Protocol C3791001

A SINGLE ARM, PROSPECTIVE, MULTI-CENTER STUDY TO EVALUATE SAFETY AND EFFICACY OF ISAVUCONAZOLE FOR PRIMARY TREATMENT OF CHINESE PATIENTS WITH INVASIVE FUNGAL DISEASE (IFD) CAUSED BY ASPERGILLUS SPECIES OR OTHER FILAMENTEOUS FUNGI

Statistical Analysis Plan
(SAP)

Version: 2

Date: 13 Mar 2024

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 24 Jun 2022	Original 25 Apr 2022	N/A	N/A
2 12 March 2024	Amendment 2 29 Jan 2024	Aligned with the changes from protocol amendment	Updated estimand for primary objective in Section 2.2 and 2.2.1. Added the following statements in Section 2.3 "All participants receiving study medication will have the visits performed as scheduled." "For all participants, the Follow-up visit will take place 4 weeks (±7 days) after the last administration of the study medication, and may occur before or after Day 42 and/or Day 84 (or Day 180 for participants with IM)." Updated sample size in Section 2.3 to accommodate the modification in protocol amendment 2. Updated content in Section 2.3 to clarify the culture and histology/ cytology antigen testing are applicable for both Aspergillus species and Mucorales species. Made the following changes in Section 3.4: • Added 'Race', 'Ethinicity', 'Country'; • Updated from 'eGFR-MDRD' to 'eGFR-CKD-EPI'; • Added 'Prior allogeneic HSCT/BMT: Yes/No', 'Solid organ transplant: Yes/No', 'Hematologic malignancy: Yes/No', 'Other malignancy: Yes/No',

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			'Chronic respiratory airway abnormality: Yes/No '; • Added primary diagnosis type • Moved primary underlying disease to a separate Section 6.5.2; CCI [redacted] • Clarified the rule of determination of baseline variables. Added timepoints of 'Day 84, every 42 days after Day 42' in Section 3.5.2-3.5.3. Updated timepoints for ECG in Section 3.5.4. Corrected a typo from 'GMc' To 'GM'in Section 4.Removed the wording about p-value from Section 5 as p-value is not applicable for the study. Added details of CI calculation from KM approach and details to define censoring participants in Section 5.2.3. Added estimand strategy and intercurrent event in Section 6.1. Modified 'supplementary analsysi' to 'sensitivity analysis' for using KM method for all-cause moratily at Day 42 using ITT in Section 6.2.1.2. Updated from 'eGFR-MDRD' to 'eGFR' in Section 6.2.1.3 and Appendix 2;

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			Modified wording to better describe missing data for estimands from Section 6.2.3-6.2.4. Added a new Section 6.5.2: Primary Underlying Disease. Added a new Section 6.5.5: Anti-infective and Medical History. Updated section title and contens by adding details of prior medications for Section 6.5.6. Added a new Section 6.5.7: Non-medication Procedure. Added definition of baseline IFD characteristics in Section 6.5.8. Updated mycological assessment categories in Section 6.5.8.1 Updated IFD categorizations by defining IM and IA separately in Section 6.5.8.1 Added details of AE summaries in Section 6.6.1. Clarified respiratory rate and temperature will not be reported in Section 6.6.3. QTcF formula is added in Section 6.6.4. Added details of interim analysis in Section 7.1 and 7.2. Updated summary of efficacy analysis Appendix 1 to reflect the changes in the main body.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			Updated analysis window in Appendix to for better interpretation of data. Corrected a typo from 'rescue medication' to 'prohibited medication' throughout the document.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3791001.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable (NA).

2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
	Primary:	**Primary:**	**Primary:**
• Safety	• To characterize the safety and tolerability of isavuconazole through observation of TEAE.	**Primary safety endpoint** • Incidence rates of TEAEs by SOC and PT.	• The incidence rates of TEAE by SOC and PT will be summarized without regard to adherence to the isavuconazole treatment and use of prohibited medication.
	Secondary:	**Secondary:**	**Secondary:**
• Efficacy	• To describe the efficacy of isavuconazole in the treatment of Chinese patients with IFD caused by *Aspergillus* species. and other filamentous fungi.	**Key secondary efficacy endpoint:** • The percentage of all-cause mortality on Day 42 following primary treatment with isavuconazole. **Other secondary efficacy endpoints:** • The percentage of all-cause mortality at Day 84 following primary treatment with isavuconazole.	• The percentage of all-cause mortality on Day 42 will be estimated in participants with IFD caused by *Aspergillus* species and other filamentous fungi, or IM, without regard to adherence to the isavuconazole treatment. • The same estimand as above will be used to estimate the percentage of all-cause mortality at Day 84 in participants with IFD caused by

Type	Objective	Endpoint	Estimand
			Aspergillus species and other filamentous fungi.
		• The crude rate of overall response at EOT, Day 42, and 84; and the crude success rates of the clinical, mycological, radiological responses based on the investigators' assessment at EOT, Day 42, and 84.	• The crude rate of overall response, clinical response, mycological response and radiological response at EOT, Day 42, and Day 84 will be estimated in participants with IFD caused by *Aspergillus* species and other filamentous fungi, or IM while participants are on the isavuconazole treatment. Data collected after use of the prohibited medications will not be used. Participants who are not available for clinical, mycological or radiological responses will be considered as a failure for overall response.
• Safety	• To observe the additional safety and tolerability profile of isavuconazole.	**Other secondary safety endpoints:** • Other AE summaries, including TEAE related to study intervention, Treatment-Emergent SAEs, TEAE leading to discontinuation of study intervention, TEAE leading to deaths, and all Deaths.	• Not applicable
		• Other safety variables, including clinical laboratory variables, vital signs, 12-lead ECG and eye examination.	• Not applicable
• *Pharmacokinetics*	• To evaluate the PK of isavuconazole in the Chinese population with IFD caused by *Aspergillus* species and other filamentous fungi.	• Isavuconazole plasma concentrations at Day 3, 7, 14 and EOT visit.	• Not applicable
	Exploratory	**Exploratory**	**Exploratory**
• Efficacy	• To describe the efficacy of isavuconazole in the treatment of Chinese participants with IM.	• The percentage of all-cause mortality on Day 42 and 84 following	• The percentage of all-cause mortality on Day 42 and 84 will be estimated in participants with

Type	Objective	Endpoint	Estimand
		primary treatment with isavuconazole. • The crude rate of overall response at EOT, Day 42, and 84; and the crude success rates of the clinical, mycological, radiological responses based on the investigators' assessment at EOT, Day 42, and 84.	IM without regard to adherence to the isavuconazole treatment. • The crude rate of overall response, clinical response, mycological response and radiological response at EOT, Day 42, and Day 84 will be estimated in participants with IM while participants are on the isavuconazole treatment. Data collected after use of the prohibited medications will not be used. Participants who are not available for clinical, mycological or radiological responses will be considered as a failure for overall response.
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2.2.1. Primary Estimand(s)

The primary estimand of this study will use the treatment policy strategy and estimate the number and percentage of Treatment Emergent Adverse Events (TEAEs) by System Organ Class (SOC) and PT, without regard to adherence to the isavuconazole treatment and use of prohibited medication. The estimand is defined according to the primary objective and is in alignment with the primary endpoint. It includes the following 4 attributes:

- Population: Participants who have proven, probable, or possible (invasive fungal disease) IFD caused by *Aspergillus* species, *Mucorales* species or other filamentous fungi as defined by the inclusion and exclusion criteria;
- Variable: Number and percentage of TEAEs by SOC and PT;
- Intercurrent event(s): Adherence to the isavuconazole treatment or the use of prohibited medication is not considered in the analysis. All data collected (after prohibited medication or after discontinuation of treatment) are included.

- Population-level summary: Number and percentage of participants with TEAEs divided by the number of participants in the polulation of interest.

2.2.2. Secondary Estimand(s)

Secondary estimands to assess secondary objectives will be:

Estimand 2.1: The key secondary estimand of this study will use the treatment policy strategy and estimate the percentage of all-cause mortality on Day 42 in participants with IFD caused by Aspergillus species and other filamentous fungi, or Invasive mucormycosis (IM), without regard to adherence to the isavuconazole treatment. The estimand is defined according to the secondary objective and is in alignment with the key secondary endpoint. It includes the following 4 attributes:

- Population: Participants who have proven, probable, or possible IFD caused by *Aspergillus* species, *Mucorales* species or other filamentous fungi as defined by the inclusion and exclusion criteria;

- Variable: Percentage of all-cause mortality on Day 42;

- Intercurrent event(s): Adherence to the isavuconazole treatment is not considered in the analysis. All data collected (after prohibited medication or after discontinuation of treatment) are included.

- Population-level summary: Number of particinpants with defined all-cause mortality divided by the number of participants in the polulation of interest.

Estimand 2.2: This estimand will use the treatment policy strategy and estimate the percentage of all-cause mortality at Day 84 in participants with IFD caused by Aspergillus species and other filamentous fungi, without regard to adherence to the isavuconazole treatment. It includes the following 4 attributes:

- Population: Participants who have proven, probable, or possible IFD caused by *Aspergillus* species, *Mucorales* species or other filamentous fungi as defined by the inclusion and exclusion criteria;

- Variable: Percentage of all-cause mortality at Day 84 ;

- Intercurrent event(s): Adherence to the isavuconazole treatment is not considered in the analysis. All data collected (after prohibited medication or after discontinuation of treatment) are included.

- Population-level summary: Number of particinpants with defined all-cause mortality divided by the number of participants in the polulation of interest.

Estimand 2.3: This estimand will use the while on-treatment policy strategy and estimate the crude rate of overall response, clinical response, mycological response and radiological

response at end of treatment (EOT), Day 42, and Day 84 in participants with IFD caused by Aspergillus species and other filamentous fungi, or IM while participants are on the isavuconazole treatment. Participants who are not available for clinical, mycological or radiological responses will be considered as a failure for overall response. It includes the following 4 attributes:

- Population: Participants who have proven, probable, or possible IFD caused by *Aspergillus* species, *Mucorales* species or other filamentous fungi as defined by the inclusion and exclusion criteria;
- Variable: Crude rate of overall response, clinical response, mycological response and radiological response at EOT, Day 42, and Day 84;
- Intercurrent event(s): All data collected after use of the prohibited medications will be excluded.
- Population-level summary: Number of participants with a success outcome divided by the number of participants in the polulation of interest.

2.2.3. Additional Estimand(s)

Estimand 3.1: This exploratory estimand will use the treatment policy strategy and estimate the percentage of all-cause mortality on Days 42 and 84 in participants with IM, without regard to adherence to the isavuconazole treatment. It includes the following 4 attributes:

- Population: Participants who have proven, probable, or possible IFD caused by *Mucorales* species as defined by the inclusion and exclusion criteria;
- Variable: Percentage of all-cause mortality on Days 42 and 84;
- Intercurrent event(s): Adherence to the isavuconazole treatment is not considered in the analysis. All data collected (after prohibited medication or after discontinuation of treatment) are included.
- Population-level summary: Number of particinpants with defined all-cause mortality divided by the number of participants in the polulation of interest.

Estimand 3.2: This exploratory estimand will use the while on-treatment policy strategy and estimate the crude rate of overall response, clinical response, mycological response and radiological response at EOT, Day 42, and Day 84 in participants with IM while participants are on the isavuconazole treatment. Participants who are not available for clinical, mycological or radiological responses will be considered as a failure for overall response. It includes the following 4 attributes:

- Population: Participants who have proven, probable, or possible IFD caused by *Mucorales* species as defined by the inclusion and exclusion criteria;

- Variable: Crude rate of overall response, clinical response, mycological response and radiological response at EOT, Day 42, and Day 84;
- Intercurrent event(s): All data collected after use of the prohibited medications will be excluded.
- Population-level summary: Number of participants with a success outcome divided by the number of participants in the polulation of interest.

2.3. Study Design

This is a single arm, prospective, multi-center study in Chinese patients with proven, probable, or possible IFD caused by *Aspergillus* species or other filamentous fungi.

Initially approximately 56 participants were planned to be enrolled in China and approximately 53 participants were expected to be treated. In protocol amendment 2, the sample size is modified to approximately 70 participants, among which approximately 66 participants are expected to be treated. The enrollment will be competitive.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

All the participants will receive isavuconazole treatment. All participants receiving study medication will have the visits performed as scheduled. The longest treatment duration in this study is 84 days (maximum 180 days for participants with IM), and the total study duration for 1 participant is around 4 months (~7 months for participants with IM). For all participants, the Follow-up visit will take place 4 weeks (±7 days) after the last administration of the study medication, and may occur before or after Day 42 and /or Day 84 (or Day 180 for participants with IM). Participants who need further antifungal treatment at the time of protocol defined longest treatment duration of isavuconazole may be switched to appropriate treatment at treating physician's discretion.

The study will consist of 3 periods: Screening Period (up to 7 days), Treatment Period (maximum 84 days for participants with invasive aspergillosis (IA) or other filamentous fungi infection, or up to 180 days for participants with IM) and Follow-up Period (4 weeks after last dose of study intervention). Following the last dose of study intervention, participants who discontinued from the study intervention and participants who completed the treatment period will enter into a 4-week follow-up period for safety monitoring.

Participants fulfilling the criteria for "possible" IFD will be eligible for enrollment; efforts of further IFD categorization as "probable" or "proven" by culture and histology/cytology antigen (for *Aspergillus* and *Mucorales* species, including galactomannan (GM)) must be completed during the screening period. However, assessments performed up to 7 days after

the first administration of study intervention may be used to confirm the categorization of IFD.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint is the incidence rates of TEAEs by SOC and PT. A TEAE is defined as any adverse event (AE) that starts on or after the first administration of study intervention until 28 days after last dose of study intervention.

3.2. Secondary Endpoint(s)

The key secondary endpoint is percentage of all-cause mortality on Day 42 following primary treatment with isavuconazole in participants with IFD.

The other secondary endpoints are for participants with IFD include:

- The percentage of all-cause mortality on Day 84 following primary treatment with isavuconazole.
- The crude rate of overall response based on the investigators' assessment at EOT, Day 42, and 84.
- The crude success rates of the clinical, mycological, radiological responses based on the investigators' assessment at EOT, Day 42 and Day 84.
- Other AE summaries, including TEAE related to study intervention, Treatment-Emergent serious adverse events (SAE), TEAE leading to discontinuation of study intervention, TEAE leading to deaths, and all Deaths.
- Other safety variables including clinical laboratory variables, vital signs, 12-lead ECG and eye examination.
- Isavuconazole plasma concentrations at Day 3, 7, 14 and EOT visit.

3.3. Other Endpoint(s)

The exploratory endpoints include:

- The percentage of all-cause mortality on Days 42 and 84 following primary treatment with isavuconazole in particpapnts with IM.
- The crude rate of overall response at EOT, Day 42, and 84 in particpapnts with IM.
- The crude success rates of the clinical, mycological, radiological responses based on the investigators' assessment at EOT, Day 42 and Day 84 in particpapnts with IM.

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3.4. Baseline Variables

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

The baseline variables in the study contain demographic and other baseline characteristics as follows.

- Age, Gender, Race, Ethnicity, Country, Height, Weight, Body mass index (BMI)
- Age category 1: ≤ 45, > 45 to ≤ 65, > 65
- Age category 2: ≤ 65, > 65 to ≤ 75, > 75
- BMI: <25, ≥ 25 to < 30, ≥ 30
- eGFR- CKD-EPI category: < 60, ≥ 60
- Baseline Neutropenic Status: Yes/No
- Use of T-cell/B-cell immunosuppressant: Yes/No
- Use of Corticosteroids: Yes/No
- Prior allogeneic HSCT/BMT: Yes/No
- Solid organ transplant: Yes/No
- Hematologic malignancy: Yes/No
- Other malignancy: Yes/No
- Chronic respiratory airway abnormality: Yes/No
- Primary diagnosis type: IA, IM, other

Details of derivation for eGFR-CKD-EPI are included in Appendix 2.

Baseline Neutropenic Status will be defined as "Yes" for participants who had Abolute Neutrophil Count (ANC) < 0.5 x10^9/L [<500/mm^3] at baseline.

Use of T-cell/B-cell immunosuppressant and Use of Corticosteroids will be determined based on clinical review with the prior medication data collected via CRF.

Prior allogeneic HSCT/BMT, Solid organ transplant, Hematologic malignancy, Other malignancy, and Chronic respiratory airway abnormality will be determined based on clinical review with the medical history data collected via CRF.

3.5. Safety Endpoints

The incidence rates of TEAEs by SOC and PT is the primary endpoint in this study. See Section 3.1. Other TEAE summaries and safety endpoints are secondary endpoints in this study.

3.5.1. Adverse Events

An AE is referred to TEAE in this study unless mentioned otherwise. See Section 3.1 for the definition of TEAE.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication

The abnormality or investigational value is clinically significant in the opinion of the investigator.

3.5.2. Laboratory Data

The laboratory data includes test values of hematology, biochemistry and urinalysis.

Samples for the full safety profile will be obtained on Screening, Days 1, 7, 14, 28, 42, every 42 days after Day 84, EOT and Follow-up.

The last value of laboratory tests obtained on Day 1 (or 72 hours) prior to the first dose of study intervention will be considered as baseline assessment. Hematology, biochemistry and urinalysis will be performed in local laboratory.

3.5.3. Vital Signs

The following vital signs will be measured at Screening and on Days 1, 7, 14, 42, 84, every 42 days after Day 84, and EOT:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (PR, beats per minute [bpm])
- Respiratory rate (times per minute)
- Body temperature (°C, oral)

If participants discontinue from study intervention prior to Day 7, the assessments on Days 7 and 14 on vital signs are not required. At the Follow-up visit, vital signs will only be obtained from participants with abnormalities observed at the previous visit.

The vital signs assessment obtained on Day 1 prior to the administration of study intervention will be considered as baseline value.

3.5.4. Twelve-lead Electrocardiogram

The electrocardiogram (ECG) measurements will include the following: Heart Rate (bpm), PR interval (msec), QTc (corrected QT) interval (msec), QRS (msec), QT (msec). Those measurements will be obtained at Screening and will also be performed on Day 1, Days 7, 14, 42, 84, every 42 days after Day 84, and EOT while the participant remains on study intervention. All participants will have an ECG at EOT. At the Follow-up visit, ECG will only be obtained from participants with abnormalities observed at EOT.

The last ECG measurement obtained at Screening visit prior to the administration of study intervention will be considered as baseline value.

3.5.5. Eye Examination

The examination will consist of visual acuity, confrontational visual field testing, and color perception testing. An eye examination will be conducted at Screening and EOT. If the participant is continuing on study intervention, an eye examination will also be performed on Days 14, 28 and 42. An eye examination will be performed at the Follow-up visit only if abnormal at EOT.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures (SOP).

Population	Description	Applicable Analysis (for additional information refer to section 6)
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not	

Population	Description	Applicable Analysis (for additional information refer to section 6)
	participate in the study, are not considered enrolled, unless otherwise specified by the protocol.	
Intent-to-Treat (ITT)	The ITT population consists of all enrolled participants who receive at least 1 dose of study intervention. The ITT is the primary efficacy population.	Key secondary endpoint, main analysis (Section 6.2.1.1) Secondary analyses and sensitivity/supplementary/subgroup analyses (Sections 6.2.1.2 - 6.2.2) Baseline and other summaries and analyses (Section 6.5)
Modified Intent-to-Treat (mITT)	The mITT population consists of ITT participants who had proven or probable IFD as determined by the investigators based on the definition specified in protocol Appendix 9, Section 10.9.	Key secondary endpoint, supplementary analysis (Section 6.2.1.2) Secondary analyses (Sections 6.2.2-6.2.4) Baseline and other summaries and analyses (Section 6.5)
Mycological Intent-to-Treat IA (myITT-IA)	The myITT-IA population consists of mITT participants with proven or probable IA based on cytology, histology, culture, or GM and assessed by the investigators.	Key secondary endpoint, supplementary analysis (Section 6.2.1.2) Secondary analyses (Sections 6.2.2-6.2.4) Baseline and other summaries and analyses (Section 6.5)
Mycological Intent-to-Treat IM (myITT-IM)	The myITT-IM population consists of mITT participants with proven or probable IM based on cytology, histology, culture, or GM and assessed by the investigators.	Exploratory analysis (Sections 6.3.1-6.3.3) Baseline and other summaries and analyses (Section 6.5)
Safety Population	The safety population consists of all enrolled participants who receive at least 1 dose of study intervention.	Primary and Secondary safety endpoints analyses (Section 6.1, 6.6)

Population	Description	Applicable Analysis (for additional information refer to section 6)
Pharmacokinetic (PK) Concentration Analysis Set	All participants who are treated and have at least 1 measurable PK concentration data, and who have no major protocol violations that can have an effect on their PK data.	Secondary analysis (Section 6.2.5) Exploratory analysis (Section 6.3.4)

5. GENERAL METHODOLOGY AND CONVENTIONS

All data analyses will be performed according to this pre-specified analysis plan. Any deviations from this plan will be documented in the clinical study report. All computations will be performed prior to rounding. The boundaries of 2-sided 95% confidence intervals (CI) will be rounded to 3 decimal places.

5.1. Hypotheses and Decision Rules

No formal statistical hypothesis testing will be conducted for efficacy analysis.

5.2. General Methods

5.2.1. Analyses for Binary and Categorical Endpoints

Binary and categorical data will be summarized by number and percentage of participants within the category.

For all-cause mortality and crude rate, the 95% CIs for the rates will be calculated based on the exact binomial distribution.

5.2.2. Analyses for Continuous Endpoints

Continuous endpoints will be summarized descriptively including number of participants (n), mean, standard deviation (SD), median, minimum and maximum.

5.2.3. Analyses for Time-to-Event Endpoints

A survival analysis of all-cause mortality will be conducted using the Kaplan-Meier (K-M) method and estimated survival curves will be displayed graphically when appropriate. Number and percent of participants who experienced the event as well as number and percent of participants who were at risk will be reported. The survival rates will be estimated using the K-M method by Day 42, and Day 84 based on ITT, mITT, and myITT-IA populations; and be estimated by Day 42, Day 84, Day 120, and Day 180 based on myITT-IM populations. The cumulative probabilities of mortality rates (100%-survival rates) will then be calculated. For 95% CI, Greenwood's method will be used to estimate the standard error for the survival rates; the 95% CI will first be constructed for the log-log transformed survival rates ie. L(t)=log(-log(S(t))); and antiloging the lower and upper bounds of this CI ie. S(t) = exp (-exp (L(t)) will be performed to get the 95% CI for survival rates in right range; the 95% CI for the mortality rate will be calculated by 100% - survival rates 95% CI boundaries.

5.3. Methods to Manage Missing Data

Any missing data were presented as part of a missing category except for those situations described as follows. For calculation of crude mortality, a participant with the last known survival status is before evaluation visit (i.e., Day 42, Day 84) or missing and the last assessment day is on or before the visit (i.e., Day 42, Day 84) will be treated as death. When change from baseline to a postbaseline value was calculated, only participants with baseline and at least one postbaseline value will be included in the calculation. In the time-to-event analysis, a participant without a reported death will be censored on the participant's last known alive day which will be the latest of randomization day, last study assessment day, latest study drug treamtment day, date with follow-up therapies, date with AEs, last contact day, last PK sampling day, or date of discontinuation. For example. if a participant's last survival status is before day 42 and this participant's last known alive day is after Day 42, say day 50, then this participant will be censored on day 50.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The primary endpoints are incidence rates of TEAEs by SOC and PT.

- Estimand stragety: Treatment (Section 2.2.1)
- Analysis set: Safety population (Section 4).
- Analysis methodology: the incidence rates will be calculated by dividing the number of participants with TEAEs by the number of participantss in the safety population. All TEAEs will be coded using MedDRA and will be summarized (number and percentage) by SOC and PT. When a participant has the same AE reported multiple times during an analysis period based on preferred terminology (SOC, PT), the participant will be counted once at the preferred terminology level (Section 5.2.1).
- Intercurrent event and missing data: All data collected (after prohibited medication or after discontinuation of treatment) will be included.

6.2. Secondary Endpoint(s)

6.2.1. Percentage of All-cause Mortality on Day 42 (Key Secondary Endpoint)

6.2.1.1. Main Analysis

- Estimand strategy: Treatment (Section 2.2.2).
- Analysis set: ITT population (Section 4). Any death that occurs after first dose of study drug through Day 42 will be included.
- Analysis methodology: The crude mortality rate will be summarized by number and percentage of participants through Day 42. The 2-sided 95% CIs for crude rate will be

calculated based on a binomial distribution. Any death that occurred after first dose of study drug through Day 42 will be included. A participant with the last known survival status is before Day 42 or missing and the last assessment day is before Day 42 will be treated as death.

- Intercurrent events and missing data: All data collected (after prohibited medication or after discontinuation of treatment) will be included. Missing data will be handled as described in Section 5.3.

6.2.1.2. Sensitivity/Supplementary Analyses

A sensitivity analysis of all-cause mortality rate by Day 42 based on ITT population will be estimated using the KM method as described in Section 5.2.3.

Supplementary analyses of the same analysis described in Section 6.2.1.1 and KM method, respectively, will be repeated for mITT and myITT-IA populations.

6.2.1.3. Subgroup Analysis

If data permits, subgroup analyses of all-cause mortality on Day 42 will be performed based on the ITT population for the following subgroups:

- Age category 1: (≤ 45, > 45 to ≤ 65, > 65)
- Age category 2: (≤ 65, > 65 to ≤ 75, > 75)
- Gender (Male, Female)
- BMI category: (<25, $\geqslant 25$ to < 30, $\geqslant 30$)
- eGFR category: < 60, $\geqslant 60$
- Baseline Neutropenic Status: Yes/No

6.2.2. Percentage of All-cause Mortality on Day 84

Percentage of all-cause mortality on Day 84 will be summarized and analyzed using the same approach as described in Sections 6.2.1.1-6.2.1.3.

6.2.3. The Crude Rate of Overall Response at EOT, Day 42, and Day 84

6.2.3.1. The Crude Rates of Overall Response at EOT

- Estimand strategy: While on-Treatment (Section 2.2.2).
- Analysis set: mITT and myITT-IA populations (Section 4).
- Analysis methodology: The crude rates of overall response based on investigator's assessment at EOT will be summarized by number and percentage of participants through

EOT. The 2-sided 95% CIs for crude rate will be calculated based on a binomial distribution.

- Intercurrent events and missing data: All data collected after use of the prohibited medications will be excluded. Missing data will be handled as described in Section 5.3.

6.2.3.1.1. Subgroup Analysis

If data permit, subgroup analyses will be performed for the overall response based on investigator's assessment at EOT based on mITT population for the aforementioned subgroups in Section 6.2.1.3, and the IFD location [lower respiratory tract disease (LRTD) only, LRTD plus Other Organ, Non LRTD only] .

6.2.3.2. The Crude Rates of Overall Response at Day 42 and Day 84

- Estimand strategy: While on-Treatment (Section 2.2.2).
- Analysis set: mITT and myITT-IA populations (Section 4).
- Analysis methodology: The crude rates of overall response based on investigator's assessment will be summarized by number and percentage of participants at Day 42 and Day 84, respectively. The 2-sided 95% CIs for crude rate will be calculated based on a binomial distribution.
- Intercurrent events and missing data: All data collected after use of the prohibited medications will be excluded. Missing data will be handled as described in Section 5.3. A participant that investigators'assessment indicated as Not Done at a visit will be considered as missing and will be included as a failure for the visit. Any death before Day 42 will be considered a failure by including in the death category for both timepoints. Any death occurring between Day 42 and Day 84 will be considered as a failure by including in the death category for Day 84.

6.2.4. Crude Success Rates of the Clinical, Mycological, Radiological Responses at EOT, Day 42 and Day 84

6.2.4.1. Clinical Response at EOT, Day 42 and Day 84

Outcome	Clinical response
Success	1. Resolution of all attributable clinical symptoms and physical findings 2. Resolution of some attributable clinical symptoms and physical findings
Failure	1. No resolution of any attributable clinical symptoms and physical findings and/or worsening 2. Results not available/Patient unevaluable
NA	No attributable signs and symptoms present at screening

- Estimand strategy: While on-Treatment (Section 2.2.2).

- Analysis set: mITT and myITT-IA populations (Section 4).
- Analysis methodology: Number and percent of participants in the categories of Success and Failure will be summarized at Day 42, Day 84 and EOT. The 2-sided 95% CIs for crude success rate will be calculated based on a binomial distribution.
- Intercurrent events and missing data: All data collected after use of the prohibited medications will be excluded. As the clinical response is one of the components toward the overall response, the results of clinical response will be summarized without regards to deaths. Missing data will be handled as described in Section 5.3. Any patient with a Not Done at a visit will be considered a missing and included as a failure. A participant with a NA assessment will be excluded from the denominators when calculating the percentages.

6.2.4.2. Mycological Response at EOT, Day 42 and Day 84

Outcome	Mycological assessment
Success	1. Eradication 2. Presumed Eradication
Failure	1. Persistence 2. Presumed Persistence
NA	1. No mycological evidence available at screening 2. No mycological follow-up results available

- Estimand strategy: While on-Treatment (Section 2.2.2).
- Analysis set: mITT and myITT-IA populations (Section 4).
- Analysis methodology: Number and percent of participantss in the categories of Success and Failure will be summarized at Day 42, Day 84 and EOT. The 2-sided 95% CIs for crude success rate will be calculated based on a binomial distribution.
- Intercurrent events and missing data: All data collected after use of the prohibited medications will be excluded. As the mycological response is one of the components toward the overall response, the results of mycological response will be summarized without regards to deaths. Missing data will be handled as described in Section 5.3. A participant with a Not Done assessment at a visit will be considered missing and is included as a failure. A participant with a NA assessment will be excluded from the denominators when calculating the percentages.

6.2.4.3. Radiological Response at EOT, Day 42 and Day 84

Outcome	Radiological assessment
Success	1. ≥ 90% improvement 2. ≥ 50% to < 90% improvement 3. ≥ 25% to <50% improvement (for Day 42 only)
Failure	1. < 25% improvement at any time 2. Results not available
NA	No signs on radiological images at screening

An improvement between 25% and 50% from baseline is considered a radiological success for Day 42 and EOT (that is before Day 42). At least 50% improvement from baseline is considered a radiological success for visits on Day 42, Day 84 and EOT (that is after Day 42).

- Estimand strategy: While on-Treatment (Section 2.2.2).
- Analysis set: mITT and myITT-IA populations (Section 4).
- Analysis methodology: Number and percent of participants in the categories of Success and Failure will be summarized at Day 42, Day 84 and EOT. The 2-sided 95% CIs for crude success rate will be calculated based on a binomial distribution.
- Intercurrent events and missing data: All data collected after use of the prohibited medications will be excluded. As the radiological response is one of the components toward the overall response, the results of radiological response will be summarized without regards to deaths. Missing data will be handled as described in Section 5.3. A participant with a Not Done assessment at a visit will be considered missing and is included as a failure. A participant with a NA assessment will be excluded from the denominators when calculating the percentages.

6.2.5. Isavuconazole Plasma Concentrations at Day 3, 7, 14 and EOT Visit

- Analysis set: PK Concentration population (Section 4).
- Analysis methodology: Observed plasma concentrations of isavuconazole will be summarized for Day 3, Day 7, Day 14, and EOT using descriptive statistics.

6.3. Exploratory Endpoints

6.3.1. Percentage of All-cause Mortality on Day 42 and Day 84 in Participants with IM

The endpoints will be analyzed using the same method from the key secondary endpoint (Section 6.2.1.1) for myITT-IM polulation (Section 4). As a supplementary analysis, all-cause mortality rate over time by Day 42, Day 84, Day 120, and Day 180 based on myITT-IM population will also be estimated using the KM method as described in Section 5.2.3. This analysis will generate a survival curve from Day 1 through Day 180.

6.3.2. The Crude Rate of Overall Response at EOT, Day 42, and Day 84 in Participants with IM.

The endpoints will be analyzed using the same method from the secondary endpoints in Section 6.2.3) for myITT-IM polulation (Section 4).

6.3.3. Crude Success Rate of the Clinical, Mycological, Radiological Responses at EOT, Day 42, and Day 84 in Participants with IM.

The endpoints will be analyzed using the same method from the secondary endpoints in Section 6.2.4 for myITT-IM polulation (Section 4).

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6.4. Subset Analyses

Subset analyses as needed were described in Sections 6.2.1.3, 6.2.3.1.1, and 6.3.4 for the corresponding endpoints.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

The demographic and baseline characteristics (see Section 3.4) will be summarized descriptively for the treatment group for the ITT, mITT, myITT-IA, and myITT-IM populations.

6.5.2. Primary Underying Disease

The primary underlying disease at baseline will be summarized descriptively for the treatment group for the ITT, mITT, myITT-IA, myITT-IA, and myITT-IM populations. The data will be coded using MedDRA. The number and percentage of participants will be summarized by diagnosis.

6.5.3. Study Conduct and Participant Disposition

Participant disposition will be summarized for ITT, mITT, myITT-IA, and myITT-IM populations including the number and percentage of participants enrolled, treated, completed the study, discontinued from the study intervention.

Additionally, number and percentage of participants who discontinued from the study will be summarized by the primary reasons of discontinuation for ITT, mITT, myITT-IA, and myITT-IM population.

6.5.4. Study Treatment Exposure

Study treatment exposure will be descriptively summarized for treatment group for the Safety population. Extent of exposure is defined as the number of days between the start and the end date of study treatment, where the duration will be calculated by: (end date – start date + 1).

The total duration in days, duration of IV dosing only, and duration of oral dosing only will be summarized descriptively with n, mean, SD, median, minimum and maximum. The number and percent of participantss with an extent of exposure will be summarized within the following day ranges: > 0 to ≤ 2 days, > 2 to ≤ 7 days, > 7 to ≤ 14 days, > 14 to ≤ 21 days, > 21 to ≤ 42 days, > 42 to ≤ 56 days, > 56 to ≤ 84 days, and > 84 days. In addition, cumulative exposure will be summarized by the number and percent of participants for the following categories: ≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 42 days, ≥ 56 days and ≥ 84 days.

6.5.5. Anti-infective and Medical History

Anti-infective history of all fungal (excluding IFD under study), viral, and bacterial infections within 4 weeks prior to first dose of study intervention and medical history will be summarized for ITT, mITT, myITT-IA, and myITT-IM. The data will be coded using MedDRA.The number and percentage of participants in each SOC/PT will be presented by alphabetic order.

6.5.6. Prior and Concomitant Medications

Prior medications are defined as any medications taken before study intervention started. The number and percentage of participants who took at least one prior medication as well as for each medication will be summarized. The number and percentage of participants with prior anti-fungal medication will be summarized separately.

Concomitant medications are defined as any medications that participants took after the first dose of study intervention and through 28 days after the last day of study intervention. The number and percentage of participants who took at least one concomitant medication as well as for each medication will be summarized. The number and percentage of participants with concomitant anti-fungal medication will be summarized separately.

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Participants taking the same concomitant (or prior) medication multiple times will be counted once per that concomitant (or prior) medication. The summaries will be performed for ITT, mITT, myITT-IA, and myITT-IM populations.

6.5.7. Non-medication Procedure

Non-medication procedures will be coded using MedDRA.

Prior procedurs are defined as procedures that participants started using prior to first administration of study intervention. Concomitant procedures are defined as any medications that participants took after the first dose of study intervention and through 28 days after the last day of study intervention.

The number and percentage of participants receiving non-medication procedures will be summarized by SOC/PT for ITT, mITT, myITT-IA, and myITT-IM populations. This summary will be done for prior and concomitant procedurs separately.

6.5.8. Baseline IFD Characteristics

The assessment of IFD at baseline will be summarized as described in the following subsections. The summaries will be performed for mITT, myITT-IA, and myITT-IM populations. Baseline IFD characteristics is defined as the test obtained prior to the first dose and up to 7 days after the first administration of study medication.

6.5.8.1. Mycological Assessments

Mycological assessments at baseline will be summarized by number and percentage of participants in the following categories:

- Histopathology /Culture evidence of IFD
- Single serum or plasma: ≥ 0.7 to < 1.0 and bronchoalveolar lavage (BAL) GM ≥ 0.8
- Single serum or plasma: ≥ 1.0
- BAL GM: ≥ 1.0
- Two consecutive values of either serum, plasma or BAL fluid between ≥ 0.5 to <1.0 (from two separate specimens of the same category)
- No mycological evidence available.

6.5.8.2. Pathogen(s) Causing IFD

Number and percentage of participants for each category of pathogen causing IFD will be summarized for the following categories (some of the categories may be updated based on data available):

- Aspergillus Species or Other Filamentous Fungi
- Mucorales Species Only
- Mould Species, Not Otherwise Specified

- Aspergillus Species Plus Other Mould Species
- No Pathogen Identified.

6.5.8.3. Location(s) of IFD

The following IFD location will be summarized by number and percentage of participants:

- LRTD only
- LRTD plus Other Organ
- Non LRTD only.

For participants with non-LRTD locations assessed, the following types of locations will be further summarized: BODY, Brain, Eye, LIVER, Sinus, Skinand Other.

6.5.8.4. Categorization of IFD

The following categories of IFD will be summarized with number and percentage of participants:

- Proven IM
- Proven IA
- Probable IM
- Probable IA
- Possible
- No IFD.

6.5.8.5. Clinical Signs and Symptoms

Clinical signs and symptoms will be summarized by number and percentage of participants in descending order. Baseline is defined as the signs and symptoms collected at Day 1 or Screening (if Day 1 data is missing). The summary will additionally based on ITT population in addition to mITT, myITT-IA, and myITT-IM populations.In addition, mycological assessments, pathogen(s) causing the IFD, location(s) of IFD, and categorization of IFD, signs and symptoms will be listed.

6.6. Safety Summaries and Analyses

- Analysis set: Safety population (Section 4).
- Analysis methodology: Different analysis methods will be performed for the safety variables as follows, respectively.

6.6.1. Adverse Events

All causality TEAEs and treatment-related TEAEs will be coded using MedDRA and will be presented as following:

- TEAEs overview (all causality TEAEs and treatment-related TEAEs)
- TEAEs by SOC and PT (all causality TEAEs and treatment-related TEAEs)
- Incidence and severity of TEAEs by SOC and PT (all causality TEAEs and treatment-related TEAEs)
- Treatment-Emergent SAEs by SOC and PT (all causality TEAEs and treatment-related TEAEs)
- Summary of TEAE Leading to Discontinuation of Study Drug (all causality TEAEs and treatment-related TEAEs)
- Summary of TEAE Leading to Deaths (all causality TEAEs and treatment-related TEAEs)
- Listing of SAE and deaths

6.6.2. Laboratory Data

All clinical laboratory values including Hematology, Chemistry and Urinalysis from a local laboratory will be summarized. Laboratory values (actual values and change from baseline) will be descriptively summarized by visit. The change from baseline for urinalysis will include pH parameter. Number and percentage of participants with shifts from baseline to post-baseline will be summarized for the following:

1) An upward shift from baseline to post-baseline (i.e. L to N, L to H, or N to H)
2) No change from baseline to post-baseline (i.e. L to L, N to N, or H to H)
3) A downward shift from baseline to post-baseline (i.e. H to N, H to L, or N to L).

The individual listing of laboratory data will also be generated with flagging of values outside the normal reference ranges

In addition, potential hepatotoxicity and nephrotoxicity will be summarize.

Assessment of Hepatotoxicity

Potential hepatotoxicity will be summarized descriptively. The number and percentage of participants who meet the following criteria based on either local or central laboratories

including post-baseline data collected within post-dosing window will be summarized for the following criteria.

- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) > 3xULN, > 5xULN, > 10xULN, >20xULN
- ALT > 3xULN, > 5xULN, > 10xULN, >20xULN
- AST > 3xULN, > 5xULN, > 10xULN, >20xULN
- Alkaline phosphatase (ALP) > 1.5xULN, >3xULN
- Total Bilirubin >2xULN
- ALT or AST > 3xULN and Total Bilirubin > 1.5xULN
- ALT or AST > 3xULN and Total Bilirubin > 2xULN
- ALT or AST > 3xULN and ALP< 2xULN and Total Bilirubin > 2xULN

A participant may be counted more than once as the categories are not mutually exclusive (ie., a participant with a value >10xULN will be counted in both 3xULN and 5xULN categories). The analysis will be conducted by taking all post-baseline values.

Assessment of Nephrotoxicity

Serum creatinine either from local or central lab will be further analyzed by the following 3 categories:

- ≥25%, ≥50%, ≥100% increase from baseline.

The categories are not mutually exclusive, thus a participant may be counted in more than one category. Participants with both baseline and at least one post-baseline will be included in this summary. The number and percentage of participants meeting the defined criteria will be summarized by treatment group in 2 ways: by taking all post-baseline values, and at EOT

6.6.3. Vital Signs

Vital signs including systolic and diastolic blood pressures (mmHg), and PR (bpm) will be descriptively summarized for actual values and change from baseline to post-baseline time-points. For the change values, participants with both values at baseline and each respective time-point for calculating the change will be included. Participants who have both baseline and at least one post-baseline will be included in this summary.

Respiratory rate and temperature data collected during the study will be considered source data and will not be reported.

6.6.4. Electrocardiograms

The ECG parameters (Heart Rate, PR interval, QRS interval, QT interval, QTc interval) will be summarized for actual values and change from baseline at baseline and/or post-baseline time-points. The number and percentage of participants who have treatment emergent changes toward worst category in the ECG interpretations assessed by investigators will be summarized. The interpretations are the followings: Normal, Abnormal-Clinically Significant and Abnormal-Clinically Not Significant.Participants with ECG findings meeting the Protocol Appendix 7 criteria will be summarized.

QTc corrected using Fridericia's formula (QTcF) will be programmatically derived from QT and HR (ie. ECG Mean Heart Rate) using the following formula:

$$QTcF(msec)=QT(msec)/\sqrt[3]{(60/EGHRMN(beats/min)}$$

The number and percentage of participants with QTcF meeting the criteria in the following table will be summarized by treatment group in 2 ways: by taking all post-baseline values, and at EOT.

Type of Analysis	Criteria
Change from Baseline	Increase > 30 msec, Increase > 60 msec, Decrease > 30 msec, Decrease > 60 msec
Actual Values	< 300 msec, < 330 msec, < 360 msec, > 450 msec, > 480 msec, > 500 msec

A participant may be counted more than once in some categories above as they are not mutually exclusive.

6.6.5. Eye Examination

The eye examination records will be listed.

6.6.6. Other Assessment

The summaries will be performed for safety populations.

6.6.6.1. Hospitalization Status

Reason for hospitalization from screening up through the 4 weeks post-treatment period will be summarized.

7. INTERIM ANALYSES

7.1. Introduction

An interim analysis will be performed to assess safety and efficacy after around 40% of the planned participants, i.e., approximately 28 participnats, complete or have sufficient time to complete their study participation. The analysis menthods in the interim report will follow the methods planned for the full study and will be based on communication with China agency.

7.2. Interim Analyses and Summaries

For development of the interim analysis report, the study database will be cleaned and a snapshot of the database will be created. As this is a single arm study and blinding is NA, final tables, figures and listings (TLFs), and interim report will be produced using snapshot data by study statistician and programmers.

Considering the small number of participnats included in the interim analysis and availabitity of data, in addition to the general analyses planned in the above sections, more specifications are described below.

For the efficacy endpoints, only all-cause mortality rate on Day 42 and/or 84 will be analyzed including main analysis, supplementary analysis and subgroup analysis.

8. REFERENCES

None.

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
The percentage of all-cause mortality on Day 42 following primary treatment with isavuconazole. (Key secondary endpoint)	Main analysis for the key secondary endpoints	ITT	All data collected (after prohibited medication or after discontinuation of treatment) will be included. See Section 5.3 for missing data handling method.	Crude rate, binomial distribution for CI.
	Sensitivity analysis	ITT	All data collected (after prohibited medication or after discontinuation of treatment) will be included. See Section 5.3 for missing data handling method.	Kaplan-Meier
	Supplementary analysis	mITT and myITT-IA	All data collected (after prohibited medication or after discontinuation of treatment) will be included. See Section 5.3 for missing data handling method	Crude rate, binomial distribution for CI.
	Supplementary analysis	mITT, and myITT-IA	See Section 5.3 for missing data handling method.	Kaplan-Meier
	Subgroup analysis if data permit	ITT	All data collected (after prohibited medication or after discontinuation of treatment) will be included. See	Crude rate, binomial distribution for CI.

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			Section 5.3 for missing data handling method.	
The percentage of all-cause mortality on Day 84 following primary treatment with isavuconazole. (Secondary endpoint)	Secondary analysis	ITT	All data collected (after prohibited medication or after discontinuation of treatment) will be included. See Section 5.3 for missing data handling method.	Crude rate, binomial distribution for CI.
	Sensitivity analysis	ITT	All data collected (after prohibited medication or after discontinuation of treatment) will be included. See Section 5.3 for missing data handling method.	Kaplan-Meier
	Supplementary analysis	mITT and myITT-IA	All data collected (after prohibited medication or after discontinuation of treatment) will be included. See Section 5.3 for missing data handling method.	Crude rate, binomial distribution for CI.
	Supplementary analysis	mITT, and myITT-IA	See Section 5.3 for missing data handling method.	Kaplan-Meier
	Subgroup analysis if data permit	ITT	All data collected (after prohibited medication or after discontinuation of treatment) will be included. See	Crude rate, binomial distribution for CI.

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			Section 5.3 for missing data handling method.	
The crude rate of overall response based on the investigators' assessment at EOT. (Secondary endpoint)	Secondary analysis	mITT and myITT-IA	All data collected after use of the prohibited medications will be excluded.	Crude rate, binomial distribution for CI.
	Subgroup analysis if data permit	mITT	All data collected after use of the prohibited medications will be excluded.	Crude rate, binomial distribution for CI.
The crude rate of overall response based on the investigators' assessment at Day 42, and 84. (Secondary endpoint)	Secondary analysis	mITT and myITT-IA	All data collected after use of the prohibited medications will be excluded. Refer to Section 5.3 for handling missing data.	Crude rate, binomial distribution for CI.
The crude success rates of the clinical, mycological, radiological responses based on the investigators' assessment at EOT, Day 42	Secondary analysis	mITT and myITT-IA	All data collected after use of the prohibited medications will be excluded.	Crude rate, binomial distribution for CI.

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
and Day 84. (Secondary endpoint)				
The percentage of all-cause mortality on Day 42 and Day 84 following primary treatment with isavuconazole. (Exploratory endpoint)	Exploratory analysis	myITT-IM	All data collected (after prohibited medication or after discontinuation of treatment) will be included. See Section 5.3 for missing data handling method.	Crude rate, binomial distribution for CI.
	Supplementary analysis	myITT-IM	See Section 5.3 for missing data handling method.	Kaplan-Meier
The crude rate of overall response based on the investigators' assessment at EOT, Day 42, and 84. (Exploratory endpoint)	Exploratory analysis	myITT-IM	All data collected after use of the prohibited medications will be excluded. Refer to Section 5.3 for handling missing data.	Crude rate, binomial distribution for CI.
The crude success rates of the clinical, mycological, radiological responses based on the investigators' assessment at EOT, Day 42 and Day 84. (Exploratory endpoint)	Exploratory analysis	myITT-IM	All data collected after use of the prohibited medications will be excluded.	Crude rate, binomial distribution for CI.

Appendix 2. Formulae for eGFR-CKD-EPI

The calculated glomerular filtration rate (GFR) will be estimated by CKD-EPI equations. Scr is baseline creatinine.

2021 CKD-EPI Scr Only	Scr *(mg/dL)*	Scys *(mg/L)*	Recommended eGFR Equation
Female	if ⩽ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ⩽ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$

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If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only). Scys is CystatinC at baseline.

2021 CKD-EPI Scr-Scys Combined	Scr *(mg/dL)*	Scys *(mg/L)*	Recommended eGFR Equation
Female	if ⩽ 0.7	if ⩽ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ⩽ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ⩽ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ⩽ 0.9	if ⩽ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ⩽ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ⩽ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

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Appendix 3. Analysis window for efficacy and safety endpoints

Investigator Assessments	Visits	Scheduled Day	Window in Days
Clinical and Mycological	Day 42	42	2 to 49
	Day 84	84	50 to 91
	Day 126	126	92 to 133
	Day 168	168	134 to 175
Radiological	Day 42	42	8 to 49
	Day 84	84	50 to 91
	Day 126	126	92 to 133
	Day 168	168	134 to 175
Clinical, Mycological and Radiological	EOT	Last Dose Day	Closest to Last Dosing Day

Safety Assessments	Visits	Scheduled Day	Window in Days
Laboratory Tests for both IA and IM	Day 1	1	1
	Day 7	7	2 to 9
	Day 14	14	10 to 20
	Day 28	28	21 to 34
	Day 42	42	35 to 63
	EOT	Last Dose Day	Closest to Last Dosing Day
	Follow Up	Nominal Follow up Visit	NA
Laboratory Tests for IM	Day 84	84	64 to 105
	Day 126	126	106 to 147
	Day 168	168	148 to 201

Safety Assessments	Visits	Scheduled Day	Window in Days
Vital Signs for both IA and IM	Day 1	1	Using CRF Day/Time
	Day 7	7	2 to 9
	Day 14	14	10 to 28
	Day 42	42	29 to 63
	Day 84	84	64 to 105
	EOT	Last Dose Day	Closest to Last Dosing Day
	Follow Up#	Nominal Follow up Visit	NA
Vital Signs for IM	Day 126	126	106 to 147
	Day 168	168	148 to 201
ECG for both IA and IM	Day 1	1	1
	Day 7	7	2 to 9
	Day 14	14	10 to 28
	Day 42	42	29 to 63
	Day 84	84	64 to 105
	EOT	Last Dose Day	Closest to Last Dosing Day
	Follow Up#	Nominal Follow up Visit	NA
ECG for IM	Day 126	126	106 to 147
	Day 168	168	148 to 201

Only in participants with abnormalities observed at EOT.

If more than one observation exists within the analysis window, the observation closest to the scheduled visit day will be selected for that visit. If there are two observations that have the same distance from the scheduled day, the value that is after the scheduled day will be selected in the analysis. If more than one observation are made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.
The Follow Up visit will use the nominal follow-up visit with no windows defined.

Appendix 4. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ALP	Alkaline Phosphatase
ANC	Abolute Neutrophil Count
AST	aspartate aminotransferase
BAL	bronchoalveolar lavage
BMI	Body mass index
bpm	beats per minute
CCI	[redacted]
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
ECG	electrocardiogram
eGFR-CKD-EPI	estimated Glomerular Filtration Rate- Chronic Kidney Disease Epidemiology Collaboration
EOT	end of treatment
GM	galactomannan
IA	invasive aspergillosis
IFD	invasive fungal disease
IM	invasive mucormycosis
ITT	intent-to-treat
IV	intravenous
KM	Kaplan-Meier
LRTD	lower respiratory tract disease
mITT	modified intent-to-treat
myITT-IA	mycological intent-to-treat IA
myITT-IM	mycological intent-to-treat IM
NA	not applicable
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time [also used in the document as "preferred term". Avoid use of the same abbreviation for 2 terms.]
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
CCI	[redacted]
TLF	figures and listing

Abbreviation	Term
ULN	upper limit of normal