Name of Sponsor/Company: Basilea Pharmaceutica, Ltd., followed by Astellas Pharma Global Development, Inc.		
Name of Finished Product: Isavuconazonium sulfate		
Name of Active Ingredient: Isavuconazole		

SYNOPSIS

Title of Study: A Phase III, Double-Blind, Randomized Study to Evaluate the Safety and Efficacy of BAL8557 Versus a Caspofungin Followed by Voriconazole Regimen in the Treatment of Candidemia and Other Invasive Candida Infections

Investigators/Coordinating Investigator: [redacted], MD

Study Center(s): This multicenter study was conducted in 116 centers in 25 countries (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: 8 years

Study Initiation Date (Date of First Enrollment): March 08, 2007

Study Completion Date (Date of Last Evaluation): March 03, 2015

Phase of Development: phase 3

Objectives: The primary objective was to compare the efficacy of treatment with isavuconazole vs caspofungin in patients with candidemia or other invasive *Candida* infections. The secondary objectives of the study were to assess safety and tolerability of treatment with isavuconazole vs caspofungin/voriconazole regimen.

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Methodology: This was a phase 3, randomized (1:1), multicenter, double-blind, double-dummy, noninferiority, comparative group study of isavuconazole vs caspofungin followed by voriconazole. Isavuconazole and caspofungin were administered using intravenous (IV) infusion for loading doses on days 1 and 2 (isavuconazole: 200 mg tid; caspofungin: 70 mg on day 1 and 50 mg on day 2), followed by IV maintenance doses from day 3 until end of treatment (EOT) (isavuconazole: 200 mg qd; caspofungin: 50 or 70 mg qd). Starting on day 11 at the discretion of the investigator, oral therapy (200 mg isavuconazole qd or 400 mg voriconazole bid on day 1 of oral dosing, then 200 mg voriconazole bid thereafter) could be given in preference to IV dosing. Patients who switched from IV to oral therapy could not be switched back to IV therapy.

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.

A blinded Data Review Committee (DRC) consisting of experts in the field of fungal infections was established to confirm, independently of the Sponsor and the Investigators, the diagnosis of candidemia or invasive

Candida infection, to evaluate the individual patient clinical and mycological responses and to assess attributable mortality.

A pharmacokinetic substudy was conducted at select centers. Measurement of concentration-time profiles of isavuconazole and possible metabolite(s) and 24-hour Holter electrocardiogram (ECG) were done on day 7 or 14. These data will be used in combination with other isavuconazole study data in population pharmacokinetic modeling. In addition, trough samples were collected from all patients.

Number of Patients (Planned, Enrolled and Analyzed): Approximately 438 consenting adult patients were planned to be enrolled. A total of 472 patients were consented for the study. Of these, 450 patients were randomized, and 440 patients (97.8%) took at least 1 dose of study drug and were included in the intent-to-treat (ITT) population. A total of 400 ITT patients had documented invasive candidiasis or candidemia at baseline based on the assessment of the independent blinded DRC and were included in the modified intent-to-treat (mITT) population.

Diagnosis and Main Criteria for Inclusion: Male and female patients ≥ 18 years of age, with candidemia or an invasive Candida infection were enrolled into the study. Patients with a known history of allergy, hypersensitivity or any serious reaction to the azole or echinocandin class of antifungals, for whom caspofungin or voriconazole was contra-indicated, at high risk for QT interval corrected for heart rate (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, everolimus, efavirenz, ritonavir, astemizole, cisapride, rifampin/rifampicin, rifabutin, ergot alkaloids, long acting barbiturates, carbamazepine, pimozide, quinidine, neostigmine, ketoconazole, valproic acid, St. John's Wort or terfenadine 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). Placebo capsules were provided to mirror the caspofungin → voriconazole treatment regimen, each containing only lactose monohydrate.

Duration of Treatment (or Duration of Study, if applicable): All patients receiving study drug were to undergo the assessments as scheduled and remain on therapy until they had reached a defined treatment endpoint or until they had received treatment for a maximum period of 56 days. The follow-up visits were to be performed 2 and 6 weeks after the last dose of study drug.

Reference Product, Dose and Mode of Administration, Batch Numbers: Caspofungin for IV administration was provided as a lyophilized powder. Each vial contained 50 or 70 mg caspofungin and included sucrose, mannitol, glacial acetic acid and sodium hydroxide as excipients to be dissolved in 250 mL of a compatible infusion solution. For oral therapy, over-encapsulated voriconazole tablets were provided, each tablet containing 200 mg of voriconazole and the inactive ingredients of lactose monohydrate, pregelatinized starch, croscarmellose sodium, povidone, magnesium stearate and a coating containing hypromellose, titanium dioxide,

lactose monohydrate and glycerol triacetate (or triacetin). Each tablet was over-encapsulated to ensure blinding. The capsules contained lactose monohydrate and the voriconazole tablet. Placebo capsules were provided to mirror the isavuconazole treatment regimen, each capsule containing lactose monohydrate, cellulose (microcrystalline) and magnesium stearate.

Caspofungin was chosen as the active comparator for this study as echinocandins are more suitable than polyenes and currently available triazoles for IV treatment of renally impaired patients and physicians are increasingly using caspofungin as a first-line agent for the treatment of candidemia and invasive *Candida* infections. In clinical practice, patients treated with IV caspofungin are often switched to an oral azole. The switch to fluconazole could have led to unblinding of a significant proportion of patients because of fluconazole-resistant pathogens. Therefore, voriconazole was chosen as the oral follow-up for this study. While a caspofungin → voriconazole regimen has not been specifically studied, in the absence of antagonism between these 2 antifungals and supported by current medical practice of switch, efficacy of this switch regimen must be expected to be in the range of that achieved by the individual compounds.

Criteria for Evaluation: The Investigator assessed clinical signs and symptoms of invasive fungal infection (as clinically indicated for individual patients) at screening and at days 7, 14, 28, 42, 56/EOT, follow-up visit 1 (FU1; 2 weeks after EOT) and follow-up visit 2 (FU2; 6 weeks after EOT).

Procedures for processing blood culture samples (from bedside to laboratory) were to be followed according to local best clinical practice. Blood samples for culture were taken prior to the start of daily study drug administration. Blood cultures were performed daily until 2 sequential negative culture results, were confirmed. Additionally, blood cultures were to be obtained for all patients (unless they were a failure previously) at FU1. Samples from normally sterile non-bloodstream sites were required to confirm invasive candidiasis. If, during the study period, relevant cultures yielded voriconazole- or caspofungin-resistant species (i.e., invasive fungal disease [IFD], not colonization of superficial surfaces, sputum or urine), patients could remain in the study in the presence of clinical improvement, or otherwise they were considered as failures and were withdrawn from the study.

If positive mycology results occurred after successful mycological response (proven or presumed eradication), an evaluation was made as to whether the infection was recurrent (same species as at baseline) or emergent (different species) compared to baseline. Patients with recurrent or emergent infection were classified as mycological failure from the visit onwards where positive cultures were reported, i.e., positive cultures before the FU1 visit were categorized as mycological failure and overall non-successful response on the primary efficacy assessment.

If clinically indicated, radiological assessments (e.g., computed tomography or high resolution computed tomography) were performed at screening and on days 7, 14, 28/42 and day 56 or EOT. For patients with abnormalities at EOT, radiological assessments were to be repeated at FU1 and FU2 unless or until the abnormalities were resolved.

Survival status was recorded at day 14, EOT, FU1 and FU2. Information on survival status was to be collected, irrespective of when treatment was discontinued.

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The Investigator evaluated safety by monitoring treatment-emergent adverse events (TEAEs) and findings from physical examination, vital signs (systolic blood pressure and diastolic blood pressure, pulse rate and body temperature), laboratory tests, 12-lead ECG, ophthalmologic evaluation, imaging and concomitant medication/surgery. In addition, findings from 24-hour Holter ECG were evaluated for patients in the pharmacokinetic substudy.

Samples for a full safety profile including hematology, biochemistry and urinalysis were collected at screening, at study visits on days 7, 14, 28, 42 (if the patient was still receiving study drug), EOT and FU1. On days 3 and 7, hematology and biochemistry tests were performed. In case of abnormalities at FU1, laboratory safety tests were repeated at FU2.

Twelve-lead ECG recordings were obtained at screening and were also performed on days 1, 14, 42 and EOT. 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 using Bazett's formula (QTcB), QT interval corrected for heart rate using Fridericia's formula (QTcF) and a qualitative ECG interpretation. In addition, patients in the pharmacokinetic substudy had two 24-hour Holter ECG assessments: a baseline assessment either at screening or on the follow-up visit and a second assessment either on day 7 or day 14. Assessments with the 24-hour Holter ECG included the same variables as those for the 12-lead ECGs.

Vital signs were assessed at screening and on days 1, 2, 3, 4, 5, 6, 7, 8, 9, 28, 42 (if the patient was still receiving study drug), EOT and FU1. At FU2, vital signs assessments were performed only in patients with abnormalities observed at the previous visit.

Physical examinations were conducted at screening and EOT. At FU1 or FU2, physical examination was only performed in patients with abnormalities observed at EOT or FU1, respectively.

An ophthalmologic evaluation was conducted within 96 (ideally 24) hours of the first dose. An ophthalmologic evaluation was repeated on days 7, 14, 28, 42 (if the patient was still receiving study drug), EOT, FU1 and FU2, if results were abnormal at the previous visit. The ophthalmologic evaluation included an examination of the external eye for lesions, inflammation or edema and an examination of the fundus to assess retinal appearance.

Blood sampling for the analysis of plasma trough concentrations was obtained for all patients immediately prior to administration of the first daily study drug (infusion or capsule) but no earlier than 1 hour prior to dosing at study visits on days 7, 14, 42, EOT and FU1. The day 42 sample was only taken if the patient was still taking study drug. The EOT sample was taken prior to the last morning administration of study drug or 24 hours after the last morning administration.

Statistical Methods: Continuous data were summarized descriptively including number of patients (n), mean, 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.

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 noninferiority margin (NIM).

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

- The ITT population consisted of all randomized patients who received at least one dose of study drug. For this population, data were analyzed by the treatment group that patients were randomized to.
- The mITT population consisted of ITT patients who had documented invasive candidiasis or candidemia at baseline based on the assessment of the independent blinded DRC.
- The ITT-excluding no IFD population consisted of all ITT patients with IFD.
- The Per Protocol Set (PPS) was a subset of mITT patients who did not meet the classification criteria for exclusion from the PPS.
- 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 PKAS consisted of a subset of the SAF who had at least one isavuconazole plasma concentration value available.

Demographic and other baseline characteristics (age, gender, race, ethnicity, height, weight, body mass index [BMI], Acute Physiology and Chronic Health Evaluation (APACHE) II score, age category 1 [≤ 45, > 45 to ≤ 65, > 65 years], age category 2 [≤ 65, > 65 to ≤ 75, > 75 years], BMI category [< 25, ≥ 25 to < 30, ≥ 30 kg/m^2], APACHE II score category [≤ 20, > 20], APACHE II score category 2 [< 15, ≥ 15], estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula (eGFR-MDRD) category [< 60, ≥ 60 mL/min/1.73 m^2], baseline neutropenic status [presence, absence] and geographical region [North America, Western Europe including Australia and New Zealand, Other Regions]) and study drug exposure were summarized descriptively by overall group and by treatment group for the ITT, mITT and PPS populations. Because 1 patient who was randomized to isavuconazole actually received caspofungin at the first dose, the summaries of demographics and study drug exposure were also performed for the SAF. Baseline neutropenia was defined as an absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L (<500/mm^3) for ≥ 10 days as entered on the electronic case report form (eCRF).

The primary efficacy endpoint was the overall response at end of intravenous treatment (EOIV) as derived based on the DRC assessments of clinical and mycological responses as well as alternative systemic antifungal therapy (AFT) use, and was analyzed in the mITT population. If the clinical or mycological response or alternative systemic AFT use in a patient at the EOIV was not assessed by the DRC or was assessed as "Unevaluable," the patient was counted as a failure. Deaths that occurred through the EOIV were also treated as failures. The treatment difference, subtracting caspofungin rate from isavuconazole rate, (isavuconazole [ISA]-caspofungin [CAS]) and the SE were calculated using a stratified Cochran-Mantel-Haenszel (CMH) method and the 95% CI was constructed based on a normal approximation. The strata included geographical region and baseline neutropenic status. The lower bound of the 95% CI for the treatment difference was compared to the protocol prespecified noninferiority margin (NIM) value of -15%. If the lower bound were

greater than -15%, isavuconazole would be declared as noninferior to caspofungin with respect to the primary efficacy endpoint.

A sensitivity analysis was conducted on the primary efficacy endpoint for the mITT population using a stratified Minimum-Risk analysis including the same stratification factors that were used in the calculation of treatment group difference and 95% CIs. In addition, a sensitivity analysis was conducted on the primary efficacy endpoint for the mITT population without using the stratification factors for the calculation of treatment group difference and 95% CIs.

Additional analyses of the primary efficacy endpoint included analyses in various populations (ITT-excluding no IFD and PPS), subsets (mITT patients with invasive candidiasis with or without candidemia and mITT patients with candidemia only), strata (mITT patients by baseline catheter status, DRC assessments of baseline site of infection and DRC assessments of baseline organism causing the IFD), subgroups (age categories, gender, race, ethnicity, BMI category, eGFR-MDRD category, APACHE II score category and APACHE II score category 2) and by persistence of neutropenia (if a patient met the criterion [i.e., laboratory ANC or WBC $< 0.5 \times 10^9$/L on consecutive days within a 7-day period] during day 2 through 1 day after EOIV at any time period, the patient was considered as having persistent neutropenia). A treatment-by-subgroup interaction was evaluated using a logistic regression model with the following factors: treatment group, geographical region, baseline neutropenic status, subgroup factor and treatment-by-subgroup interaction. The interaction was evaluated at the significance level of 0.15. Subgroup levels with fewer than 10 patients within any treatment group were excluded when the interaction was assessed.

The key secondary efficacy endpoint, success rate of overall response at FU1 derived from the clinical and mycological responses and systemic AFT use as assessed by the DRC, was assessed using the same method as for the primary efficacy endpoint and in various populations, subsets, strata and subgroups. A patient that was not evaluated by the DRC at a visit was considered as missing under failure category for that visit. A patient that was labeled as "Unevaluable" by the DRC at a visit was considered as unevaluable under failure category for that visit. Any death by EOT (FU1 or FU2) was considered as a failure for that visit and any subsequent visits. After the noninferiority for the primary efficacy endpoint was declared, the noninferiority for the key secondary endpoint was established if the lower limit of the 95% CI was greater than -15%.

DRC-assessed secondary efficacy endpoints included success rate of overall response as derived from the DRC assessments at EOT, success rate of overall response as derived from the DRC assessments at FU2 and mycological response and clinical response as assessed by the DRC at EOIV, EOT, FU1 and FU2. Investigator-assessed secondary efficacy endpoints included clinical assessment and mycological assessments. The DRC-assessed and Investigator-assessed secondary efficacy endpoints were assessed in the mITT population using the same method as for the primary efficacy endpoint.

Secondary efficacy endpoints related to time-to-event analysis included all-cause mortality and time to first confirmed negative blood culture. All-cause mortality was assessed in the ITT and mITT populations using the same method as for the primary efficacy endpoint. A time-to-event analysis was performed using Kaplan-Meier method that generated a survival function. A patient without a reported death was censored on the patient's last assessment day. Time to first confirmed negative blood culture was analyzed using Kaplan-Meier in the subset of mITT population who were assessed to be 'Candidemia Only.' A patient without a confirmed negative blood culture was censored on the patient's last assessment day.

Other efficacy endpoints included DRC-assessed attributable mortality, DRC-assessed emergence and recurrence of infection and Investigator-assessed emergence and recurrence of infection. Attributable mortality during the study was categorized by the DRC as directly due to consequences of progressive IFD, associated with no evidence of residual or ongoing IFD, indeterminate cause or no known death. The number and percentage of patients within each category were presented for the mITT population. For the DRC-assessed emergence of infection, the number and percentage of mITT patients at EOIV, EOT, FU1 and FU2 were presented according to any emergent infection, type and site of infection and organism. For the DRC-assessed recurrence of infection, the number and percentage of mITT patients at EOT, FU1 and FU2 were presented according to the following DRC-assessed variables in the subset of the mITT population who achieved an overall response at the prior visit: any recurrent infection, site of infection and organism. The Investigator-assessed emergence and recurrence of infection was presented in listings.

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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.

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 by acute pancreatitis SMQ (narrow); Hallucinations by selected PTs; Potential hypersensitivity reactions including infusion/injection site reactions (HLT) and Anaphylaxis SMQ (narrow) and severe cutaneous adverse reactions (SCAR) SMQ (narrow); Visual disturbances by selected PTs (presented by medical concept/PT; the 4 medical concepts were visual impairment, photophobia, visual field defect and colour blindness); Torsade de pointes SMQ (broad); and Potential Infusion-related Reactions (IRRs) by selected PTs.

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, day 7, day 14, day 28, day 42, EOIV, EOT, FU1 and FU2. 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 upper limit of normal) in liver chemistries (i.e., alanine transaminase [ALT], aspartate transaminase [AST],

alkaline phosphatase [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).

Nephrotoxicity was assessed using serum creatinine and further analyzing the values by the following 3 categories: ≥ 25%, ≥ 50% and ≥ 100% increase from baseline.

Vital signs including systolic and diastolic blood pressure (mmHg), pulse rate (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 the Investigator 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 criteria for change from baseline were summarized by treatment group in 4 ways: by taking the greatest or smallest postdose change from baseline and the greatest or smallest postdose change from baseline during IV, at EOIV and at EOT. For the prolonged categories, the greatest change from baseline was used, while the smallest change was used for the shortened category.

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.

Summary of Results/Conclusions:

Patient disposition and the primary reasons for discontinuation during treatment and follow-up periods for the mITT 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 mITT population as shown in Table 3.

The total study drug duration was similar between the isavuconazole and caspofungin groups. The median duration of study drug administration was 15 days for total dosing, 11 days for IV dosing and 8 days for oral dosing. A total of 157 (35.7%) patients (72 [32.7%] patients in the isavuconazole group and 85 [38.6%] patients in the caspofungin group) switched from IV to oral study drug dosing.

Efficacy/Pharmacokinetic Results:

Efficacy Results: The overall response rates at EOIV were 60.3% in the isavuconazole group and 71.1% in the caspofungin group. The 95% CI around the adjusted treatment difference (ISA-CAS: -10.8%) was (-19.9%, -1.8%) Table 4. The lower bound of the 95% CI for the treatment difference (-19.9%) was less than the prespecified NIM of -15%, therefore, this study did not demonstrate noninferiority of isavuconazole relative to caspofungin. Similar results were obtained in the sensitivity analyses (minimum-risk method, no stratification factors) of the DRC-assessed overall response at EOIV.

Rates for the DRC-assessed overall response at EOIV were lower in the isavuconazole group than in the caspofungin group for all 4 populations analyzed (i.e., mITT patients with candidemia only, mITT patients with invasive candidiasis with or without candidemia, ITT patients excluding no IFD and the PPS).

The DRC-assessed overall response at EOIV was evaluated in several subgroups (age, gender, race, ethnicity, BMI, eGFR-MDRD and APACHE II score). Treatment-by-subgroup interaction was tested and a treatment-by-subgroup factor interaction was observed for BMI (P = 0.069; logistic regression) and eGFR-MDRD (P = 0.094; logistic regression). Most patients had BMI < 25 kg/m^2 and success rates were similar among isavuconazole (68.3%, 71/104) and among caspofungin (70.5%, 86/122) treated patients. Patients with BMI ≥ 25 kg/m^2 had a lower success rate in the isavuconazole group (53.2%, 42/79) than in the caspofungin group (73.2%, 52/71). The vast majority of patients had eGFR-MDRD ≥ 60 mL/min/1.73 m^2 and success rates in isavuconazole and caspofungin treated patients were 65.0% (91/140) and 70.5% (93/132), respectively. Patients with eGFR-MDRD < 60 mL/min/1.73 m^2 had a lower success rate in the isavuconazole group (49.0%, 25/51) than in the caspofungin group (73.1%, 49/67).

The key secondary efficacy endpoint of DRC-assessed overall response at FU1 was analyzed for the mITT population and response rates for success were similar in the isavuconazole group (54.8%) and caspofungin group (57.2%). The 95% CI around the adjusted treatment difference (ISA-CAS: -2.7%) was (-12.2%, 6.8%) Table 5. The results of the sensitivity analyses (minimum-risk method, no stratification factors) of DRC-assessed overall response at FU1 were consistent with the key secondary analysis of the DRC-assessed overall response at FU1 in the mITT population.

When analyzed by various populations (i.e., mITT patients with candidemia only, mITT patients with invasive candidiasis with or without candidemia and ITT patients excluding no IFD) and subgroups, the results for the DRC-assessed overall response at FU1 were generally similar to the overall analysis.

The DRC-assessed overall response rate at EOT was lower in the isavuconazole group (61.3%) than in the caspofungin group (72.1%). The DRC-assessed overall response rate at FU2 was similar in the isavuconazole group (43.2%) and the caspofungin group (48.3%).

In the isavuconazole vs caspofungin groups, all-cause mortality rates were similar between the 2 treatment groups through day 14 (14.6% vs 12.4%) and through day 56 (30.7% vs 29.9%).

Median time to first confirmed negative blood culture was similar between the isavuconazole and caspofungin groups (4.0 vs 3.0 days).

The DRC-assessed clinical response rates in the isavuconazole group vs caspofungin group were 76.4% vs 84.1% at EOIV, 76.4% vs 84.6% at EOT, 67.8% vs 67.7% at FU1 and 52.8% vs 58.2% at FU2.

The DRC-assessed mycological response rates in the isavuconazole group vs caspofungin group were 70.9% vs 85.6% at EOIV, 71.9% vs 87.6% at EOT, 66.8% vs 65.7% at FU1 and 51.8% vs 56.7% at FU2.

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Safety Results: During the entire treatment period, 1 or more TEAEs were reported by 95.0% of patients in the isavuconazole group and 94.5% of patients in the caspofungin group [Table 6]. During the IV treatment period, 1 or more TEAEs were reported by 87.7% of patients in the isavuconazole group and 87.3% of patients in the caspofungin group. The 5 most common TEAEs in both treatment groups were hypokalemia, pyrexia, diarrhea, vomiting and constipation during the entire treatment period [Table 7] and hypokalemia, diarrhea, vomiting, pyrexia and hypotension during the IV treatment period.

Approximately half of all patients experienced a serious TEAE during the entire treatment period [Table 6], which may be expected based on the underlying diseases in these patients. The most common serious TEAEs that occurred in ≥ 1% of patients in either the isavuconazole or caspofungin groups were septic shock, sepsis, respiratory failure, renal failure acute, multi-organ failure, respiratory distress, cardiac arrest, pulmonary embolism, bacterial sepsis, pneumonia aspiration, hypotension, bacteremia , oxygen saturation decreased, pneumonia, hypokalemia, anemia and vomiting [Table 8].

As expected in this patient population, the rate of fatal TEAEs was high [Table 6]. The most common TEAEs leading to death that occurred in ≥ 2% of patients in either the isavuconazole or caspofungin groups were septic shock, sepsis, respiratory failure and multi-organ failure. Very few patients experienced a fatal event that was considered related to study drug (during the entire treatment period: 3 isavuconazole treated patients [redacted] vs 1 caspofungin treated patient [redacted]; during the IV treatment period: 1 isavuconazole treated patient [redacted] vs no caspofungin treated patients).

The proportion of patients who permanently discontinued study drug due to a TEAE was low in both treatment groups [Table 6]. The most common TEAEs leading to study drug discontinuation that were reported in more than 1 patient in either the isavuconazole or caspofungin groups were septic shock, systemic candida, renal failure acute, chest discomfort, multi-organ failure and hepatic enzyme increased.

Important differences between the isavuconazole and caspofungin groups were noted relating to the incidence of sepsis-type events and events of respiratory and renal failure. More patients in the isavuconazole group experienced events of sepsis and septic shock, some of them being fatal. However, in the analysis of study drug-related TEAEs, the incidence of sepsis and septic shock was similar between the treatment groups. A posthoc analysis revealed that the higher rate of sepsis-type events for isavuconazole was observed among patients who had an overall response of failure at EOIV. More patients in the isavuconazole group experienced events of respiratory and renal failure, with more isavuconazole than caspofungin treated patients permanently discontinuing study drug due to respiratory-type events.

More isavuconazole than caspofungin treated patients experienced an infusion/injection site reaction, but the overall incidence was low (5.0%). In addition, more isavuconazole than caspofungin treated patients experienced an Infusion-related Reaction (8.2% vs 5.5%). Of note, none of the isavuconazole treated patients as opposed to 2 caspofungin treated patients experienced a hallucination-type event during the IV treatment period. When the entire treatment period was considered, 2 isavuconazole treated patients and 4 caspofungin treated

patients experienced such events. More isavuconazole than caspofungin treated patients experienced visual disturbances: in the isavuconazole vs caspofungin groups, visual disturbances were experienced by 6 vs 2 patients during the IV treatment period and by 7 vs 4 patients during the entire treatment period. Very few patients in either treatment group experienced an event of pancreatitis or an anaphylaxis/SCAR-type event.

Analysis of potential hepatotoxicity showed similar proportions of isavuconazole treated patients and caspofungin treated patients with an increase in liver chemistries. This similarity was also noted for increases in concomitant transaminases and total bilirubin. When all postbaseline results were analyzed, 6 isavuconazole treated patients and 4 caspofungin treated patients experienced a combined increase in ALT or AST > 3 x ULN and ALP < 2 x ULN and total bilirubin > 2 x ULN. No important differences were observed between the treatment groups for changes in hematology and chemistry safety laboratory measures.

No important changes from baseline for quantitative ECG measures, including QTcF, were noted in either treatment group. In the categorical analyses, however, more isavuconazole treated patients experienced a decrease in QTcF and more caspofungin treated patients experienced an increase in QTcF.

However, when ECGs were centrally analyzed for qualitative abnormalities, no differences between treatment groups were noted, including T/U wave abnormalities and ventricular rhythm disorders. Also, when events potentially associated with shortening of cardiac repolarization were analyzed, no differences between treatment groups were found.

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:

While this study did not meet the primary endpoint (DRC-assessed overall response at EOIV, NIM -15%) and thus noninferiority of isavuconazole to caspofungin was not demonstrated, response rates were similar between the isavuconazole and caspofungin groups for the key secondary efficacy endpoint of DRC-assessed overall response at FU1 (2 weeks after EOT) and for the DRC-assessed overall response at FU2 (6 weeks after EOT). The results for the DRC-assessed overall response rate at EOT were similar to those for the primary endpoint. All-cause mortality through day 14 and through day 56 and median time to first confirmed negative blood culture were similar between the treatment groups. The DRC-assessed mycological response rates were lower in the isavuconazole group than in the caspofungin group at EOIV and EOT and were similar between treatment groups at FU1 and FU2.

Isavuconazole was well tolerated and its tolerability was similar to that of caspofungin.

Date of Report: 11 Jan 2016

Table 1 Patient Disposition and Primary Reasons for Treatment and Study Discontinuation (mITT Population)

Number of Patients Consented	472		
Number of Patients Randomized	450		
Number of Patients Treated (mITT)	**ISA (n = 199)**	**CAS (n = 201)**	**Total (n = 400)**
Treatment Discontinuation			
Completed	119 (59.8%)	132 (65.7%)	251 (62.8%)
Treatment Completion Status			
Successful overall outcome plus 14 days further therapy	114 (57.3%)	124 (61.7%)	238 (59.5%)
Maximum 56 days treatment	5 (2.5%)	8 (4.0%)	13 (3.3%)
Discontinued	79 (39.7%)	69 (34.3%)	148 (37.0%)
Primary Reason for Discontinuation			
Adverse Event/Intercurrent Illness	13 (6.5%)	16 (8.0%)	29 (7.3%)
Death	20 (10.1%)	21 (10.4%)	41 (10.3%)
Insufficient Therapeutic Response	23 (11.6%)	10 (5.0%)	33 (8.3%)
Violation of Selection at Entry	2 (1.0%)	3 (1.5%)	5 (1.3%)
Other Protocol Violation	3 (1.5%)	5 (2.5%)	8 (2.0%)
Did Not Cooperate	11 (5.5%)	6 (3.0%)	17 (4.3%)
Refused treatment	3 (1.5%)	2 (1.0%)	5 (1.3%)
Withdrew consent	8 (4.0%)	4 (2.0%)	12 (3.0%)
Admin/Other	7 (3.5%)	8 (4.0%)	15 (3.8%)
Study Discontinuation			
Completed	115 (57.8%)	121 (60.2%)	236 (59.0%)
Discontinued	83 (41.7%)	80 (39.8%)	163 (40.8%)
Primary Reason for Discontinuation			
Death	51 (25.6%)	52 (25.9%)	103 (25.8%)
Failure to Return/Lost-to-follow-up	12 (6.0%)	15 (7.5%)	27 (6.8%)
Admin/Other	12 (6.0%)	12 (6.0%)	24 (6.0%)
Withdrew Consent†	8 (4.0%)	1 (0.5%)	9 (2.3%)
Missing‡	1 (0.5%)	0	1 (0.3%)

CAS: caspofungin; ISA: isavuconazole; mITT: modified intent-to-treat.

Only the primary reason for discontinuation was collected.

The isavuconazole group included patients who switched to oral isavuconazole (mITT: 69/199 patients).

The caspofungin group included patients who switched to oral voriconazole (mITT: 80/201 patients).

† This information was collected from amendment 4.

‡ Patients who did not have treatment or study completion status collected.

Source: 12.1.1.3.2

Table 2 Patient Disposition and Analysis Sets

Populations for Analysis	ISA	CAS	Total
Randomized	223 (100%)	227 (100%)	450 (100%)
ITT	221 (99.1%)	219 (96.5%)	440 (97.8%)
mITT	199 (89.2%)	201 (88.5%)	400 (88.9%)
mITT Patients with Invasive Candidiasis with or without Candidemia	29	38	67
mITT Patients with Candidemia Only	170	163	333
PPS	161 (72.2%)	173 (76.2%)	334 (74.2%)
SAF	220 (98.7%)	220 (96.9%)	440 (97.8%)
PKAS	184 (82.5%)	0	

CAS: caspofungin; ISA: isavuconazole; ITT: intent-to-treat; mITT: modified intent-to-treat; PKAS: Pharmacokinetic Analysis Set; PPS: Per Protocol Set; SAF: Safety Analysis Set.
Percentages were calculated based upon the Randomized population.
Caspofungin: Intravenous caspofungin with optional switch to oral voriconazole regimen.
Source: Table 12.1.1.2

Table 3 Demographics and Baseline Characteristics (mITT Population)

Parameter Statistics	ISA (n = 199)	CAS (n = 201)	Total (n = 400)
Age (years)			
Mean	57.7	57.7	57.7
Median	60.0	59.0	59.0
Min - Max	18 - 93	19 – 90	18 - 93
Age Category			
≤ 45 years	50 (25.1%)	44 (21.9%)	94 (23.5%)
> 45 - ≤ 65 years	76 (38.2%)	86 (42.8%)	162 (40.5%)
> 65 years	73 (36.7%)	71 (35.3%)	144 (36.0%)
Sex			
Male	128 (64.3%)	113 (56.2%)	241 (60.3%)
Female	71 (35.7%)	88 (43.8%)	159 (39.8%)
Race			
White	133 (66.8%)	131 (65.2%)	264 (66.0%)
Black or African American	11 (5.5%)	6 (3.0%)	17 (4.3%)
Asian	52 (26.1%)	61 (30.3%)	113 (28.3%)
Other	3 (1.5%)	3 (1.5%)	6 (1.5%)
Ethnicity			
Hispanic or Latino	21 (10.9%)	16 (8.2%)	37 (9.5%)
Not Hispanic or Latino	171 (89.1%)	180 (91.8%)	351 (90.5%)
Missing	7	5	12
BMI (kg/m^2)			
n	183	193	376
Mean	24.69	24.50	24.59
Median	24.22	22.77	23.61
Min - Max	12.9 – 48.8	13.3 – 64.3	12.9 – 64.3
Geographical Region†			
North America	36 (18.1%)	28 (13.9%)	64 (16.0%)
Western Europe plus Australia and New Zealand	47 (23.6%)	51 (25.4%)	98 (24.5%)
Other Regions	116 (58.3%)	122 (60.7%)	238 (59.5%)

Table continued on next page

Parameter Statistics	ISA (n = 199)	CAS (n = 201)	Total (n = 400)
APACHE II Score			
n	193	193	386
Mean	14.0	14.0	14.0
Median	13.0	13.0	13.0
Min - Max	0 – 37	2 – 39	0 – 39
APACHE II Score Category			
≤ 20	160 (82.9%)	159 (82.4%)	319 (82.6%)
> 20	33 (17.1%)	34 (17.6%)	67 (17.4%)
Missing	6	8	14
APACHE II Score Category 2			
< 15	115 (59.6%)	109 (56.5%)	224 (58.0%)
≥ 15	78 (40.4%)	84 (43.5%)	162 (42.0%)
Missing	6	8	14
eGFR-MDRD (mL/min/1.73 m^2)			
< 60	51 (26.7%)	67 (33.7%)	118 (30.3%)
≥ 60	140 (73.3%)	132 (66.3%)	272 (69.7%)
Missing	8	2	10
Baseline Neutropenic Status			
Presence	24 (12.1%)	24 (11.9%)	48 (12.0%)
Absence	175 (87.9%)	177 (88.1%)	352 (88.0%)

Age was calculated relative to informed consent date.

APACHE: Acute Physiology and Chronic Health Evaluation; BMI: body mass index; CAS: caspofungin; eGFR-MDRD: estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; ISA: isavuconazole; Max: maximum; Min: minimum; mITT: modified intent-to-treat.

† North America consists of Canada and the US. Western Europe in this analysis consists of Belgium, France, Germany, Italy, Spain and Switzerland. Other Regions consists of Argentina, Brazil, Chile, China, Hungary, India, Israel, Lebanon, Malaysia, Mexico, Philippines, Russia, Singapore, South Africa and Thailand.

Source: Table 12.1.2.1.2

Table 4 DRC-assessed Overall Response at EOIV (mITT Population)

Outcome Response	ISA (n = 199)	CAS (n = 201)
Success	120 (60.3%)	143 (71.1%)
Adjusted Treatment Difference (ISA-CAS) (%) 95% CI (%)	-10.8 (-19.9, -1.8)	
Failure	79 (39.7%)	58 (28.9%)
Death	11 (5.5%)	8 (4.0%)
Unsuccessful Response	58 (29.1%)	44 (21.9%)
Unsuccessful due to systemic AFT use only	11 (5.5%)	15 (7.5%)
Unevaluable	10 (5.0%)	6 (3.0%)

AFT: antifungal therapy; CAS: caspofungin; CMH: Cochran-Mantel-Haenszel; DRC: Data Review Committee; EOIV: end of intravenous treatment; ISA: isavuconazole; IV: intravenous; mITT: modified intent-to treat

The isavuconazole group included patients who switched to oral isavuconazole (mITT: 69/199 patients).

The caspofungin group included patients who switched to oral voriconazole (mITT: 80/201 patients).

Crude rates of overall response were calculated within treatment group. Success was defined as clinical response (complete or partial) and mycological response (Eradication or Presumed Eradication), without the use of alternative systemic AFT within 48 hours after the last dose of IV study medication. Deaths that occurred through EOIV were treated as failures.

Footnotes continued on next page

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of Geographical Region and Baseline Neutropenic Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

Source: Table 12.3.1.1

Table 5 DRC-assessed Overall Response at FU1 (mITT Population)

Outcome Response	**ISA (n = 199)**	**CAS (n = 201)**
Success	109 (54.8%)	115 (57.2%)
Adjusted Treatment Difference (ISA-CAS) (%) 95% CI (%)	-2.7 (-12.2, 6.8)	
Failure	90 (45.2%)	86 (42.8%)
Death	39 (19.36%)	44 (21.9%)
Recurrent or Emergent	2 (1.0%)	4 (2.0%)
Unsuccessful Response	33 (16.6%)	21 (10.4%)
Unsuccessful due to systemic AFT use only	23 (11.6%)	17 (8.5%)
Unevaluable	16 (8.0%)	17 (8.5%)

AFT: antifungal therapy; CAS: caspofungin; CMH: Cochran-Mantel-Haenszel; DRC: Data Review Committee; FU1: follow-up visit 1; ISA: isavuconazole; IV: intravenous; mITT: modified intent-to-treat

The isavuconazole group included patients who switched to oral isavuconazole (mITT: 69/199 patients).

The caspofungin group included patients who switched to oral voriconazole (mITT: 80/201 patients).

Crude rates of overall response were calculated within treatment group. Success was defined as clinical response (complete or partial) and mycological response (Eradication or Presumed Eradication), without the use of alternative systemic AFT within 48 hours after the last dose of IV study medication. Deaths that occurred through EOIV were treated as failures.

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of Geographical Region and Baseline Neutropenic Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

Source: Table 12.3.2.1

Table 6 Overview of Deaths and TEAEs

Category	**ISA (n = 220) n (%)**	**CAS (n = 220) n (%)**
TEAEs	209 (95.0)	208 (94.5)
Study Drug-related TEAEs†	78 (35.5)	71 (32.3)
Serious TEAEs‡	112 (50.9)	106 (48.2)
Study Drug-related Serious TEAEs†, ‡	19 (8.6)	12 (5.5)
TEAEs Leading to Permanent Discontinuation of Study Drug	22 (10.0)	23 (10.5)
TEAEs Leading to Death§	55 (25.0)	55 (25.0)
Study Drug-related TEAEs Leading to Permanent Discontinuation of Study Drug†	11 (5.0)	11 (5.0)
Study Drug-related TEAEs Leading to Death§	3 (1.4)	1 (0.5)
Deaths Through 28 Days after the Last Dose of Study Drug	55 (25.0)	52 (23.6)
Deaths¶	66 (30.0)	68 (30.9)

CAS: caspofungin; ISA: isavuconazole; TEAE: treatment-emergent adverse event.

All patients who received at least 1 dose of study medication (Safety Analysis Set)

A TEAE was an adverse event starting after first study drug administration until 28 days after the last dose of study drug.

Caspofungin: Intravenous caspofungin with optional switch to oral voriconazole regimen.

Footnotes continued on next page

† Study drug-related TEAEs include 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.

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

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

Source: Table 12.6.1.1.2

Table 7 Most Common TEAEs (≥ 5% of Patients in Either Treatment Group) by PT

MedDRA v12.1 PT	ISA (n = 220) n (%)	CAS (n = 220) n (%)
Patients with ≥ 1 TEAE	209 (95.0)	208 (94.5)
Hypokalaemia	43 (19.5)	45 (20.5)
Pyrexia	40 (18.2)	41 (18.6)
Diarrhoea	34 (15.5)	41 (18.6)
Vomiting	34 (15.5)	39 (17.7)
Constipation	32 (14.5)	24 (10.9)
Hypotension	25 (11.4)	28 (12.7)
Nausea	22 (10.0)	31 (14.1)
Septic shock	20 (9.1)	11 (5.0)
Hypomagnesaemia	19 (8.6)	29 (13.2)
Tachycardia	19 (8.6)	9 (4.1)
Hyperkalaemia	18 (8.2)	18 (8.2)
Sepsis	18 (8.2)	11 (5.0)
Abdominal pain	16 (7.3)	21 (9.5)
Dyspnoea	16 (7.3)	15 (6.8)
Oedema peripheral	15 (6.8)	16 (7.3)
Respiratory failure	15 (6.8)	10 (4.5)
Hypophosphataemia	15 (6.8)	9 (4.1)
Anaemia	14 (6.4)	21 (9.5)
Decubitus ulcer	14 (6.4)	10 (4.5)
Phlebitis	14 (6.4)	15 (6.8)
Bacteraemia	13 (5.9)	9 (4.1)
Staphylococcal bacteraemia	13 (5.9)	9 (4.1)
Pain in extremity	13 (5.9)	6 (2.7)
Renal failure acute	13 (5.9)	7 (3.2)
Hyponatraemia	12 (5.5)	15 (6.8)
Insomnia	12 (5.5)	10 (4.5)
Pleural effusion	11 (5.0)	12 (5.5)
Anxiety	11 (5.0)	7 (3.2)
Chills	11 (5.0)	7 (3.2)
Metabolic acidosis	11 (5.0)	7 (3.2)
Cough	10 (4.5)	13 (5.9)
Pneumonia	10 (4.5)	13 (5.9)
Hypertension	10 (4.5)	12 (5.5)
Urinary tract infection bacterial	7 (3.2)	13 (5.9)
Agitation	5 (2.3)	13 (5.9)
Gamma-glutamyl transferase increased	5 (2.3)	11 (5.0)
Blood alkaline phosphatase increased	4 (1.8)	11 (5.0)

CAS: caspofungin; ISA: isavuconazole; PT: preferred term; TEAE: treatment-emergent adverse event.

All patients who received at least 1 dose of study medication (Safety Analysis Set)

Footnotes continued on next page

Caspofungin: Intravenous caspofungin with optional switch to oral voriconazole regimen.

PTs are sorted by descending incidence in the isavuconazole group, followed by descending order in the caspofungin group, followed by descending order alphabetically.

Source: Tables 12.6.1.1.2 and 12.6.1.5.2

Table 8 Most Common (≥ 1% in Either Treatment Group) Serious TEAEs by PT

MedDRA v12.1 PT	**ISA (n = 220) n (%)**	**CAS (n = 220) n (%)**
Patients with ≥ 1 Serious TEAE	112 (50.9)	106 (48.2)
Septic shock	19 (8.6)	11 (5.0)
Sepsis	16 (7.3)	9 (4.1)
Respiratory failure	12 (5.5)	8 (3.6)
Renal failure acute	10 (4.5)	3 (1.4)
Multi-organ failure	5 (2.3)	7 (3.2)
Respiratory distress	5 (2.3)	1 (0.5)
Cardiac arrest	4 (1.8)	6 (2.7)
Pulmonary embolism	4 (1.8)	2 (0.9)
Bacterial sepsis	3 (1.4)	4 (1.8)
Pneumonia aspiration	3 (1.4)	2 (0.9)
Hypotension	3 (1.4)	1 (0.5)
Bacteraemia	3 (1.4)	0
Oxygen saturation decreased	3 (1.4)	0
Pneumonia	2 (0.9)	6 (2.7)
Hypokalaemia	2 (0.9)	3 (1.4)
Anaemia	1 (0.5)	3 (1.4)
Vomiting	1 (0.5)	3 (1.4)

CAS: caspofungin; ISA: isavuconazole; PT: preferred term; TEAE: treatment-emergent adverse event.

All patients who received at least 1 dose of study medication (Safety Analysis Set)

Caspofungin: Intravenous caspofungin with optional switch to oral voriconazole regimen.

PTs are sorted by descending incidence in the isavuconazole group, followed by descending order in the caspofungin group, followed by descending order alphabetically.

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

Source: Tables 12.6.1.1.2 and 12.6.1.11.2.2