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

SYNOPSIS

Title of Study: Open-Label Study of Isavuconazole in the Treatment of Patients with Aspergillosis and Renal Impairment or of Patients with Invasive Fungal Disease Caused by Rare Moulds, Yeasts or Dimorphic Fungi (ISN 9766-CL-0103/WSA-CS-003)

Investigators/Coordinating Investigator: [redacted], MD

Study Centers: This multicenter study was conducted at 34 centers globally including sites in the US, European Union (EU), South America, Asia and the Middle East.

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): April 22, 2008

Study Completion Date (Date of Last Evaluation): January 03, 2014

Phase of Development: Phase 3

Objectives: The primary objective was to describe the efficacy of isavuconazole in the treatment of invasive aspergillosis in patients with renal impairment or in patients with invasive fungal disease (IFD) caused by rare moulds, yeasts or dimorphic fungi. The secondary objectives of the study were to characterize the safety and tolerability while assessing additional efficacy of treatment with isavuconazole.

[redacted]

Methodology: This was a phase 3, open-label, multicenter study of isavuconazole in the treatment of invasive aspergillosis in patients with renal impairment or in patients with IFD caused by rare moulds, yeasts or dimorphic fungi. Patients were administered either IV infusion or oral capsules three times daily on day 1 and 2, followed by a maintained dose once daily from day 3 to end of treatment (EOT). 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. Patients who were enrolled under Amendment 1 (6 patients) were treated up to a maximum period of 84 days, whereas, most patients who were enrolled from Amendment 3 onwards were treated up to a maximum period of 180 days. For all patients, the follow-up visit took place 4 weeks after the last administration of study drug, and occurred before or after day 42 and/or day 84 (i.e., the follow-up visit was not necessarily the end of study visit for a given patient). An additional follow-up visit 8 weeks after EOT was made if abnormalities (e.g., adverse events [AEs]) were still

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ongoing at the 4-week follow-up visit. An allowance was made to extend isavuconazole dosing beyond 180 days under country-specific Amendment 4 (US, Israel and Belgium), based on Investigator request and Sponsor approval, for patients who demonstrated clinical improvement while on isavuconazole and for whom isavuconazole was deemed the best therapeutic choice for management of their IFD over other available options. Study visits for efficacy and safety assessments occurred every 4 weeks (± 7 days) for patients who received isavuconazole dosing beyond 180 days.

[redacted]

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.

Number of Patients (Planned, Enrolled and Analyzed): The study was planned to be conducted at approximately 150 centers globally. Approximately 100 consenting patients, with proven or probable IFD caused by moulds, yeasts or dimorphic fungi meeting the inclusion and exclusion criteria, were to be enrolled in the study. The final sample size was increased to 150 patients and enrollment of patients with certain infections was limited so as to ensure that there were at least 30 renally impaired (RI) patients with IFD, as well as adequate numbers of patients with proven or probable invasive mucormycosis.

A total of 149 patients were enrolled for the study. Of these, 146 patients (98.0%) received at least 1 dose of study drug and were included in the Intent-to-treat (ITT) population. Of these, 140 patients (94.0%) were included in the modified ITT (mITT) population, which includes ITT patients that were determined by a data-review committee to have proven or probable IFD.

The primary reasons for discontinuation during treatment and follow-up periods for the ITT, mITT-Mucorales and mITT-*Aspergillus* populations, as recorded on the Study Termination eCRF page, can be found in Table 2 and Table 3, respectively. Patients identified as completed under Treatment Discontinuation received the maximum amount of treatment allowed per the protocol they enrolled under or had a success overall outcome as assessed by the Investigator and received a minimum of 7 days of treatment. Patients who discontinued during the treatment period were to complete a follow-up visit after their EOT visit. Fifteen patients were approved to receive treatment beyond 180 days as part of the extension amendment. Five of these 15 patients were actively receiving study drug as of September 30, 2013.

Diagnosis and Main Criteria for Inclusion: Male and female patients aged ≥ 18 years of age, with proven, probable or possible IFD caused by *Aspergillus* species, rare molds, yeasts, or other dimorphic fungi (i.e. fungal pathogens other than *Aspergillus fumigatus* or *Candida* species) were enrolled into the study. Patients with a known history of allergy, hypersensitivity, or any serious reaction to the azole class of antifungals or to any component of the study drug, at high risk for QT prolongation or with risk factors for Torsades de Pointes or use of concomitant medications that are known to prolong QT interval, with evidence of hepatic dysfunction or

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concomitant use of astemizole, cisapride, rifampin/rifampicin, rifabutin, ergot alkaloids, long acting barbiturates, ritonavir, efavirenz, carbamazepine, pimozide, quinidine, neostigmine, terfenadine, ketoconazole, valproic acid or St. John's Wort in the 5 days prior to first administration of study drug were excluded from the study.

Test Product, Dose and Mode of Administration, Batch Numbers: Isavuconazole for IV administration was provided as a lyophilized powder for IV infusion. Each IV vial contained 372.6 mg of isavuconazonium sulfate (BAL8557) corresponding to 200 mg isavuconazole (BAL4815) and included mannitol and sulfuric acid as excipients. Isavuconazole (200 mg) was 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). Ten different lots of capsules and 9 different lots of powder for infusion were used in this study.

Duration of Treatment (or Duration of Study, if applicable): An IV isavuconazole loading regimen was administered during the first 48 hours (200 mg q8h [± 2h]) followed by a maintenance dose from day 3 to EOT (200 mg q24h [± 2h]). The first maintenance dose (day 3) was not to have been administered earlier than 12h [+ 2h] after the last loading dose. Full instructions for infusion requirements were provided to the centers. Intravenous drug was to only have been administered by trained and qualified healthcare professionals. Infusions were given over a period of at least 1 hour. Oral isavuconazole was taken without regard to food intake. An oral isavuconazole loading regimen was administered during the first 48 hours (2 x 100 mg capsules q8h [± 2h]) followed by a maintenance dose from day 3 to EOT (2 x 100 mg capsules qd). The first dose of isavuconazole was administered in a hospital or outpatient clinic with appropriate study staff supervision.

Isavuconazole was administered during the study as either IV or oral. Patients who started on oral therapy or patients who had already switched from IV to oral therapy may have switched (back) to IV therapy at any time if the Investigator felt it was necessary, e.g., it was in the patient's best interest or for the appropriate clinical management of the patient.

Reference Product, Dose and Mode of Administration, Batch Numbers: The choice of a uniform comparator was not feasible for this study due to the variety of conditions and the allowance for renally impaired patients to be included, which excluded the common azoles from consideration. Additionally, commonly prescribed antifungal agents that might serve as an active comparator are not active against mucorales (e.g. voriconazole and caspofungin).

Criteria for Evaluation: Baseline was defined as the last observation prior to or on the day of the first administration of study drug unless otherwise specified.

Survival status was recorded at day 42, day 84 and at follow-up visit 1. Information on survival status on days 42 and 84 were collected in all patients, irrespective of when treatment was discontinued.

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The Investigator assessed clinical symptoms and physical findings of IFD at all subsequent visits from day 3 onward. The DRC and Investigators evaluated the clinical response to treatment for patients at day 42, day 84 and EOT. Baseline mycological assessment (screening through day 7) of the patient's IFD status was performed according to best local practice using local and central laboratories, including suitable samples for fungal culture as well as samples from the infected site for histology and cytology. Baseline radiological assessments of IFD were performed during the screening period. However, assessments performed up to 7 days after the first administration of study drug could be used to confirm the diagnosis of IFD. Radiological assessments were ideally made by computed tomography scan (high resolution computed tomography if available) or magnetic resonance imaging (MRI). A central reading laboratory manual with guidelines for recording and shipping radiological images was provided. Mycological and radiological assessments were also performed at day 42, day 84 and EOT.

A DRC, which consisted of experts in the field of fungal infections, was established to conduct a data review for all patients who received at least one dose of study drug. The DRC adjudicated, independently from Astellas and the study Investigators, the categorization of the IFD and evaluated clinical, mycological, radiological and overall responses at day 42, day 84 and EOT. The DRC also assessed location of disease, therapy status (i.e., primary, refractory or intolerant) and attributable mortality.

Serum galactomannan (GM) antigen was to be drawn at Screening and on days 1 and 2 for those patients suspected to have invasive aspergillosis, while the patient is on study drug. A single GM value of ≥ 0.7 or 2 consecutive values of ≥ 0.5-< 0.7 were considered a positive result except in patients receiving concomitant amoxicillin-clavulanate, or Plasma-Lyte™ (Baxter) within 7 days prior to sampling. If Screening and day 1 occur on the same day, 2 samples should be obtained pre-dose at least 1 hour apart. Serum and 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.

At screening, renal impairment was evaluated based on estimated glomerular filtration rate (eGFR), calculated using serum (or plasma) creatinine and the Cockroft-Gault equation. Renal impairment was defined as yes for patients who had a baseline eGFR-MDRD < 60 mL/min/1.73 m^2, no for patients who had a baseline eGFR-MDRD ≥ 60 mL/min/1.73 m^2. For a patient with missing baseline eGFR-MDRD, the renal status was determined by the Investigator's assessment.

[redacted]

The Investigator evaluated safety by monitoring treatment-emergent adverse events (TEAEs) and findings from physical examination (including eye exam), vital signs, laboratory tests, 12-lead electrocardiogram (ECG) and concomitant medication/surgery. Events of interest (EOI) were evaluated in this study based on standardized

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MedDRA queries (SMQs) of TEAEs and on select System Organ Classes (SOCs), Higher Level Terms (HLTs) or Preferred Terms (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 SOC); Potential hypersensitivity reactions including Infusion/Injection Site Reactions (HLT) and anaphylactic reaction (SMQ, narrow) and severe cutaneous adverse reactions (SMQ, narrow); Potential ocular toxicity (select PTs from Eye Disorders SOC); and Torsade de pointes (SMQ, broad).

Samples for a full safety profile including hematology, biochemistry, urinalysis and hepatotoxicity were collected at screening, at study visits on days days 7, 14, 28, 42, 84, and every 4 weeks thereafter through EOT and at follow-up visit 1. Laboratory safety tests were only required while the patient was receiving study drug, with the exception of the screening and follow-up visit 1.

Blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]; mmHg), pulse rate (PR [beats per minute]), and body temperature (BT, °C or °F) (the most abnormal temperature within this window was recorded) were assessed at screening and on days 1, 2, 3, 7, 14, 28, 42, 84, and every 4 weeks thereafter through EOT and follow-up visit 1. At the follow-up visit 2, vital signs assessments were performed only in patients with abnormalities observed at the previous visit. Vital signs were measured after at least 3 minutes in the supine position.

Twelve-lead ECG recordings were obtained at screening, on days 1, 14, 42, and 84, and every 4 weeks thereafter until EOT. As applicable, the ECG was performed 15 minutes prior to the end of the first infusion of the day or approximately 3 hours after the first oral dose while the patient remained on study drug, with the exception of the screening and follow-up visit 1. All patients were to have an ECG at the EOT and follow-up visit 1 visits. 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, QRS interval, QT interval, QT interval corrected for heart rate – Bazett's formula (QTc Bazett), QTc Fridericia, RR interval and a qualitative ECG interpretation.

The number and percentage of patients who met the criteria for hepatotoxicity based on either central or local laboratory results collected during the analysis window were summarized.

Serum creatinine results from central and local laboratories were analyzed for potential nephrotoxicity.

Physical examinations were conducted at screening, EOT and follow-up visit 1. At the follow-up visit 2, physical examinations were performed only in patients with abnormalities observed at the follow-up visit 1. Physical exams were also performed throughout the study when clinically indicated as determined by the Investigator.

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Vital signs, ECG, and physical and eye examinations were performed at the follow-up visits, if results were abnormal at the EOT visit.

[redacted]

The different analysis sets used in this study are described below and number of patients in each analysis set is presented in [Table 4].

- The ITT population and Safety Analysis Set (SAF) were defined as all enrolled patients who received at least one administration of study drug. The safety analysis set is identical to the ITT population as this was a non-comparative open-label study.
- The mITT populations were defined as all ITT patients who have proven or probable IFD classified by type of pathogen as determined by the DRC.
- The mITT population was split into the mITT-*Aspergillus*, the mITT-Mucorales and mITT-Other Pathogens, which includes other filamentous fungi, Mould NOS, dimorphic fungi, non-*Candida* yeasts and mixed fungal infections. The mITT-Other population also included 8 patients who had Mucorales infection and 11 patients who had *Aspergillus* infection in combination with an additional fungal pathogen.
- [redacted]

The primary efficacy endpoint for this study is the crude success rate of overall outcome of treatment evaluated by the DRC. Success rates were tabulated at day 42, day 84 and EOT. 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 was before day 42 was treated as death.

The secondary efficacy outcomes included clinical, mycological and radiological response assessed by the DRC at day 42, day 84 and EOT. Additional secondary efficacy endpoints were the survival rate of patients at multiple time points.

All-cause mortality through day 42 and day 84 was assessed using the same method as for the primary efficacy endpoint. Any death that occurred after the first dose for study drug through day 42 and day 84 were included, a patient with the last known survival status was before day 42 or before day 84 or missing and the last

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assessment day was before day 42 or before day 84 was treated as death. A time-to-event analysis was performed using Kaplan-Meier method that generated a survival function by day 42, day 84, day 120 and day 180, and was summarized for the ITT, mITT-*Aspergillus* and mITT-Mucorales populations. A patient without a reported death was censored on the patient's last assessment day.

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. Each category was summarized for the ITT, mITT-Mucorales, mITT-*Aspergillus* and all other mITT analysis sets.

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, MIC_{50} and MIC_{90}. The MIC values for study drug were summarized using descriptive statistics for patients with appropriate data.

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. All computations were performed prior to rounding.

Summary of Results/Conclusions:

Population: The treatment groups were balanced for demographics and baseline characteristics as shown in [Table 5], [Table 6] and [Table 7].

[redacted]

Efficacy Results: In the ITT population, the all-cause mortality rate through day 42 was 18.5% (22.0% of RI patients and 16.1% NRI patients) [Table 8]. The all-cause mortality rate through day 84 was 24.7% of patients (30.5% RI patients and 20.7% NRI patients).

In the mITT-Mucorales population, the all-cause mortality rate through day 42 was 37.8% (33.3% of primary therapy patients, 45.5% of refractory patients and 40.0% of intolerant patients) [Table 9]. All-cause mortality through day 84 was 43.2% (42.9% of primary therapy patients, 45.5% of refractory patients and 40.0% of intolerant patients).

In the mITT-*Aspergillus* population, the all-cause mortality rate through day 42 was 12.5% (15.0% RI patients and 0 NRI patients) [Table 10]. Through day 84, the all-cause mortality rate was 25.0% (25.0% RI patients and 25% NRI patients.

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Survival rates were calculated using the Kaplan-Meier (K-M) method. In the mITT-Mucorales population, the K-M estimates of survival rates were 64.9% at day 42 and 59.2% at day 84. In the mITT-*Aspergillus* population, the K-M estimates of survival rate were 87.5% at day 42 and 75.0% at day 84.

An independent review by experts in infectious disease was conducted to determine overall response, the DRC assessed clinical, mycological and radiological responses. The DRC-assessed overall response was the rate of patients with either complete-success or partial-success. The key secondary efficacy endpoint of DRC-assessed overall response at EOT was analyzed for the mITT-Mucorales population and the mITT-*Aspergillus* population and response rates were similar (31.4% and 34.8%, respectively) [Table 12 and Table 13].

In the mITT-Mucorales population, 31.4% of patients experienced a successful response, with 14.3% of patients having a complete success and 17.1% having partial success. For primary therapy patients, 31.6% had a successful response, with complete and partial success each seen in 15.8% of patients. In the mITT-*Aspergillus* population, 34.8% of patients experienced a successful response, with complete and partial success each seen in 17.4% of patients. For RI patients, 30.0% had a successful response, with complete and partial success each seen in 15.0% of patients.

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 on Antimicrobial Susceptibility Testing (EUCAST) methodologies. In the mITT-Mucorales population, the isavuconazole CLSI MIC values ranged from 0.25 to 32 µg/mL. The EUCAST MIC range values for isavuconazole were similar to the values tested under CLSI methodology. In the mITT-*Aspergillus* population, the isavuconazole CLSI MIC values ranged from 0.25 to 8 µg/mL. The EUCAST MIC range values for isavuconazole were similar, with MIC values within 1 to 2 two-fold dilutions higher than the values tested under CLSI methodology.

[redacted]

[redacted]

Safety Results: Overall, 95.2% of patients experienced at least one TEAE; 100% of RI patients and 92.0% of NRI patients [Table 15]. The most common TEAEs that occurred in ≥ 5% of patients overall are presented in [Table 16]. TEAEs by PT that occurred in ≥ 20% of patients overall were vomiting (24.7% overall: 27.1% RI patients and 23.0% NRI patients) and nausea (23.3% overall: 32.2% RI patients and 17.2% NRI patients). In addition, diarrhea was seen in 18.5% of patients (27.1% of RI patients and 12.6% of NRI patients).

Overall, 41.1% of patients experienced a study drug related TEAE; among these, there were 44.1% RI patients and 39.1% NRI patients. The most common study drug related TEAEs that occurred in ≥ 2% of patients overall were nausea (7.5%; 11.9% RI patients and 4.6% NRI patients), and vomiting (6.2%; 5.1% RI patients and 6.9% NRI patients).

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The proportion of patient deaths through 28 days after the last dose of study drug was 28.8% (33.9% in RI patients and 25.3% in NRI patient), and the proportion of all patient deaths was 32.2% (40.7% in RI patients and 26.4% in NRI patients) [Table 15]. All deaths includes all reported deaths after first dose of study drug, regardless of the number of study days after the last dose of study drug. Overall, 30.1% of patients experienced TEAEs leading to death (35.6% of RI patients and 26.4% of NRI patients). Few TEAEs leading to death were experienced by more than one patient.

The most common TEAEs leading to death by PT that occurred in ≥ 2% of either RI and NRI patients were septic shock (6.8% and 0% patients, respectively), malignant neoplasm progression (0% patients and 2.3% respectively) and pneumonia (0% patients and 2.3% respectively).

Overall, 61.0% of patients experienced a serious TEAE, (72.9% RI patients and 52.9% NRI patients). The most common serious TEAEs that occurred in ≥ 3% of patients were renal failure acute (5.5% overall: 10.2% RI patients and 2.3% NRI patients), pneumonia (4.8% overall: 1.7% RI patients and 6.9% NRI patients), septic shock (4.1% overall: 10.2% RI patients and 0 NRI patients), respiratory failure (3.4% overall: 6.8% RI patients and 1.1% NRI patients) and abdominal pain (3.4% overall: 3.4% RI patients and 3.4% NRI patients) [Table 17]. Overall, 8.9% of patients experienced a study drug related serious TEAE (6.8% RI patients and 10.3% NRI patients). Few study drug related serious TEAEs were experienced by more than one patient.

Overall, 13.0% of patients experienced a TEAE leading to permanent discontinuation of study drug, seen in fewer NRI patients (9.2%) than RI patients (18.6%). Overall, 4.8% of patients experienced a study drug-related TEAE leading to permanent discontinuation: (8.5% RI patients and 2.3% NRI patients). When comparing RI and NRI patients, no real difference in the pattern of individual TEAEs was noted.

Analysis of the EOI showed that 1 patient experienced Acute Pancreatitis. Overall, 25.3% of patients experienced a TEAE in the Psychiatric EOI (30.5% RI patients and 21.8% NRI patients). The most frequently reported TEAEs occurring in ≥ 5% of patients overall were: 8.9% insomnia (8.5% RI patients and 9.2% NRI patients); 6.8% confusional state (13.6% RI patients and 2.3% NRI patients) and 3.4% somnolence (3.4% RI and 3.4% NRI patients). Hallucinations occurred in 2.7% of patients (3.4% RI patients and 2.3% NRI patients). Confusional state (6.8%) demonstrated an important difference between RI and NRI patients, with more RI patients experiencing confusional state than NRI patients (13.6% RI patients and 2.3% NRI patients).

Of patients receiving intravenous study drug, 5.0% of patients experienced an infusion/injection site reaction (8.5% RI patients and 1.9% NRI patients)

There were no reported incidences of anaphylaxis SMQ (narrow) or severe cutaneous adverse reactions (SCAR) SMQ (narrow)

Overall, 5.5% of patients experienced a TEAE in the Potential Ocular Toxicity EOI (3.4% RI patients and 6.9% NRI patients). There was only 1 NRI patient with blurred vision and 1 NRI patient with reduced visual acuity.

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Overall, 2.1% of patients experienced a TEAE in the Torsade de Pointes EOI (3.4% RI patients and 1.1% NRI patients).

Overall, mean changes from baseline for the hematology parameters were not clinically important and mean changes from baseline for the chemistry parameters were small.

Overall there was a low incidence of potential hepatotoxicity. No clinically relevant differences were seen between RI and NRI patients.

Increases in creatinine of 25% and 50% were observed. Few patients experienced an increase of 100%: only 5.0% of patients at EOT and 9.3% of patients postbaseline. Categorical increases in creatinine were no more frequent in RI compared to NRI patients.

There were no vital sign changes of clinical importance observed in this study.

Overall, the mean changes from baseline for heart rate, PR, RR, QRS, QT, QTcB, and QTcF were small in both groups. Categorized absolute values in QTcF based on extreme value at EOT and for any postbaseline value showed that, overall, at EOT no patients had QT of < 300 ms or > 480 ms. At postbaseline, no patients had a QT of < 300 ms and 1.4% of patients had QT of > 450 ms. This was similar for RI and NRI patients.

At EOT, less than 10% of patients experienced a prolongation of QTcF of > 30 ms or > 60 ms. However, a decrease of > 30 ms was experienced by 23.7% patients. Very few patients (3%) experienced a decrease of > 60 ms at EOT.

No important differences between RI and NRI patients were observed.

At EOT and postbaseline the number of patients who experienced a clinically significant abnormal ECG was low both overall and for RI and NRI patients. At EOT, there were 4.8% of patients with a shift from normal to clinically significant abnormal for ECG findings; (4.5% RI patients and 5.0% NRI patients). At postbaseline, there were 6.3% of patients with a shift from normal to clinically significant abnormal for ECG findings; among these, there were 8.7% RI patients and 4.9% NRI patients. In addition, there was 1.7% of patients with abnormal ECG findings at baseline, which became clinically significant at EOT; among these, there were 0% RI patients and 2.9% NRI patients at EOT. This was also similar for postbaseline analysis.

In general, the treatment differences observed for the overall analysis of TEAEs and serious TEAEs were consistent with subgroup analyses by age category, gender, race and geographical region. Of note, there were no patients in the Hispanic or Latino groups, 10 patients in the > 75 years of age group, 9 patients in the Black/African American group, 23 patients in the Asian group and 4 patients in the Other Race group. Therefore, results in these subgroups should be interpreted with caution.

CONCLUSIONS:

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Isavuconazole was well tolerated and demonstrated effectiveness for the treatment of invasive mucormycosis and invasive aspergillosis in patients with renal impairment and a broad range of other filamentous, dimorphic moulds and non-*candida* yeasts as measured by mortality and DRC-assessed response outcomes. Safety outcomes were within the range of that observed in the randomized double-blind comparative invasive aspergillosis/filamentous study (9766-CL-0104) and provide clinical experience in a more heterogenic patient group, including those with baseline renal impairment.

Date of Report: June 11, 2014

Table 1 Primary Reasons for Discontinuation during Treatment and Follow-up Period (ITT Population)

	RI (n = 59)	NRI (n = 87)	Total (n = 146)
Treatment Discontinuation			
Completed	23 (39.0%)	49 (56.3%)	72 (49.3%)
Discontinued	34 (57.6%)	35 (40.2%)	69 (47.3%)
Primary reason for discontinuation			
Death	13 (22.0%)	9 (10.3%)	22 (15.1%)
Adverse event/intercurrent illness	10 (16.9%)	8 (9.2%)	18 (12.3%)
Insufficient therapeutic response	3 (5.1%)	7 (8.0%)	10 (6.8%)
Did not cooperate	0	5 (5.7%)	5 (3.4%)
Violation of selection at entry	1 (1.7%)	3 (3.4%)	4 (2.7%)
Other protocol violation	3 (5.1%)	1 (1.1%)	4 (2.7%)
Admin/other	2 (3.4%)	2 (2.3%)	4 (2.7%)
Failure to return/lost to follow-up	2 (3.4%)	0	2 (1.4%)
Discontinuation During Follow-up Period			
Completed	30 (50.8%)	52 (59.8%)	82 (56.2%)
Discontinued	27 (45.8%)	32 (36.8%)	59 (40.4%)
Primary reason for discontinuation			
Death	23 (39.0%)	22 (25.3%)	45 (30.8%)
Failure to return/lost to follow-up	2 (3.4%)	5 (5.7%)	7 (4.8%)
Admin/other	2 (3.4%)	2 (2.3%)	4 (2.7%)
Withdrew consent†	0	3 (3.4%)	3 (2.1%)
Ongoing‡	2 (3.4%)	3 (3.4%)	5 (3.4%)

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

eGFR: estimated glomerular filtration rate; ITT: intent-to-treat; MDRD: Modification of Diet in Renal Disease; NRI: not renally impaired; RI: renally impaired.

† This information was collected from Amendment 3 onwards.

‡ Patients who were still actively receiving study treatment as of September 30, 2013.

Source: Table 12.1.1.3.1

Table 2 Primary Reason for Treatment and Study Discontinuation (mITT-Mucorales Population)

	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Treatment Discontinuation				
Completed	6 (28.6%)	2 (18.2%)	3 (60.0%)	11 (29.7%)
Discontinued	13 (61.9%)	9 (81.8%)	2 (40.0%)	24 (64.9%)
Primary reason for discontinuation				
Death	6 (28.6%)	3 (27.3%)	2 (40.0%)	11 (29.7%)
Adverse event/intercurrent illness	2 (9.5%)	4 (36.4%)	0	6 (16.2%)
Did not cooperate	3 (14.3%)	1 (9.1%)	0	4 (10.8%)
Insufficient therapeutic response	1 (4.8%)	1 (9.1%)	0	2 (5.4%)
Admin/other	1 (4.8%)	0	0	1 (2.7%)
Discontinuation during follow-up period				
Completed	7 (33.3%)	3 (27.3%)	2 (40.0%)	12 (32.4%)
Discontinued	12 (57.1%)	8 (72.7%)	3 (60.0%)	23 (62.2%)
Primary reason for discontinuation				
Death	10 (47.6%)	6 (54.5%)	2 (40.0%)	18 (48.6%)
Admin/other	0	1 (9.1%)	1 (20.0%)	2 (5.4%)
Withdrew consent†	1 (4.8%)	1 (9.1%)	0	2 (5.4%)
Failure to return/lost to follow-up	1 (4.8%)	0	0	1 (2.7%)
Ongoing‡	2 (9.5%)	0	0	2 (5.4%)

Only the primary reason for discontinuation was collected.

IFD: invasive fungal disease.

† This information was collected from Amendment 3 on.

‡ Patients who were still actively receiving study treatment as of September 30, 2013.

Source: Table 12.1.1.3.2

Table 3 Primary Reason for Treatment Discontinuation (mITT-*Aspergillus* Population)

	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Treatment discontinuation			
Completed	8 (40.0%)	1 (25.0%)	9 (37.5%)
Discontinued	12 (60.0%)	2 (50.0%)	14 (58.3%)
Primary reason for discontinuation			
Adverse event/intercurrent illness	4 (20.0%)	1 (25.0%)	5 (20.8%)
Death	3 (15.0%)	1 (25.0%)	4 (16.7%)
Insufficient therapeutic response	2 (10.0%)	0	2 (8.3%)
Other protocol violation	2 (10.0%)	0	2 (8.3%)
Failure to return/lost to follow-up	1 (5.0%)	0	1 (4.2%)
Discontinuation during follow-up period			
Completed	10 (50.0%)	1 (25.0%)	11 (45.8%)
Discontinued	10 (50.0%)	2 (50.0%)	12 (50.0%)
Primary reason for discontinuation			
Death	9 (45.0%)	2 (50.0%)	11 (45.8%)
Failure to return/lost to follow-up	1 (5.0%)	0	1 (4.2%)
Ongoing†	0	1 (25.0%)	1 (4.2%)

Only the primary reason for discontinuation was collected.

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; mITT: modified intent-to-treat; NRI: not renally impaired; RI: renally impaired.

† Patients who were still actively receiving study treatment as of September 30, 2013.

Source: Table 12.1.1.3.3

Table 4 Patient Disposition and Analysis Set

	RI (n = 59)	NRI (n = 90)	Total (n = 149)
Signed informed consent			149
Enrolled	59 (100.0%)	90 (100.0%)	149 (100.0%)
Intent-to-Treat (ITT)	59 (100.0%)	87 (96.7%)	146 (98.0%)
Modified Intent-to-Treat (mITT)	54 (91.5%)	86 (95.6%)	140 (94.0%)
mITT-Mucorales	11 (18.6%)	26 (28.9%)	37 (24.8%)
mITT-*Aspergillus*	20 (33.9%)	4 (4.4%)	24 (16.1%)
mITT-Other filamentous fungi (not *Aspergillus* or Mucorales)	9 (15.3%)	8 (8.9%)	17 (11.4%)
mITT-Mold species not otherwise specified	5 (8.5%)	2 (2.2%)	7 (4.7%)
mITT-Dimorphic fungi	2 (3.4%)	27 (30.0%)	29 (19.5%)
mITT-*Non-Candida* yeast	4 (6.8%)	7 (7.8%)	11 (7.4%)
mITT-Mixed infection	3 (5.1%)	12 (13.3%)	15 (10.1%)
Safety (SAF)	59 (100.0%)	87 (96.7%)	146 (98.0%)
[redacted]	[redacted]	[redacted]	[redacted]

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

eGFR: estimated glomerular filtration rate; ITT: intent-to-treat; MDRD: Modification of Diet in Renal Disease; mITT: modified ITT; NRI: not renally impaired; [redacted]; RI: renally impaired; SAF: Safety Analysis Set.

Source: Table 12.1.1.2

Table 5 Summary of Demographics and Baseline Characteristics (ITT Population)

Parameter Category/Statistic	RI (n = 59)	NRI (n = 87)	Total (n = 146)
Age (years)			
n	59	87	146
Mean (SD)	52.9 (18.05)	47.8 (15.62)	49.9 (16.78)
Min	19	18	18
Median	57.0	50.0	52.0
Max	92	79	92
Sex			
Male	38 (64.4%)	62 (71.3%)	100 (68.5%)
Female	21 (35.6%)	25 (28.7%)	46 (31.5%)
Race			
White	48 (81.4%)	60 (69.0%)	108 (74.0%)
Black or African American	3 (5.1%)	7 (8.0%)	10 (6.8%)
Asian	8 (13.6%)	16 (18.4%)	24 (16.4%)
Other	0	4 (4.6%)	4 (2.7%)
Ethnicity			
Hispanic or Latino	2 (3.4%)	20 (23.0%)	22 (15.1%)
Not Hispanic or Latino	57 (96.6%)	67 (77.0%)	124 (84.9%)
Geographic region			
North America	30 (50.8%)	26 (29.9%)	56 (38.4%)
Western Europe	7 (11.9%)	10 (11.5%)	17 (11.6%)
Other Regions†	22 (37.3%)	51 (58.6%)	73 (50.0%)
Therapy status			
Primary Therapy	33 (57.9%)	60 (69.8%)	93 (65.0%)
Refractory	17 (29.8%)	21 (24.4%)	38 (26.6%)
Intolerant	7 (12.3%)	5 (5.8%)	12 (8.4%)
Missing	2	1	3
Hematologic malignancy	31 (52.5%)	32 (36.8%)	63 (43.2%)
Allogeneic BMT/HSCT	16 (27.1%)	10 (11.5%)	26 (17.8%)
Uncontrolled malignancy	18 (30.5%)	28 (32.2%)	46 (31.5%)
Neutropenic	14 (26.9%)	24 (46.2%)	38 (36.5%)
Corticosteroid use	20 (33.9%)	15 (17.2%)	35 (24.0%)
T-cell immunosuppressant use	32 (60.4%)	29 (51.8%)	61 (56.0%)

Age is calculated relative to informed consent date.

Therapy status was assessed by the Data Review Committee.

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

BMT: bone marrow transplant; eGFR: estimated glomerular filtration rate; HSCT: hematopoietic stem cell transplant; MDRD: Modification of Diet in Renal Disease; NRI: not renally impaired; RI: renally impaired.

† Other regions included Russia, Mexico, Brazil, Thailand, South Korea, India, Lebanon, and Israel.

Source: Table 12.1.2.1

Table 6 Summary of Demographics and Baseline Characteristics by Therapy Status (mITT-Mucorales Population)

Parameter Category/Statistic	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Age (years)				
n	21	11	5	37
Mean (SD)	51.7 (14.72)	46.4 (16.55)	39.6 (15.22)	48.5 (15.51)
Min	25	22	23	22
Median	51.0	50.0	42.0	50.0
Max	77	79	57	79
Sex				
Male	17 (81.0%)	8 (72.7%)	5 (100.0%)	30 (81.1%)
Female	4 (19.0%)	3 (27.3%)	0	7 (18.9%)
Race				
White	12 (57.1%)	10 (90.9%)	3 (60.0%)	25 (67.6%)
Black or African American	1 (4.8%)	1 (9.1%)	2 (40.0%)	4 (10.8%)
Asian	8 (38.1%)	0	0	8 (21.6%)
Ethnicity				
Hispanic or Latino	1 (4.8%)	0	0	1 (2.7%)
Not Hispanic or Latino	20 (95.2%)	11 (100.0%)	5 (100.0%)	36 (97.3%)
Geographic region				
North America	7 (33.3%)	4 (36.4%)	5 (100.0%)	16 (43.2%)
Western Europe	1 (4.8%)	4 (36.4%)	0	5 (13.5%)
Other Regions†	13 (61.9%)	3 (27.3%)	0	16 (43.2%)
Hematologic malignancy	11 (52.4%)	7 (63.6%)	4 (80.0%)	22 (59.5%)
Allogeneic BMT/HSCT status	4 (19.0%)	4 (36.4%)	5 (100.0%)	13 (35.1%)
Uncontrolled malignancy	11 (52.4%)	6 (54.5%)	1 (20.0%)	18 (48.6%)
Neutropenic	4 (19.0%)	5 (45.5%)	1 (20.0%)	10 (27.0%)
Corticosteroid use	5 (23.8%)	3 (27.3%)	2 (40.0%)	10 (27.0%)
T-cell immunosuppressant use	7 (33.3%)	6 (54.5%)	5 (100.0%)	18 (48.6%)
eGFR-MDRD category (mL/min/1.73 m^2)				
< 60	6 (28.6%)	3 (27.3%)	2 (40.0%)	11 (29.7%)
≥ 60	15 (71.4%)	8 (72.7%)	3 (60.0%)	26 (70.3%)

Age was calculated relative to informed consent date.

Hematologic malignancy status and T-cell immunosuppressant use involved an Astellas medical review.

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

BMT: bone marrow transplant; eGFR: estimated glomerular filtration rate; HSCT: hematopoietic stem cell transplant; MDRD: Modification of Diet in Renal Disease; mITT: modified intent-to-treat.

† Other regions included Russia, Mexico, Brazil, Thailand, South Korea, India, Lebanon, and Israel.

Source: Table 12.1.2.2

Table 7 Summary of Demographics and Baseline Characteristics by Renal Status (mITT-*Aspergillus* Population)

Parameter Category/Statistic	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Age (years)			
n	20	4	24
Mean (SD)	55.7 (20.65)	41.5 (25.72)	53.3 (21.63)
Min	19	18	18
Median	61.0	38.5	60.5
Max	92	71	92
Sex			
Male	12 (60.0%)	3 (75.0%)	15 (62.5%)
Female	8 (40.0%)	1 (25.0%)	9 (37.5%)
Race			
White	17 (85.0%)	4 (100.0%)	21 (87.5%)
Black or African American	0	0	0
Asian	3 (15.0%)	0	3 (12.5%)
Other	0	0	0
Ethnicity			
Hispanic or Latino	1 (5.0%)	0	1 (4.2%)
Not Hispanic or Latino	19 (95.0%)	4 (100.0%)	23 (95.8%)
Geographic region			
North America	11 (55.0%)	1 (25.0%)	12 (50.0%)
Western Europe	4 (20.0%)	0	4 (16.7%)
Other Regions†	5 (25.0%)	3 (75.0%)	8 (33.3%)
Hematologic malignancy	11 (55.0%)	3 (75.0%)	14 (58.3%)
Allogeneic BMT/HSCT status	7 (35.0%)	2 (50.0%)	9 (37.5%)
Uncontrolled malignancy	5 (25.0%)	2 (50.0%)	7 (29.2%)
Neutropenic	5 (25.0%)	3 (75.0%)	8 (33.3%)
Corticosteroid use	12 (60.0%)	1 (25.0%)	13 (54.2%)
T-cell immunosuppressant use	15 (75.0%)	3 (75.0%)	18 (75.0%)
eGFR-MDRD category (mL/min/1.73 m^2)			
< 60	20 (100.0%)	0	20 (83.3%)
≥ 60	0	4 (100.0%)	4 (16.7%)

Age was calculated relative to informed consent date.

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

Hematologic malignancy status and T-cell immunosuppressant use involved an AST medical review.

BMT: bone marrow transplant; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; mITT: modified intent-to-treat; NRI: not renally impaired; RI: renally impaired.

† Other regions included Russia, Mexico, Brazil, Thailand, South Korea, India, Lebanon, and Israel.

Source: Table 12.1.2.3

Table 8 All-cause Mortality Through Day 42 and Day 84 (ITT Population)

Outcome	RI (n = 59)	NRI (n = 87)	Total (n = 146)
All-Cause Mortality Through Day 42	13 (22.0%)	14 (16.1%)	27 (18.5%)
Deaths	12 (20.3%)	12 (13.8%)	24 (16.4%)
Unknown Survival Status	1 (1.7%)	2 (2.3%)	3 (2.1%)
All-Cause Mortality Through Day 84	18 (30.5%)	18 (20.7%)	36 (24.7%)
Deaths	17 (28.8%)	16 (18.4%)	33 (22.6%)
Unknown Survival Status	1 (1.7%)	2 (2.3%)	3 (2.1%)

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; NRI: not renally impaired; RI: renally impaired.

Source: Table 12.3.11.1

Table 9 All-cause Crude Mortality Through Day 42 and Day 84 (mITT-Mucorales Population)

Outcome	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
All-Cause Mortality Though Day 42†	7 (33.3%)	5 (45.5%)	2 (40.0%)	14 (37.8%)
Deaths	7 (33.3%)	4 (36.4%)	2 (40.0%)	13 (35.1%)
Unknown Survival Status	0	1 (9.1%)	0	1 (2.7%)
All-Cause Mortality Through Day 84†	9 (42.9%)	5 (45.5%)	2 (40.0%)	16 (43.2%)
Deaths	9 (42.9%)	4 (36.4%)	2 (40.0%)	15 (40.5%)
Unknown Survival Status	0	1 (9.1%)	0	1 (2.7%)

† A patient with the last known survival status was before day 42 or before day 84 or missing and the last assessment day was before day 42 or before day 84 was counted as death

Source: Table 12.3.11.2

Table 10 All-cause Mortality Through Day 42 and Day 84 (mITT-*Aspergillus* Population)

Outcome	RI (n = 20)	NRI (n = 4)	Total (n = 24)
All-cause Mortality Through Day 42†	3 (15.0%)	0	3 (12.5%)
Deaths	3 (15.0%)	0	3 (12.5%)
All-cause Mortality Through Day 84†	5 (25.0%)	1 (25.0%)	6 (25.0%)
Deaths	5 (25.0%)	1 (25.0%)	6 (25.0%)

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m2 by the MDRD formula.

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; mITT: modified intent-to-treat; NRI: not renally impaired; RI: renally impaired.

† A patient with a last known survival status before day 42 or before day 84, or missing, with the last assessment day before day 42 or before day 84, was counted as a death.

Source: Table 12.3.11.3

Table 11 All-cause Crude Mortality Through Day 42 and Day 84 (All Other mITT Populations)

Timepoint Outcome	Other Filamentous Fungi (n = 17)	Mould Species NOS (n = 7)	Dimorphic Fungi (n = 29)	Non-*Candida* Yeast (n = 11)	Mixed Infection (n = 15)
Day 42					
All-cause Mortality†	2 (11.8%)	0	2 (6.9%)	1 (9.1%)	3 (20.0%)
Deaths	2 (11.8%)	0	2 (6.9%)	1 (9.1%)	2 (13.3%)
Unknown Survival Status	0	0	0	0	1 (6.7%)
Day 84					
All-cause Mortality†	3 (17.6%)	1 (14.3%)	2 (6.9%)	1 (9.1%)	5 (33.3%)
Deaths	3 (17.6%)	1 (14.3%)	2 (6.9%)	1 (9.1%)	4 (26.7%)
Unknown Survival Status	0	0	0	0	1 (6.7%)

mITT: modified intent-to-treat; NOS: not otherwise specified.

† A patient with a last known survival status before day 42 or before day 84, or missing, with the last assessment day before day 42 or before day 84, was counted as a death.

Source: Table 12.3.11.4

Table 12 DRC-assessed Overall Response at EOT by Therapy Status (mITT-Mucorales Population)

Outcome Response	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n =37)
Success	6/19 (31.6%)	4/11 (36.4%)	1/5 (20.0%)	11/35 (31.4%)
Complete	3/19 (15.8%)	2/11 (18.2%)	0	5/35 (14.3%)
Partial	3/19 (15.8%)	2/11 (18.2%)	1/5 (20.0%)	6/35 (17.1%)
Failure	13/19 (68.4%)	7/11 (63.6%)	4/5 (80.0%)	24/35 (68.6%)
Stable	6/19 (31.6%)	2/11 (18.2%)	2/5 (40.0%)	10/35 (28.6%)
Progression	7/19 (36.8%)	5/11 (45.5%)	2/5 (40.0%)	14/35 (40.0%)

Patients who were still actively participating in the study at the interim cut of the database were not included in this analysis at the EOT time point

DRC: Data Review Committee; EOT: end of treatment; mITT: modified intent-to-treat.

Source: Table 12.3.1.1.1

Table 13 DRC-assessed Overall Response at EOT by Renal Status (mITT-*Aspergillus* Population)

Outcome Response	RI (n = 20)	NRI (n = 4)	Total (n = 24)
Success	6 (30.0%)	2/3 (66.7%)	8/23 (34.8%)
Complete	3 (15.0%)	1/3 (33.3%)	4/23 (17.4%)
Partial	3 (15.0%)	1/3 (33.3%)	4/23 (17.4%)
Failure	14 (70.0%)	1/3 (33.3%)	15/23 (65.2%)
Stable	4 (20.0%)	0	4/23 (17.4%)
Progression	10 (50.0%)	1/3 (33.3%)	11/23 (47.8%)

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m2 by the MDRD formula.

Patients who were still actively participating in the study at the interim cut of the database were not included in this analysis at the EOT time point.

DRC: Data Review Committee; eGFR: estimated glomerular filtration rate; EOT: end of treatment; MDRD: Modification of Diet in Renal Disease; mITT: modified intent-to-treat; NRI: not renally impaired; RI: renally impaired.

Source: Table 12.3.1.1.2

Table 14 DRC-Assessed Overall Response at EOT (All Other mITT Populations)

Outcome Response	Other Filamentous Fungi (n = 17)	Mould Species NOS (n = 7)	Dimorphic Fungi (n = 29)	Non-*Candida* Yeast (n = 11)	Mixed Infection (n = 15)
Success	11 (64.7%)	2 (28.6%)	18 (64.3%)	8 (72.7%)	2 (14.3%)
Complete	7 (41.2%)	1 (14.3%)	5 (17.9%)	3 (27.3%)	0
Partial	4 (23.5%)	1 (14.3%)	13 (46.4%)	5 (45.5%)	2 (14.3%)
Failure	6 (35.3%)	5 (71.4%)	10 (35.7%)	3 (27.3%)	12 (85.7%)
Stable	3 (17.6%)	2 (28.6%)	5 (17.9%)	2 (18.2%)	5 (35.7%)
Progression	3 (17.6%)	3 (42.9%)	5 (17.9%)	1 (9.1%)	7 (50.0%)

Patients who were still actively participating in the study at the interim cut of the database are not included in this analysis at the EOT time point.

DRC: Data Review Committee; EOT: end of treatment; mITT: modified intent-to-treat; NOS: not otherwise specified.

Source: Table 12.3.1.1.3

Table 15 Overview of TEAEs

	RI (n = 59)	NRI (n = 87)	Total (n = 146)
TEAEs	59 (100.0%)	80 (92.0%)	139 (95.2%)
Study Drug-Related TEAEs	26 (44.1%)	34 (39.1%)	60 (41.1%)
Serious TEAEs	43 (72.9%)	46 (52.9%)	89 (61.0%)
Study Drug-Related Serious TEAEs	4 (6.8%)	9 (10.3%)	13 (8.9%)
TEAEs Leading to Permanent Discontinuation of Study Drug	11 (18.6%)	8 (9.2%)	19 (13.0%)
Study Drug-Related TEAEs Leading to Permanent Discontinuation of Study Drug	5 (8.5%)	2 (2.3%)	7 (4.8%)
TEAEs Leading to Death	21 (35.6%)	23 (26.4%)	44 (30.1%)
Study Drug-Related TEAEs Leading to Death	1 (1.7%)	0	1 (0.7%)
Deaths†	24 (40.7%)	23 (26.4%)	47 (32.2%)
Deaths Through 28 Days after the Last Dose of Study Drug	20 (33.9%)	22 (25.3%)	42 (28.8%)

A TEAE is any adverse event that starts after the first administration of study drug until 28 days after the last dose of study drug.

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.

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

† All reported deaths after first dose of study drug were summarized, regardless of the number of study days after the last dose of study drug.

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; NRI: not renally impaired; RI: renally impaired; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.1

Table 16 Most Common TEAEs (≥ 5% of Patients Overall) by PT

MedDRA v12.1 PT	RI (n = 59)	NRI (n = 87)	Total (n = 146)
Overall	59 (100.0%)	80 (92.0%)	139 (95.2%)
Vomiting	16 (27.1%)	20 (23.0%)	36 (24.7%)
Nausea	19 (32.2%)	15 (17.2%)	34 (23.3%)
Diarrhoea	16 (27.1%)	11 (12.6%)	27 (18.5%)
Headache	11 (18.6%)	15 (17.2%)	26 (17.8%)
Pyrexia	9 (15.3%)	15 (17.2%)	24 (16.4%)
Oedema peripheral	9 (15.3%)	8 (9.2%)	17 (11.6%)
Constipation	6 (10.2%)	10 (11.5%)	16 (11.0%)
Cough	3 (5.1%)	12 (13.8%)	15 (10.3%)
Back pain	6 (10.2%)	8 (9.2%)	14 (9.6%)
Dyspnoea	6 (10.2%)	8 (9.2%)	14 (9.6%)
Abdominal pain	8 (13.6%)	5 (5.7%)	13 (8.9%)
Insomnia	5 (8.5%)	8 (9.2%)	13 (8.9%)
Hyperkalaemia	8 (13.6%)	4 (4.6%)	12 (8.2%)
Hypokalaemia	6 (10.2%)	6 (6.9%)	12 (8.2%)
Pneumonia	3 (5.1%)	9 (10.3%)	12 (8.2%)
Hypotension	6 (10.2%)	5 (5.7%)	11 (7.5%)
Upper respiratory tract infection	5 (8.5%)	6 (6.9%)	11 (7.5%)
Confusional state	8 (13.6%)	2 (2.3%)	10 (6.8%)
Decreased appetite	4 (6.8%)	6 (6.9%)	10 (6.8%)
Gamma-glutamyltransferase increased	4 (6.8%)	6 (6.9%)	10 (6.8%)
Urinary tract infection	8 (13.6%)	2 (2.3%)	10 (6.8%)
Hypomagnesaemia	2 (3.4%)	7 (8.0%)	9 (6.2%)
Musculoskeletal chest pain	4 (6.8%)	5 (5.7%)	9 (6.2%)
Pruritus	2 (3.4%)	7 (8.0%)	9 (6.2%)
Respiratory failure	5 (8.5%)	4 (4.6%)	9 (6.2%)
Asthenia	1 (1.7%)	7 (8.0%)	8 (5.5%)
Chills	5 (8.5%)	3 (3.4%)	8 (5.5%)
Dizziness	3 (5.1%)	5 (5.7%)	8 (5.5%)
Hypertension	3 (5.1%)	5 (5.7%)	8 (5.5%)
Neutropenia	6 (10.2%)	2 (2.3%)	8 (5.5%)
Renal failure acute	6 (10.2%)	2 (2.3%)	8 (5.5%)
Tachycardia	4 (6.8%)	4 (4.6%)	8 (5.5%)

A TEAE is any adverse event that starts after the first administration of study drug until 28 days after the last dose of study drug.

Overall is the total number of patients who had TEAEs.

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; NRI: not renally impaired; PT: preferred term; RI: renally impaired; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.5

Table 17 Most Common Serious TEAEs (≥ 1% Overall) by PT

MedDRA v12.1 PT	RI (n = 59)	NRI (n = 87)	Total n = 146)
Overall	43 (72.9%)	46 (52.9%)	89 (61.0%)
Renal failure acute	6 (10.2%)	2 (2.3%)	8 (5.5%)
Pneumonia	1 (1.7%)	6 (6.9%)	7 (4.8%)
Septic shock	6 (10.2%)	0	6 (4.1%)
Respiratory failure	4 (6.8%)	1 (1.1%)	5 (3.4%)
Abdominal pain	2 (3.4%)	3 (3.4%)	5 (3.4%)
Vomiting	0	4 (4.6%)	4 (2.7%)
Acute respiratory failure	0	3 (3.4%)	3 (2.1%)
Aspergillosis	1 (1.7%)	2 (2.3%)	3 (2.1%)
Bacteraemia	3 (5.1%)	0	3 (2.1%)
Cerebral infarction	2 (3.4%)	1 (1.1%)	3 (2.1%)
Death	1 (1.7%)	2 (2.3%)	3 (2.1%)
Dehydration	2 (3.4%)	1 (1.1%)	3 (2.1%)
Gastrointestinal haemorrhage	3 (5.1%)	0	3 (2.1%)
Pneumonia bacterial	1 (1.7%)	2 (2.3%)	3 (2.1%)
Sepsis	2 (3.4%)	1 (1.1%)	3 (2.1%)
Acute graft versus host disease	2 (3.4%)	0	2 (1.4%)
Acute myeloid leukaemia	2 (3.4%)	0	2 (1.4%)
Acute myeloid leukaemia recurrent	0	2 (2.3%)	2 (1.4%)
Anaemia	1 (1.7%)	1 (1.1%)	2 (1.4%)
Atrial fibrillation	2 (3.4%)	0	2 (1.4%)
Cardio-respiratory arrest	1 (1.7%)	1 (1.1%)	2 (1.4%)
Convulsion	0	2 (2.3%)	2 (1.4%)
Cytomegalovirus infection	1 (1.7%)	1 (1.1%)	2 (1.4%)
Deep vein thrombosis	1 (1.7%)	1 (1.1%)	2 (1.4%)
Diarrhoea	1 (1.7%)	1 (1.1%)	2 (1.4%)
Dysphagia	1 (1.7%)	1 (1.1%)	2 (1.4%)
Febrile neutropenia	1 (1.7%)	1 (1.1%)	2 (1.4%)
Graft versus host disease	1 (1.7%)	1 (1.1%)	2 (1.4%)
Haemoptysis	1 (1.7%)	1 (1.1%)	2 (1.4%)
Herpes zoster	0	2 (2.3%)	2 (1.4%)
Hypotension	2 (3.4%)	0	2 (1.4%)
Malignant neoplasm progression	0	2 (2.3%)	2 (1.4%)
Mucormycosis	0	2 (2.3%)	2 (1.4%)
Musculoskeletal chest pain	2 (3.4%)	0	2 (1.4%)
Nausea	0	2 (2.3%)	2 (1.4%)
Non-cardiac chest pain	1 (1.7%)	1 (1.1%)	2 (1.4%)
Pneumonia aspiration	1 (1.7%)	1 (1.1%)	2 (1.4%)
Pneumonia fungal	0	2 (2.3%)	2 (1.4%)
Pseudomonal sepsis	0	2 (2.3%)	2 (1.4%)
Pyrexia	1 (1.7%)	1 (1.1%)	2 (1.4%)
Zygomycosis	0	2 (2.3%)	2 (1.4%)

A TEAE is any AE that starts after the first administration of study drug until 28 days after the last dose of study drug.

Overall is the total number of patients who had serious TEAEs.

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; NRI: not renally impaired; PT: preferred term; RI: renally impaired; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.11