriconazole treatment groups were visual impairment (1.6% versus 7.3%), vision blurred (1.6% versus 2.3%), visual acuity reduced (0.4% versus 2.3%), eye pain (0.4% versus 1.5%) and cataract (0.4% versus 1.2%). The maximum intensity of the majority of TEAEs was mild. Although photophobia is not a predefined preferred term for the Potential Ocular Toxicity EOI, the finding that fewer isavuconazole than voriconazole treated patients experienced photophobia (2 versus 6 patients, respectively) correlates with the results from this analysis.

There was a numerically lower proportion of isavuconazole treated patients (5.8%) compared to voriconazole treated patients (7.3%) with TEAEs in the Torsade de Pointes SMQ. The most common TEAEs in the Torsade de Pointes SMQ that occurred in ≥ 1% of patients in either the respective isavuconazole or voriconazole treatment groups were syncope (2.7% versus 0.8%), loss of consciousness (1.2% versus 0), ECG prolonged QT (0.8% versus 3.1%) and cardiac arrest (0.4% versus 2.3%). Syncope and loss of consciousness were reported in a higher proportion of isavuconazole than voriconazole treated patients, while QT prolonged and cardiac arrest were reported in a lower proportion of isavuconazole than voriconazole treated patients.

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The number and percentage of patients with a shift from one category (i.e., low, normal, high) at baseline to another category for the highest or lowest postbaseline value for an individual chemistry parameter was generally similar between isavuconazole and voriconazole treated patients. There was a notably lower number of isavuconazole than voriconazole treated patients, respectively, with a decrease in calcium (37.3%, 38/102 and 50.5%, 48/95) and an increase in AST (39.1%, 79/202 and 49.0%, 101/206), ALT (36.8%, 64/174 and 43.6%, 82/188), GGT (61.5%, 48/78 and 71.0%, 66/93) and ALP (36.0%, 62/172 and 47.3%, 79/167).

In general, fewer isavuconazole than voriconazole treated patients experienced increases in transaminases or increases in transaminases concurrently with increases in total bilirubin. In the postbaseline analysis, 3 isavuconazole treated patients and 7 voriconazole treated patients experienced this pattern of liver enzyme elevations.

There was a similar proportion of patients with categorical increases in serum creatinine in both treatment groups for both the EOT and postbaseline analyses. A higher number of patients in the voriconazole treatment group (17 patients) had creatinine increases ≥ 100% at EOT compared to the isavuconazole group (8 patients).

There were no mean vital sign changes of clinical importance observed in either treatment group in this study.

For the EOT analysis of categorized absolute values in QTcF, fewer isavuconazole treated patients than voriconazole treated patients had QTcF values > 450 msec (7/250, 2.8% versus 17/252, 6.7%, respectively). Conversely, a higher number of isavuconazole treated patients had QTcF values < 360 msec than voriconazole treated patients (27/250, 10.8% versus 19/252, 7.5%, respectively). Very few patients in either treatment group had extreme values of QTcF > 500 msec (none) or QTcF < 300 msec (ISA: 1/250, 0.4%; VRC: 0/252). No patient at baseline had a QTcF of < 330 or > 500 msec.

For the postbaseline analysis, fewer isavuconazole treated patients than voriconazole treated patients had QTcF values > 450 msec (25/250, 10.0% versus 46/252, 18.3%, respectively). Conversely, a higher number of isavuconazole treated patients had QTcF values < 360 msec than voriconazole treated patients (51/250, 20.4% versus 41/252, 16.3%, respectively). Very few patients in either treatment group had extreme values of QTcF > 500 msec (ISA: 1/250, 0.4%; VRC: 3/252, 1.2%) or QTcF < 300 msec (ISA: 1/250, 0.4%; VRC: 0/252).

Results for categorized changes from baseline in QTcF based on extreme values showed that fewer isavuconazole than voriconazole treated patients had increases from baseline in QTcF of > 30 msec and > 60 msec at EOT (ISA 25, 11.0% and 6, 2.6% versus VRC 48, 21.4% and 9, 4.0%) or postbaseline (ISA 47, 20.7% and 10, 4.4% versus VRC 91, 40.6% and 21, 9.4%). Conversely, a higher number of isavuconazole than voriconazole treated patients had decreases from baseline in QTcF of > 30 msec and > 60 msec at EOT (ISA 45, 19.8% and 11, 4.8% versus VRC 35, 15.6% and 6, 2.7%) or postbaseline (ISA 73, 32.2% and 17, 7.5% versus VRC 68, 30.4% and 10, 4.5%).

The number and proportion of patients with qualitative 12-lead ECG abnormalities, including T/U wave abnormalities and ventricular rhythm disorders, was generally similar between the 2 treatment groups at EOT

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and postbaseline (EOT: 71, 28.4% and 75, 29.8%; Postbaseline: 110, 44.0% and 103, 40.9% for ISA and VRC, respectively). It should be noted that there was a lower incidence of atrioventricular (AV) conduction disorders in isavuconazole treated patients compared to the voriconazole treated patients at EOT (ISA 2, 0.8%; VRC 7, 2.8%) and postbaseline (ISA 8, 3.2%; VRC 17, 6.7%). No isavuconazole patient experienced ventricular tachycardia or fibrillation. Two voriconazole treated patients experienced serious TEAEs of ventricular tachycardia.

When TEAEs, serious TEAEs, laboratory shifts, and cardiac repolarization were analyzed by subgroups, the observations were generally consistent with those of the overall analyses.

CONCLUSIONS:

Isavuconazole was effective and safe for the treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi.

Date of Report: 03 June 2014

Table 1 Patient Disposition and Primary Reasons for Discontinuation During Treatment and Follow-up Periods (ITT Population)

Number of Patients Consented	532		
Number of Patients Randomized	527		
Number of Patients Treated (ITT)	**ISA (n = 258)**	**VRC (n = 258)**	**Total (n = 516)**
Treatment Discontinuation			
Completed	118 (45.7%)	120 (46.5%)	238 (46.1%)
Discontinued	140 (54.3%)	138 (53.5%)	278 (53.9%)
Primary Reason for Discontinuation			
Adverse Event/Intercurrent Illness	31 (12.0%)	53 (20.5%)	84 (16.3%)
Death	17 (6.6%)	21 (8.1%)	38 (7.4%)
Insufficient Therapeutic Response	39 (15.1%)	23 (8.9%)	62 (12.0%)
Failure to Return/Lost-to-follow-up	2 (0.8%)	1 (0.4%)	3 (0.6%)
Violation of Selection at Entry	17 (6.6%)	10 (3.9%)	27 (5.2%)
Other Protocol Violation	10 (3.9%)	6 (2.3%)	16 (3.1%)
Did Not Cooperate	12 (4.7%)	9 (3.5%)	21 (4.1%)
Refused treatment	7 (2.7%)	5 (1.9%)	12 (2.3%)
Withdrew consent	5 (1.9%)	4 (1.6%)	9 (1.7%)
Admin/Other	12 (4.7%)	15 (5.8%)	27 (5.2%)
Discontinuation During Follow-up Period			
Completed	170 (65.9%)	155 (60.1%)	325 (63.0%)
Discontinued	88 (34.1%)	103 (39.9%)	191 (37.0%)
Primary Reason for Discontinuation			
Adverse Event/Intercurrent Illness†	2 (0.8%)	5 (1.9%)	7 (1.4%)
Death	56 (21.7%)	67 (26.0%)	123 (23.8%)
Failure to Return/Lost-to-follow-up	8 (3.1%)	9 (3.5%)	17 (3.3%)
Admin/Other	15 (5.8%)	15 (5.8%)	30 (5.8%)
Withdrew Consent‡	7 (2.7%)	7 (2.7%)	14 (2.7%)

Patients identified as completed under Treatment Discontinuation, received a maximum of 84 days of treatment or had a successful overall outcome and received a minimum of 7 days of therapy. Patients identified as completed under Discontinuation During the Follow-up Period, completed a follow-up visit after the EOT visit.

ISA: isavuconazole; ITT: intent-to-treat; VRC: voriconazole.

† This information was collected up to amendment 2.

‡ This information was collected from amendment 3.

Source: 12.1.1.3.1

Table 2 Patient Disposition and Analysis Set

Populations for Analysis	**ISA**	**VRC**	**Total**
Randomized	263 (100%)	264 (100%)	527 (100%)
ITT	258 (98.1%)	258 (97.7%)	516 (97.9%)
mITT	143 (54.4%)	129 (48.9%)	272 (51.6%)
mITT-FDA	147 (55.9%)	128 (48.5%)	275 (52.2%)
PPS-ITT	172 (65.4%)	175 (66.3%)	347 (65.8%)
PPS-mITT	108 (41.1%)	96 (36.4%)	204 (38.7%)
SAF	257 (97.7%)	259 (98.1%)	516 (97.9%)

Percentages were calculated based upon the Randomized population.

ISA: isavuconazole; VRC: voriconazole.

Source: Tables 12.1.1.2 and 12.3.2.4

Table 3 Demographics and Baseline Characteristics (ITT Population)

Parameter Statistics	ISA (n = 258)	VRC (n = 258)	Total (n = 516)
Age (years)			
Mean	51.1	51.2	51.1
Median	54.0	53.5	54.0
Min - Max	17 - 82	18 - 87	17 - 87
Age Category			
≤ 45 years	94 (36.4%)	101 (39.1%)	195 (37.8%)
> 45 - ≤ 65 years	108 (41.9%)	99 (38.4%)	207 (40.1%)
> 65 - ≤ 75 years	46 (17.8%)	51 (19.8%)	97 (18.8%)
> 75 years	10 (3.9%)	7 (2.7%)	17 (3.3%)
Sex			
Male	145 (56.2%)	163 (63.2%)	308 (59.7%)
Female	113 (43.8%)	95 (36.8%)	208 (40.3%)
Race			
White	211 (81.8%)	191 (74.3%)	402 (78.1%)
Black or African American	1 (0.4%)	1 (0.4%)	2 (0.4%)
Asian	45 (17.4%)	64 (24.9%)	109 (21.2%)
Other	1 (0.4%)	1 (0.4%)	2 (0.4%)
Missing	0	1	1
Ethnicity			
Hispanic or Latino	22 (8.5%)	9 (3.5%)	31 (6.0%)
Not Hispanic or Latino	236 (91.5%)	248 (96.5%)	484 (94.0%)
Missing	0	1	1
BMI (kg/m^2)			
n	251	249	500
Mean	24.2	23.7	23.9
Median	23.4	23.4	23.4
Min - Max	13.9 - 50.0	14.5 - 38.0	13.9 - 50.0
Geographical Region†			
North America	30 (11.6%)	28 (10.9%)	58 (11.2%)
Western Europe plus Australia and New Zealand	105 (40.7%)	107 (41.5%)	212 (41.1%)
Other Regions	123 (47.7%)	123 (47.7%)	246 (47.7%)
Hematologic malignancy	211 (81.8%)	222 (86.0%)	433 (83.9%)
Prior Allogeneic BMT	54 (20.9%)	51 (19.8%)	105 (20.3%)
Uncontrolled Malignancy at Baseline	173 (67.1%)	187 (72.5%)	360 (69.8%)
Neutropenic‡	163 (63.2%)	175 (67.8%)	338 (65.5%)
Use of Corticosteroids	48 (18.6%)	39 (15.1%)	87 (16.9%)
Use of T-Cell Immunosuppressant	111 (43.0%)	109 (42.2%)	220 (42.6%)
eGFR-MDRD ($mL/min/1.73\ m^2$)			
< 60	20 (8.0%)	33 (13.2%)	53 (10.6%)
≥ 60	231 (92.0%)	217 (86.8%)	448 (89.4%)
Missing	7	8	15

Age was calculated relative to informed consent date.
ANC: absolute neutrophil count; BMT: bone marrow transplant; eGFR-MDRD: estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; ISA: isavuconazole; ITT: intent-to-treat; VRC: voriconazole.
† North America consists of Canada and the US. Western Europe consists of Belgium, France, Germany, Italy, The Netherlands, Spain and Switzerland. Other Regions consists of Argentina, Brazil, Chile, China, Egypt, Hungary, India, Israel, Malaysia, Mexico, Poland, Russia, South Korea, Thailand and Turkey.
‡ The presence or absence of neutropenia was defined as ANC < 0.5×10^9/L (< $500/mm^3$) and was determined by the Investigator.
Source: Table 12.1.2.1.1

Table 4 All-cause Mortality Through Day 42 (ITT Population)

	ISA (n = 258)	VRC (n = 258)
All-cause Mortality	48 (18.6%)	52 (20.2%)
Adjusted Treatment Difference (ISA-VRC) (%) 95% CI (%)	-1.0 (-7.759, 5.683)	
Known Deaths	45 (17.4%)	50 (19.4%)
Unknown Survival Status†	3 (1.2%)	2 (0.8%)

Adjusted treatment difference (ISA-VRC) was calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic BMT Status and Uncontrolled Malignancy Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

BMT: bone marrow transplant; CMH: Cochran-Mantel-Haenszel; ISA: isavuconazole; ITT: intent-to-treat; VRC: voriconazole.

† A patient with unknown survival status was treated as a death.

Source: Table 12.3.1.1

Table 5 All-cause Mortality Through Day 42 and Day 84 for Various Populations

	ISA		VRC		Treatment Difference (%) 95% CI (%)†
	n	n (%)	n	n (%)	
Through Day 42					
mITT	143	28 (19.6)	129	30 (23.3)	−2.6 (−12.184, 6.916)
mITT–FDA‡	147	28 (19.0)	128	28 (21.9)	−2.1 (−11.422, 7.215)
PPS-ITT	172	26 (15.1)	175	31 (17.7)	−2.6 (−10.283, 5.079)
PPS-mITT	108	16 (14.8)	96	19 (19.8)	−5.1 (−15.166, 5.024)
ITT-excluding no IFD§	231	43 (18.6)	237	49 (20.7)	−1.3 (−8.424, 5.830)
myITT¶	123	23 (18.7)	108	24 (22.2)	−2.7 (−12.893, 7.542)
Through Day 84					
ITT	258	75 (29.1)	258	80 (31.0)	-1.4 (-9.150, 6.340)
mITT	143	43 (30.1)	129	48 (37.2)	-5.5 (-16.059, 5.148)
mITT–FDA‡	147	41 (27.9)	128	43 (33.6)	-4.7 (-15.099, 5.748)
PPS-ITT	172	43 (25.0)	175	48 (27.4)	-2.8 (-11.861, 6.234)
PPS-mITT	108	29 (26.9)	96	31 (32.3)	-5.7 (-17.735, 6.303)
ITT-excluding no IFD	231	67 (29.0)	237	75 (31.6)	-1.9 (-10.055, 6.216)
myITT¶	123	35 (28.5)	108	39 (36.1)	-5.7 (-17.062, 5.577)

A patient with unknown survival status was treated as a death.

BAL: bronchoalveolar lavage; BMT: bone marrow transplant; CMH: Cochran-Mantel-Haenszel; GM: galactomannan; GMc: galactomannan criteria; IFD: invasive fungal disease; ISA: isavuconazole; VRC: voriconazole.

† The adjusted treatment difference (ISA-VRC) was calculated by a stratified CMH method with Geographical Region, Allogeneic BMT Status and Uncontrolled Malignancy Status as the stratification factors. The 95% CI for the adjusted treatment difference was based on a normal approximation.

‡ The GMc used for the mITT population was 2 consecutive serum GM values ≥ 0.5 or at least one serum GM value ≥ 0.7 as defined in the protocol. The GMc used for the mITT-FDA population was 2 consecutive serum GM values ≥ 0.5 or at least 1 serum or BAL GM value ≥ 1.0.

§ The ITT-excluding no IFD population is the ITT population excluding those who were assessed by the DRC as not having adequate evidence of proven, probable or possible IFD.

¶ The myITT population consisted of mITT patients with proven or probable invasive aspergillosis based on cytology, histology, culture or GMc.

Source: Tables 12.3.1.2.1, 12.3.1.4 and 12.3.7.1.3 (day 42); Tables 12.3.1.6, 12.3.1.8, 12.3.7.1.4 and 12.3.7.1.6 (day 84)

Table 6 DRC-assessed Overall Response at EOT (mITT Population)

Outcome Response	ISA (n = 143)	VRC (n = 129)
Success	50 (35.0%)	47 (36.4%)
Adjusted Treatment Difference (VRC-ISA) (%) 95% CI (%)	1.6 (-9.336, 12.572)	
Complete	17 (11.9%)	13 (10.1%)
Partial	33 (23.1%)	34 (26.4%)
Failure	93 (65.0%)	82 (63.6%)
Stable	42 (29.4%)	33 (25.6%)
Progression	51 (35.7%)	49 (38.0%)

Adjusted treatment difference (VRC-ISA) was calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic BMT Status and Uncontrolled Malignancy Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

BMT: bone marrow transplant; CMH: Cochran-Mantel-Haenszel; DRC: Data Review Committee; EOT: end of treatment; ISA: isavuconazole; VRC: voriconazole.

Source: Table 12.3.2.1

Table 7 DRC-assessed Overall Response for Various Populations

Success by Analysis Set	ISA		VRC		Treatment Difference (%) 95% CI (%)†
	n	n (%)	n	n (%)	
At EOT					
mITT–FDA‡	147	52 (35.4%)	128	47 (36.7%)	1.8 (-9.004, 12.605)
PPS-mITT	108	43 (39.8%)	96	42 (43.8%)	2.8 (-9.990, 15.585)
myITT§	123	43 (35.0%)	108	42 (38.9%)	4.0 (-7.973, 15.875)
At Day 42					
mITT	143	51 (35.7%)	129	46 (35.7%)	-0.5 (-11.277, 10.329)
myITT§	123	44 (35.8%)	108	41 (38.0%)	0.5 (-11.442, 12.502)

BAL: bronchoalveolar lavage; BMT: bone marrow transplant; CMH: Cochran-Mantel-Haenszel; DRC: Data Review Committee; EOT: end of treatment; GM: galactomannan; GMc: galactomannan criteria; ISA: isavuconazole; VRC: voriconazole.

† Adjusted treatment difference (VRC-ISA) was calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic BMT Status and Uncontrolled Malignancy Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

‡ The GMc used for the mITT population was 2 consecutive serum GM values ≥ 0.5 or at least one serum GM value ≥ 0.7. The GMc used for the mITT-FDA population was 2 consecutive serum GM values ≥ 0.5 or at least 1 serum or BAL GM value ≥ 1.0.

§ The myITT population consisted of mITT patients with proven or probable invasive aspergillosis based on cytology, histology, culture or GMc.

Source: Tables 12.3.2.4 and 12.3.2.5 (EOT); 12.3.2.9 and 12.3.2.12 (day 42)

Table 8 Overview of Deaths and TEAEs

	ISA (n = 257) n (%)	VRC (n = 259) n (%)
TEAEs	247 (96.1%)	255 (98.5%)
Study Drug-related TEAEs†	109 (42.4%)	155 (59.8%)
Serious TEAEs‡	134 (52.1%)	149 (57.5%)
Study Drug-related Serious TEAEs	28 (10.9%)	29 (11.2%)
TEAEs Leading to Permanent Discontinuation of Study Drug	37 (14.4%)	59 (22.8%)
TEAEs Leading to Death	62 (24.1%)	72 (27.8%)
Study Drug-related TEAEs Leading to Permanent Discontinuation of Study Drug	21 (8.2%)	35 (13.5%)
Study Drug-related TEAEs Leading to Death	7 (2.7%)	6 (2.3%)
Deaths Through 28 Days after the Last Dose of Study Drug	62 (24.1%)	70 (27.0%)
Deaths§	81 (31.5%)	87 (33.6%)

TEAEs leading to death were counted regardless of time after the last dose of study drug.

ISA: isavuconazole; TEAE: treatment-emergent adverse event; VRC: voriconazole.

† Study drug-related TEAEs includes those reported as remotely, possibly or probably related to the study drug by the Investigator and those with a missing relationship.

‡ A TEAE with a missing seriousness was considered a serious TEAE.

§ Includes all deaths reported after the first dose of study drug.

Source: Table 12.6.1.1

Table 9 Most Common TEAEs Occurring in ≥ 5% of Patients in Either Treatment Arm by Preferred Term

MedDRA v12.1 Preferred Term	ISA (n = 257) n (%)	VRC (n = 259) n (%)
Patients with ≥ 1 TEAE	247 (96.1)	255 (98.5)
Nausea	71 (27.6)	78 (30.1)
Vomiting	64 (24.9)	73 (28.2)
Diarrhoea	61 (23.7)	60 (23.2)
Pyrexia	57 (22.2)	78 (30.1)
Hypokalaemia	45 (17.5)	56 (21.6)
Headache	41 (16.0)	38 (14.7)
Constipation	36 (14.0)	54 (20.8)
Dyspnoea	34 (13.2)	29 (11.2)
Cough	33 (12.8)	35 (13.5)
Febrile neutropenia	32 (12.5)	38 (14.7)
Chills	27 (10.5)	23 (8.9)
Fatigue	27 (10.5)	18 (6.9)
Back pain	26 (10.1)	19 (7.3)
Oedema peripheral	26 (10.1)	31 (12.0)
Abdominal pain	25 (9.7)	36 (13.9)
Hypertension	25 (9.7)	31 (12.0)
Insomnia	23 (8.9)	24 (9.3)
Mucosal inflammation	23 (8.9)	14 (5.4)
Decreased appetite	22 (8.6)	28 (10.8)
Epistaxis	21 (8.2)	28 (10.8)
Hypotension	21 (8.2)	28 (10.8)
Anxiety	20 (7.8)	17 (6.6)
Pruritus	19 (7.4)	15 (5.8)

MedDRA v12.1 Preferred Term	ISA (n = 257) n (%)	VRC (n = 259) n (%)
Table continued on next page		
Rash	17 (6.6)	28 (10.8)
Asthenia	16 (6.2)	20 (7.7)
Confusional state	16 (6.2)	20 (7.7)
Gamma-glutamyl transferase increased	16 (6.2)	22 (8.5)
Haemoptysis	16 (6.2)	17 (6.6)
Abdominal pain upper	15 (5.8)	25 (9.7)
Cytomegalovirus infection	15 (5.8)	23 (8.9)
Dyspepsia	15 (5.8)	13 (5.0)
Septic shock	15 (5.8)	10 (3.9)
Hypomagnesaemia	14 (5.4)	27 (10.4)
Oropharyngeal pain	14 (5.4)	14 (5.4)
Respiratory failure	14 (5.4)	17 (6.6)
Alanine aminotransferase increased	13 (5.1)	17 (6.6)
Oedema	13 (5.1)	18 (6.9)
Oral herpes	13 (5.1)	14 (5.4)
Anaemia	12 (4.7)	23 (8.9)
Blood alkaline phosphatase increased	12 (4.7)	15 (5.8)
Tachycardia	12 (4.7)	21 (8.1)
Aspartate aminotransferase increased	11 (4.3)	14 (5.4)
Pain in extremity	11 (4.3)	15 (5.8)
Thrombocytopenia	11 (4.3)	25 (9.7)
Dizziness	10 (3.9)	15 (5.8)
Hyperglycaemia	10 (3.9)	13 (5.0)
Erythema	9 (3.5)	15 (5.8)
Staphylococcal bacteraemia	7 (2.7)	13 (5.0)
Hypoglycaemia	5 (1.9)	13 (5.0)
Rales	5 (1.9)	14 (5.4)
Bacteraemia	4 (1.6)	14 (5.4)
Visual impairment	4 (1.6)	19 (7.3)

ISA: isavuconazole; TEAE: treatment-emergent adverse event; VRC: voriconazole.

Source: Table 12.6.1.5

Table 10 Most Common Serious TEAEs Occurring in ≥ 1% of Patients in Either Treatment Arm by Preferred Term

MedDRA v12.1 Preferred Term	ISA (n = 257) n (%)	VRC (n = 259) n (%)
Patients with ≥ 1 Serious TEAE	134 (52.1)	149 (57.5)
Respiratory failure	14 (5.4)	12 (4.6)
Septic shock	14 (5.4)	10 (3.9)
Febrile neutropenia	14 (5.4)	5 (1.9)
Pyrexia	8 (3.1)	10 (3.9)
Sepsis	7 (2.7)	8 (3.1)
Renal failure acute	6 (2.3)	8 (3.1)
Pneumonia	5 (1.9)	10 (3.9)
Acute respiratory failure	5 (1.9)	5 (1.9)
Dyspnoea	5 (1.9)	1 (0.4)
Aspergillosis	4 (1.6)	3 (1.2)
Neutropenia	4 (1.6)	3 (1.2)
Pancytopenia	4 (1.6)	3 (1.2)
Respiratory distress	4 (1.6)	3 (1.2)
Acute myeloid leukemia	3 (1.2)	8 (3.1)
Thrombocytopenia	3 (1.2)	4 (1.5)
Fungal infection	3 (1.2)	3 (1.2)
Renal failure	3 (1.2)	2 (0.8)
Convulsion	3 (1.2)	1 (0.4)
Haemorrhage intracranial	2 (0.8)	3 (1.2)
Multi-organ failure	1 (0.4)	7 (2.7)
Cardiac arrest	1 (0.4)	5 (1.9)
Gastrointestinal haemorrhage	0	3 (1.2)
Bacterial sepsis	0	4 (1.5)
Staphylococcal bacteraemia	0	3 (1.2)
Acute myeloid leukemia recurrent	0	5 (1.9)
Epistaxis	0	4 (1.5)
Lung infiltration	0	3 (1.2)
Pulmonary embolism	0	3 (1.2)

A TEAE with a missing seriousness was considered as a serious TEAE.

ISA: isavuconazole; TEAE: treatment-emergent adverse event; VRC: voriconazole.

Source: Table 12.6.1.11