Title Page

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 FILAMENTOUS FUNGI

Study Intervention Number:	PF-07062254
Study Intervention Name:	Cresemba® (Isavuconazonium sulfate)
US IND Number:	NA
[EudraCT/CTIS] Number:	NA
ClinicalTrials.gov ID:	NCT05630976
Pediatric Investigational Plan Number:	NA
Protocol Number:	C3791001
Phase:	4
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Brief Title: Cresemba® in Treating Chinese Patients With IFD Caused by *Aspergillus* species or Other Filamentous Fungi	

Document History

Document	Version Date
Amendment #2	29 January 2024
Amendment #1	04 November 2022
Original protocol	25 April 2022

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 2 (29 January 2024)

Overall Rationale for the Amendment: update the sample size according to Center for Drug Evaluation (CDE) request and added an interim analysis. Clarifications for protocol required data for defined visits are added to study design.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Sample Size is increased from 56 participants to 70 participants and 66 participants instead of 53 participants are expected to be treated.	The sample size is amended based on the suggestion from CDE.	1.1. Synopsis; 4. Study Design; 9.5. Sample Size Determination
An interim analysis is added to this study.	For internal reference to support compound development.	9.4. Interim Analyses
Laboratory conducting mycological assessments for pathogen isolates is clarified.	To clarify mycological assessment is based on the results of local lab and pathogen isolates will be shipped to central lab for confirmation.	8.2.5. Mycological Assessment of Invasive Fungal Infection
Non-substantial Modifications		
Potential risk of clinical significance is updated.	To keep consistent with China RMP 2023.	2.3.1. Risk Assessment
Defined visits for protocol required data are added to study design.	To incorporate changes in PACL dated 28 Aug 2023 and to further clarify the window requirement for laboratory and radiological assessment.	1.3 Schedule of Activities footnotes a, s, t, k and q. 1.3.1. Schedule of Activities; 8.2.7 Survival Status; 8.3.3. Electrocardiograms
Remove “IA” and replace by “IFD” in footnote of Table 6.	To clarify the success assessment of radiological response.	8.2.9 Definition of Response and Outcome

Description of Change	Brief Rationale	Section # and Name
Add statement "In the KM analysis, time to death will be observed until Day 84 for participants with IA and Day 180 for participants with IM".	To ensure the survival status to be collected as complete as possible since the Kaplan-Meier survival rates will be estimated at multiple timepoints until Day 84 for IA participants and Day 180 for IM participants.	9.3.1 Efficacy Analyses
Specific text adjustments/additions are made.	To ensure consistency with the mandatory language provided in the latest clinical pharmacology protocol template (14 Apr 2023).	10.1.6. Dissemination of Clinical Study Data; 10.1.9. Study and Site Start and Closure; 10.1.10 Use of Medical Records; 10.6.3 Adverse Event Grading for Kidney Safety Laboratory Abnormalities; 10.9. Appendix 9; 10.10. Appendix 10
Add statement "or other severe viral pneumonia, such as coronavirus disease 2019 [COVID-19]" to host factors.	Added other possible host factors for potential participants.	10.9 Appendix 9: Diagnosis Criterial for Proven, Probable, or Possible IFD Caused by *Aspergillus* Species, Mucorales Species or Other Filamentous Fungi
Remove statement: at Screening, Days 1 between Day 7, 14, 28, 42, 84 and EOT.	To keep consistent with text.	10.10 Appendix 10: Protocol Amendment History

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Single Arm, Prospective, Multi-Center Study to Evaluate Safety and Efficacy of Isavuconazole for Primary Treatment of Chinese Patients with IFD Caused by *Aspergillus* Species or Other Filamentous Fungi

Brief Title: Cresemba® in Treating Chinese Patients With IFD Caused by *Aspergillus* species or Other Filamentous Fungi

Regulatory Agency Identification Number(s):

US IND Number:	NA
EudraCT Number:	NA
ClinicalTrials.gov ID:	NCT05630976
Protocol Number:	C3791001
Phase:	4

Rationale:

Cresemba®, isavuconazonium sulfate, is a water-soluble prodrug of the active triazole isavuconazole, which is an antifungal agent for the treatment of adults with IA and IM through inhibition of lanosterol 14-alpha-demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi. Cresemba® was approved in China for the treatment of IA and IM in adults in January 2022 and December 2021, respectively.

Isavuconazole has a broad spectrum of in vitro activity against *Aspergillus* species, several species of *Mucorales*, and *Candida* spp. Administration of isavuconazonium in animal models of fungal infection showed in vivo efficacy against these same pathogens. These data suggest that isavuconazonium could have therapeutic benefit for the treatment of patients with invasive fungal infections.

The global clinical development program consisted of 44 studies and included 2166 participants of whom 1692 participants received isavuconazole by 08 September 2016. Forty Phase 1 studies, 2 Phase 2 and 2 Phase 3 studies characterized the clinical pharmacology, efficacy and/or safety of isavuconazole in healthy participants/patients. Primary efficacy and safety data came from the 2 Phase 3 studies, including SECURE Study [NCT00412893], for IA indication, and VITAL Study [NCT00634049] for IM indication.

There were 2 studies carried out including Chinese participants, which evaluated the pharmacokinetics, efficacy, and safety of isavuconazole. A total of 62 Chinese participants were included in the 2 completed clinical studies, as part of the global development program for IA and IM. One was a China-alone Phase 1 study in 36 healthy volunteers (Study

9766-CL-0038) which was completed in 2012, and the other was a global Phase 3 pivotal study conducted in patients with IA (SECURE Study 9766-CL-0104) in which a total of 26 Chinese participants were enrolled, and the study was completed in 2013.

The China-alone Phase 1 Study 9766-CL-0038 was conducted in 36 healthy Chinese volunteers, single and multiple doses of oral and IV 200 mg isavuconazole were demonstrated to be safe and well tolerated by male and female Chinese participants. In this study, the pharmacokinetic exposures measured by mean plasma C_{max} and AUC values were generally higher compared with participants from Western countries.

A 2-compartment popPK model was developed that included data from Phase 1 and Phase 3 studies. Chinese participants were found to have, on average, a 40% lower clearance compared with participants from Western countries. Monte Carlo simulations were then performed using mean population estimates. Based on the safety profile and PK/PD modeling and simulation for the antifungal activity of isavuconazole, the differences were not considered clinically significant. No dose adjustment is required for the Chinese population.

In the pivotal active-controlled study (SECURE Study, 9766-CL-0104), there were a total of 26 Chinese participants who received at least 1 dose of study intervention, including 10 participants randomized to the isavuconazole group. In the Chinese sub-population of the SECURE study, analysis for the primary efficacy endpoint of all-cause mortality by Day 42 appeared to be 10% (1/10) in the isavuconazole group and 25% (4/16) in the voriconazole group (treatment difference was -15.0% with a 95% CI of [-43.2%, 13.2%]). In general, efficacy of isavuconazole in Chinese participants was consistent with the findings in the overall population, indicating comparable mortality and overall response rates in the isavuconazole and voriconazole treatment groups. The safety profile in Chinese participants was also similar to the overall population.

This study is a post-approval commitment to RA, and is designed to further evaluate the safety and efficacy of isavuconazole in a relatively larger Chinese population who will receive isavuconazole treatment in a post-marketing setting. The isavuconazole dose and regimen to be administered in this study are completely in accordance with the approved prescribing information.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• 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 TEAEs by SOC and PT will be summarized without regard to adherence to the isavuconazole treatment and use of prohibited medication.
Secondary:	**Secondary:**	**Secondary:**
• 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 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 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 *Aspergillus* species and other filamentous fungi. • 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.
• 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. • Other safety variables, including clinical laboratory variables, vital signs, 12-lead ECG and eye examination.	• Not applicable • Not applicable
• 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

Overall 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.

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 (up to 180 days for participants diagnosed 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.

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 examination and antigen test (for *Aspergillus* and *Mucorales* species, including 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.

The primary objective is to characterize the safety and tolerability of isavuconazole through observing the treatment emergent adverse events (TEAE).

For the clinical evaluation, investigators will need to review/evaluate the following: categorization of the diagnosis of IFD at enrollment (including data up to Day 7 as relevant); the participant's overall response, clinical, radiological and mycological responses at Day 42, at EOT and Day 84 (or Day 180 for participants with IM); and whether or not the participant has LRTD.

Number of Participants:

Approximately 70 participants are planned to be enrolled in China and approximately 66 participants are expected to be treated. With 66 treated participants, for AEs that are as common as 3% or more, there is a probability of 86.6% to observe at least 1 participant experiencing such AEs.

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.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

Age and Sex:

1. Male and female Chinese participants aged ≥18 years at the time of providing informed consent.

Disease Characteristics:

2. Participants must have proven, probable, or possible IFD caused by *Aspergillus* species, *Mucorales* species or other filamentous fungi, refer to guidelines of EORTC/MSG (version 2019) or EORTC/MSG ICU (version 2021).

Weight:

3. Participants with a body weight >40 kg at screening.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

Medical Conditions:

1. Participants with either chronic aspergillosis, aspergilloma or ABPA.
2. Advanced HIV infection with CD4 count <200 or acquired immunodeficiency syndrome-defining condition.
3. Any known or suspected condition of the participant that may jeopardize adherence to the protocol requirements or impede the accurate measurement of efficacy, for example, neutropenia not expected to resolve, participants with fungal endocarditis, fungal osteomyelitis, fungal meningitis, palliative therapy only for underlying condition.
4. Participants who are unlikely to survive 5 days or participants on mechanical ventilation.
5. Known history of allergy, hypersensitivity to or any serious reaction to the azole class of antifungals or to any component of the study intervention.
6. Participants with severe hepatic impairment (Child-Pugh Class C) at the time of enrollment.

7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

8. Concomitant use of efavirenz, ritonavir, etravirine, rifampicin/rifampin, rifabutin, nafcillin, ketoconazole, or St. John's Wort in the 5 days prior to first administration of study intervention.

9. Participants who have been administered more than 4 cumulative days of itraconazole, voriconazole, or posaconazole, for any reason, within the 7 days prior to the first administration of study intervention.

    1) Participants with applicable host factors who develop new evidence of IFD while on prophylactic therapy, for at least 14 days, with either an amphotericin B product or an echinocandin, will be eligible for enrollment.

    2) Prior use of fluconazole of any duration and for any reason will be eligible for enrollment.

Prior/Concurrent Clinical Study Experience:

10. Previous administration with an investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

11. Pregnant female participants; breastfeeding female participants; fertile male participants and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of study intervention.

Diagnostic Assessments:

12. Participants with familial short QT syndrome

Other Exclusion Criteria:

13. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

Study Arms and Duration:

The study starts with the signing of the informed consent document, and is divided into 3 periods including: Screening Period (up to 7 days), Treatment Period (maximal 84 days for IA or other filamentous fungi infection, or up to 180 days for participants with IM) and Follow-up Period (4 weeks ±7 days after last dose of study intervention).

An isavuconazole loading regimen will be administered during the **first 48 hours** followed by a maintenance dose from Day 3 to EOT:

- 0–48 hours: IV infusion of 200 mg isavuconazole (q8h [±2h] – 3 total infusions administered over a 24 hour period)

OR,

- 0–48 hours: 200 mg isavuconazole (two capsules with each containing 100 mg isavuconazole, q8h[±2h] – 3 total dosages over a 24 hour period PO.

From **Day 3 to EOT** participants will receive:

- One IV infusion of 200 mg isavuconazole once daily.

OR

- 200 mg isavuconazole (2 capsules with each containing 100 mg isavuconazole) PO once daily.

The first maintenance dose (Day 3) is recommended to start between 12 to 24 hours after the last loading dose. Subsequent doses will be administered daily. The infusion must be administered via an infusion set with an in-line filter.

The switch to oral therapy should be made as early as possible from Day 3 onwards. Reasons for not switching to oral therapy must be documented, eg, unable to swallow, gastric suction, concerns about adequate dosing. Participants who do not switch will remain on IV treatment. Participants who switch from IV to oral therapy after the loading dose may switch back to IV therapy at any time during the study if it is necessary.

Participants will be treated until they reach a defined discontinuation criterion (see Section 7.1), up to a maximum of 84 days (up to 180 days for participants with IM).

Participants who are considered by the investigator to have experienced a successful overall outcome will continue treatment for a minimum of 7 days after resolution of all clinical symptoms and physical findings. The maximum treatment period of 84 days (180 days for participants with IM) must not be exceeded.

Non-study systemic antifungal medication is only allowed after the Day 42 visit, unless the participant has failed treatment with study medication prior to the Day 42 visit.

Stopping administration of study intervention ≥48 hours will be considered as cessation of study intervention. The reasons for cessation of study intervention will be recorded in the eCRF.

Study Intervention(s)	
Intervention Name	Cresemba® (Isavuconazonium sulfate, PF-07062254)
Arm Name (group of participants receiving a specific treatment or no treatment)	NA. This is a single arm study, all enrolled participants will receive the study intervention.
Unit Dose Strength(s)	• 200 mg isavuconazole for injection per vial • 100 mg isavuconazole per capsule
Route of Administration	• Intravenous Infusion • Oral Capsules
IMP or NIMP/AxMP	IMP

Statistical Methods:

The primary safety endpoint is the incidence rates of TEAEs by SOC and Preferred Term. A TEAE is defined as any adverse event that starts on or after the first administration of study medication until 28 days after last dose of study intervention. Safety variables will be summarized descriptively for the safety population.

No formal statistical hypothesis testing will be conducted for efficacy analyses. The key secondary efficacy endpoint of crude rate of all-cause mortality on Day 42 will be analyzed on the ITT population. The 95% CI of the crude mortality rate will be calculated based on an exact binomial distribution. Other secondary efficacy endpoints will be summarized similarly.

PK analysis will be conducted using the PK concentration analysis set. Observed plasma concentrations of isavuconazole will be summarized for Day 3, Day 7, Day 14 and EOT using descriptive statistics.

Ethical Considerations:

The results of previous studies have demonstrated the efficacy and safety of isavuconazole for treatment of IA and IM in adults, and there is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to participants, the potential risks associated with isavuconazole are justified by the anticipated benefits that

may be afforded to participants with IA and other filamentous fungi infections. More information for Benefit and Risk assessment can be found in the LPD.

- Based on the experience with isavuconazole, the potential risks for isavuconazole include:
  - Changes in blood tests of liver enzymes (Elevated liver transaminases) and hepatitis
  - Side-effects during the isavuconazole infusion (Infusion-related reactions)
  - Severe skin reactions (Severe cutaneous adverse reactions)
  - Abnormal heart rhythm caused by shortened QT interval (Arrhythmia due to QT shortening)
- Participants will be expected to commit time and may experience some discomfort while undergoing study assessments.
- In addition, participants of childbearing potential must agree to use appropriate contraception methods.

1.2. Schema

Pre-Study Activities	Isavuconazole IV/Oral Loading Dose	Isavuconazole IV or Oral Maintenance Dose	Post-Treatment FU
Screening 7 days prior to first dose of study medication	Study Day 1 and Day 2	Starting from Day 3 up to EOT (maximum 84 days for IA or other filamentous fungi infection; or up to 180 days for participants with IM)	EOT + 4 week

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Period	**Screening**	**Study Treatment**									**Follow-Up**
Visit Identifier	**Screening D-7 to D-1**	**Day 1**	**Day 2[p]**	**Day 3[p]**	**Day 7[p]**	**Day 14[p]**	**Day 28[p]**	**Day 42[k]**	**Day 84[k,q] /Every 42 days after Day 84[q]**	**End of Treatment (EOT)[k,m] or Discontinuation**	**Post Treatment Follow-up[k] (4 weeks after EOT)**
Visit Window (Day)[a]					±2	±3	±3	±7	±7	±3	±7
General											
Informed consent	X										
Participant Number assignment	X										
Inclusion/Exclusion	X	X									
Medical history	X										
Anti-infective history (4 wks prior)[b]	X										
Physical examination	X	X[e]						X	X	X	X[h]
Weight/Height	X							X		X	
Prior medication[c]	X[c]										
Concomitant medication	X	X Ongoing----------→									X
Non-medication procedures	X	X Ongoing----------→									X
Pregnancy test (WOCBP only)[d,e] Contraception check	X[d]	X[e]						X[p]	X[p]	X	X
Study intervention administration[f,q]		----------X Daily----------→									
Study intervention accountability		X Ongoing----------→									
Hospitalization status	X	X Ongoing----------→									
Safety Assessment											
Serious and non-serious Adverse Events monitoring[g]	X	X Ongoing----------→									

Period	Screening	Study Treatment									Follow-Up
Visit Identifier	Screening D-7 to D-1	Day 1	Day 2[p]	Day 3[p]	Day 7[p]	Day 14[p]	Day 28[p]	Day 42[k]	Day 84[k,q] /Every 42 days after Day 84[q]	End of Treatment (EOT)[k,m] or Discontinuation	Post Treatment Follow-up[k] (4 weeks after EOT)
Visit Window (Day)[a]					±2	±3	±3	±7	±7	±3	±7
Laboratory											
Hematology	X[t]	X[e]			X	X	X	X		X	X
Blood chemistry	X[t]	X[e]			X	X	X	X		X	X
Urinalysis	X	X[e]			X	X	X	X		X	X
Vital Sign (BP, PR, RR, BT)	X	X[i]			X[j]	X[j]		X[j]	X[j]	X[j]	X[h]
12 lead ECG[n]	X	X				X		X	X	X	X[h]
Eye examination	X					X[p]	X[p]	X[p]		X	X[h]
Efficacy assessment											
Investigator's assessment of responses								X	X	X	
Assessment of Clinical Signs and Symptoms of IFD	X	X		X	X	X	X	X	X	X	X
GM antigen [r]	X	X[e,l]				X[l]	X[l]	X[l]	X[l]	X[l]	
Radiology assessment (CT/HRCT/MRI)	X[s]	X[o]				X[l]	X[l]	X	X	X	
Bronchoscopic assessment[l,]	X[l]	X[o]				X[l]	X[l]	X[l]	X[l]	X[l]	
Mycological assessment (Microbiology/Histopathology/Cytopathology/Tissue Nucleic Acid)	X	X[l]						X	X	X	
Neutropenic status/ANC	X	X Ongoing----------→									
Survival status[k]		X Ongoing----------→									

a. Day related to start of study treatment (Day 1), Day −1 can be the same calendar day as Day 1.
b. Anti-infective history taken within 4 weeks prior to the first dose of study intervention will be collected in the eCRF.
c. All medication (except for anti-infective agents, T-cell & B-cell immunosuppressants and corticosteroids) given within 2 weeks prior to the first dose of study intervention will be collected in eCRF. T-cell & B-cell immunosuppressants given within 3 months prior to the first dose of study intervention, anti-infective agents and corticosteroids given within 4 weeks prior to the first dose of study intervention will be collected in eCRF.
d. A serum β-hCG testing should be performed at screening for all WOCBP according to Section 8.3.6. A negative serum or urine β-hCG test must be obtained before the first dose of study intervention.
e. Samples/assessments obtained within 72 hours prior to the first dose of study intervention could be accepted as the Day 1 results.
f. Study intervention administration will occur every day from Day 1 to Day 84 (Day 180 for IM) or EOT.
g. Adverse events will be recorded from the sign-off of informed consent to at least 28 days after last dose of study intervention.
h. Only in participants with abnormalities observed at EOT.
i. On Day 1, vital signs will be measured within 1 hour before and 1 hour after the end of each study intervention administration.

Period	Screening	Study Treatment									Follow-Up
Visit Identifier	Screening D-7 to D-1	Day 1	Day 2[p]	Day 3[p]	Day 7[p]	Day 14[p]	Day 28[p]	Day 42[k]	Day 84[k,q] /Every 42 days after Day 84[q]	End of Treatment (EOT)[k,m] or Discontinuation	Post Treatment Follow-up[k] (4 weeks after EOT)
Visit Window (Day)[a]					±2	±3	±3	±7	±7	±3	±7

j. Measuring once prior to study intervention administration.
k. EOT, Day 42, Day 84 and Follow-up assessments are required for all participants. Participants with a successful overall response are required to return for all these visits. Participants withdrawn from study intervention or with an unsuccessful overall response prior to Day 42 are required to return to conduct a clinic visit for the EOT visit but will not be asked to return for the Day 42 or Day 84 visits; however, the participant will be contacted by telephone to obtain survival status at these time points. For participants with IM, survival status on Day 126, Day 168 and Day 180 should be collected. A Follow-up visit will be performed 4 weeks (± 7d) after last dose of isavuconazole administration.
l. If clinically indicated.
m. If EOT occurs within 1 week of a scheduled visit, the visits and assessment can be combined; however, the schedule of assessments for EOT must be applied.
n. 12-lead ECG is performed 15 minutes prior to the end of the first daily infusion or approximately 3 hours post oral dose during the treatment period.
o. If the assessments are performed at screening, the additional assessments between Day 1 and Day 7 are not required.
p. Applicable for participants continuing on study intervention.
q. For participants with IA or other filamentous fungi infection other than IM, if study treatment needs to be extended to longer than 84 days, sponsor should be notified. For participants with IM, procedures on Day 84, Day 126 and Day 168 should follow requirements of Day 42, maximum of study treatment is 180 days or until EOT visit.
r. GM antigen will be tested at screening. If clinically indicated, it can be tested during Day 1 to Day 7 for participants with IA only. Any 1 of the following: 1) A single serum or plasma value ⩾ 1.0; 2) BAL fluid ⩾1.0; 3) single serum or plasma: ⩾0.7 and BAL fluid ⩾0.8; 4) two consecutive values of either serum, plasma or BAL fluid between ⩾ 0.5 to <1.0 (from two separate specimens of the same category) is considered a positive result. GM meeting the protocol defined requirements within 7 days prior to first dose of study drug are eligible for enrollment.
s. Radiology imaging obtained within 1 week (if available) prior to screening could be used.
t. Samples/assessments obtained within 72 hours prior to screening could be used.

1.3.1. Pharmacokinetic Sampling Schema

Visit Identifier															
Study Day	**Day 3**		**Day 7[e]**						**Day 14[e]**						**EOT**
Hours[a]	**Predose (0)**	**1.5[d]**	**Predose (0)**	**1.5[d]**	**3**	**6**	**12**	**24**	**Predose (0)**	**1.5[d]**	**3**	**6**	**12**	**24**	**Predose (0) or 24[b]**
PK blood sampling	X[c]	X[d]	X[c]	X[d]	X	X	X	X	X[c]	X[d]	X	X	X	X	X[c]

a. Nominal time (hours) after start of infusion or capsule intake.
b. For EOT, blood sample will be predose or exceptionally, 24 hours after last dose.
c. Blood will be drawn within 1 hour prior to the administration of study intervention.
d. Blood will be drawn anytime within 15 minutes prior to or 15 minutes after stopping study intervention administration if IV infusion or 1.5 ± 0.15 hours after study intervention dosing if oral administration. For IV infusion, if the PK sampling time window has overlap with next one due to infusion period, it is suggested to collect different PK sample according to their own time window, respectively, if possible.
e. On Day 7 and Day 14, additional blood will be drawn at 3 hours, 6 hours, 12 hours, and 24 hours (24 hours PK sample should be collected prior to the administration on Day 8 and Day 15) after study intervention administration.

2. INTRODUCTION

Cresemba®, isavuconazonium sulfate, is the water-soluble prodrug of the active triazole isavuconazole, which is an antifungal agent for the treatment of adults with IA and IM through inhibition of lanosterol 14-alpha-demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi. Cresemba was approved in China for the treatment of IA and IM in adults in January 2022 and December 2021, respectively.

2.1. Study Rationale

This single arm, prospective study is a commitment to regulatory authority, and is designed to further evaluate the safety profile and the effectiveness of isavuconazole in a relatively larger Chinese population who will receive isavuconazole treatment in a post-marketing setting. The isavuconazole dose and regimen to be administered in this study are completely in accordance with the approved prescribing information.

A total of 62 Chinese participants were included in 2 completed clinical studies, as part of the global development program for IA and IM. One was a China-alone Phase 1 study in 36 healthy volunteers (Study 9766-CL-0038) which was completed in 2012, and the other was the global Phase 3 pivotal study conducted in patients with IA (SECURE Study, 9766-CL-0104) in which a total of 26 Chinese participants were enrolled, which was completed in 2013.

In a China-alone Phase 1 study (9766-CL-0038) in 36 healthy Chinese volunteers, single and multiple doses of oral and IV 200 mg isavuconazole were safe and well tolerated by male and female Chinese participants. In this study, the mean plasma C_{max} and AUC values were generally higher compared with participants from Western countries (Table 1).

Table 1. Comparison of Isavuconazole Exposure in Healthy Chinese and Western Participants after Single- and Multiple-Dose Oral Administration of Isavuconazonium (200 mg eq. Isavuconazole)

Parameter	Single Dose		Multiple Dose	
	Chinese Subjects	Western Subjects	Chinese Subjects	Western Subjects
Study	9766 CL 0038	9766 CL 0041	9766 CL 0038	9766 CL 0017
n	12	24	12	37
C_{max} (µg/mL)	3.391 (0.500)	2.318 (0.524)	8.891 (1.651)	7.499 (1.893)
AUC (µg×h/mL)†	116.4 (36.3)	96.26 (27.7)	140.4 (32.8)	121.4 (35.8)

Values of pharmacokinetics parameters are mean (SD).
†AUC = AUC_{inf} for single dose results, AUC_{tau} for multiple dose results.
Source: 9766 CL 0038 Tables 12.4.2.1.1, 12.4.2.3.1; 9766 CL 0017 Table 12.4.2.1; 9766 CL 0041 Table 12.4.2.1.

A 2-compartment population PK model was developed that included data from Phase 1 and Phase 3 studies. Chinese participants were found to have, on average, a 40% lower clearance compared with participants from Western countries. Monte Carlo simulations were then performed using mean population estimates. Based on the safety profile and PK/PD modeling and simulation for the antifungal activity of isavuconazole, the differences were not considered clinically significant. No dose adjustment is required for the Chinese population.

In the pivotal controlled study (SECURE Study, 9766-CL-0104), there were in total 26 Chinese participants who received at least 1 dose of study intervention, among them 10 participants were randomized to receive isavuconazole. Analysis of the efficacy in the China sub-group in SECURE Study showed the primary efficacy endpoints of all-cause mortality by Day 42 to be 10% (1/10) in the isavuconazole group and 25% (4/16) in the voriconazole group (difference of –15.0% with 95% CI [- 43.2%, 13.2%]). In general, efficacy of isavuconazole in Chinese participants was consistent with the findings in the overall population, indicating comparable mortality and overall response rates in the isavuconazole and voriconazole treatment groups. The safety profile was also comparable in Chinese participants to the overall population.

In summary, the clinical data of isavuconazole in Chinese population have been obtained from 46 Chinese participants including 36 healthy participants and 10 participants with IA. The overall PK, safety and efficacy of isavuconazole has been demonstrated in Chinese.

2.2. Background

2.2.1. Disease Prevalence

IA is a life-threatening angio-invasive infection that is seen predominantly in immunocompromised patients. Patients at greatest risk for IFD are those with prolonged neutropenia related to antineoplastic chemotherapy and/or HSCT, those receiving immunosuppressants following solid organ transplants, and those given high doses of corticosteroids. [1,2,3,4] IFD remains a major cause of morbidity and mortality, particularly among immunocompromised patients.[5,6]

The disease burden data of IA in China is similar to that reported from other countries. In general, IA is not common, but is increasing with the increase of predisposing underlying diseases or conditions. In a 10-year population-based study in Taiwan, 346 cases of IPA were identified from 2002 to 2011 with an average incidence of IPA of 1.51 per million person-years and an increasing trend from 0.94 to 2.06 per million person-years was observed ($p<0.0001$).[7]

IM is a devastating fungal infection caused by the filamentous fungi of the Mucorales order from the phylum of Zygomycota. Many of the conditions predisposing patients to mucormycosis are the same as for IA and include hematological malignancy with or without stem cell transplantation and prolonged neutropenia. Other groups of patients at risk are diabetics with uncontrolled hyperglycemia as well as dialysis patients.[8]

In a review of the literature from 1885 to 2003, Roden[9] found an overall mortality rate of 97% in untreated patients and 82% mortality in patients who received no antifungal treatment. Despite aggressive surgical and antifungal treatments, mucormycosis is associated with high mortality. Published mortality rates vary widely depending on the underlying disease and extent of infection. Roden[9] reported mortality rates of 66%, 44% and 96% in patients with hematological malignancy, diabetes, and disseminated disease, respectively.

2.2.2. Unmet Medical Needs

IA is treated with systemic antifungal agents, such as polyenes, mold active triazoles, and echinocandins. AmB deoxycholate was the first line of therapy for IA for many years but its use was associated with significant toxicity and also lack of efficacy in high-risk patients.[10,11] While lipid-associated formulations of AmB (l-AmB) were developed to circumvent the nephrotoxic potential of AmB, renal- as well as infusion-related toxicities continue to be treatment limiting and comparative clinical studies did not demonstrate superior efficacy of l-AmB formulations over AmB.[12]

The current treatment guidelines, issued in 2016 by IDSA recommend voriconazole as first-line therapy.[13] The basis for this is the study by Herbrecht, which demonstrated reduced mortality and improved outcomes in patients receiving voriconazole compared to AmB for primary therapy of IA. Herbrecht and colleagues reported a mortality rate of 30% for voriconazole-treated patients in the first 12 weeks of treatment.[14]

While voriconazole demonstrates good activity against *Aspergillus* strains, its safety profile limits its use in a number of patient populations. The main shortcomings of voriconazole include PK variability and drug-drug interactions related to its metabolism via the cytochrome P450 enzymes. The use of cyclodextrin in the voriconazole solution for IV administration, which is excreted via the kidney and can accumulate in patients with moderate to severe renal impairment, makes the use of IV voriconazole difficult in patients with compromised renal function.[15,16] In addition, voriconazole administration is associated with visual disturbances, with the most commonly noted being blurred vision, photophobia, and altered color perception.[12,17] In clinical trials of voriconazole, uncommon cases of serious hepatic reactions occurred during treatment (eg, clinical hepatitis, cholestasis, and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur more commonly in patients with serious underlying medical conditions, but also occurred in patients with no underlying risk factors.

For the treatment of mucormycosis, present guidelines recommend antifungal treatment, surgical debridement, and correction of underlying predisposing disorders.[18] Although AmB and posaconazole show in-vitro activity against Mucorales molds, their clinical use is often restricted.[19,20] Nephrotoxicity remains a common adverse effect of AmB,[21] and posaconazole has mainly been studied in the salvage setting.[22,23]

2.2.3. Development of Isavuconazole

Isavuconazonium sulfate is the water-soluble prodrug of the active triazole isavuconazole, which is an antifungal agent for the treatment of adults with IA and IM through inhibition of lanosterol 14-alpha-demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi.

Following IV administration, isavuconazonium sulfate is rapidly converted by plasma esterases to the active moiety isavuconazole. Following oral administration, isavuconazonium sulfate predominantly undergoes chemical hydrolysis in the GI lumen.

Isavuconazole has a broad spectrum of in vitro activity against *Aspergillus* species, several species of *Mucorales*, and *Candida* spp. Administration of isavuconazonium in animal models of fungal infection showed in vivo efficacy against these same pathogens. These data suggest that isavuconazonium could have therapeutic benefit for the treatment of patients with invasive fungal infections.

Voriconazole is currently recommended for the primary treatment of IA on the basis of results from a study in which voriconazole significantly improved survival compared with AmB deoxycholate,[14] but voriconazole is not active against Mucorales.[24] It displays highly variable non-linear PK in adults, which has triggered recommendations for therapeutic drug monitoring.[25,26] By contrast, isavuconazole, which has activity against Mucorales, demonstrates predictable and linear PK with low interpatient variability.[27]

In addition, isavuconazole has a favorable safety profile when compared with voriconazole. Cyclodextrin is not used in the isavuconazole solution for IV administration, which avoids the potential accumulation in patients with moderate to severe renal impairment. In the pivotal controlled study (SECURE Study, 9766-CL-0104), the most important differentiating feature between isavuconazole and voriconazole was the tolerability and safety profile of isavuconazole, which could allow safer therapy. Of the drug-related hepatobiliary AEs reported in this study, 26 (10%) were noted in the voriconazole group compared with 5 (2%) in the isavuconazole group. In this study, key AEs known to be related to voriconazole (including eye, hepatic, and skin disorders) and discontinuations due to AEs were significantly less common among participants treated with isavuconazole. Therefore, the broad spectrum of antifungal infection and favorable safety profile make isavuconazole an attractive alternative. The ESCMID/ECMM guidelines issued in 2018 added isavuconazole in the first–line treatment.[28]

2.2.4. Clinical Overview

The global clinical development program consisted of 44 studies and included 2166 participants of whom 1692 participants received isavuconazole by 08 September 2016. Forty Phase 1 studies, 2 Phase 2 and 2 Phase 3 studies characterized the clinical pharmacology, efficacy and/or safety of isavuconazole in healthy participants/patients. The 2 Phase 2 studies (Studies 0101 and 0102) evaluated isavuconazole in participants with esophageal candidiasis and in neutropenic participants with AML as prophylaxis. Primary efficacy and safety data came from the 2 Phase 3 studies (SECURE study [IA] and VITAL study [IM]).

The PK of isavuconazole are linear and dose-proportional following both oral and IV administration. Isavuconazole has a long half-life (~130 hours) enabling once- daily maintenance dosing. Further, with rapid absorption, oral bioavailability of 98%, and an absence of a food or gastric pH effect, isavuconazole can be administered via both routes of administration under fed or fasting conditions or with medications that alter gastric pH with no need for dose adjustment.

SECURE study

The efficacy for the indication of IA is primarily supported by data from a randomized (1:1), double-blind, multicenter, non-inferiority, comparative group study (SECURE study, NCT00412893), which evaluated the efficacy and safety of isavuconazole compared to voriconazole for the treatment of IA and other filamentous fungi.[29] SECURE Study included 516 adult participants with suspected IFD caused by *Aspergillus* species or other filamentous fungi. A blinded, independent DRC assessed participants' IFD diagnosis and overall response.

All-cause mortality from the first dose of study intervention to day 42 for the ITT population was 19% with isavuconazole (48 participants) and 20% with voriconazole (52 participants), with an adjusted treatment difference of –1.0% (95% CI −7.8% to 5.7%). Non-inferiority was shown since the upper bound of the 95% CI (5.7%) is lower than the pre-specified margin of 10%. Most participants (247 [96%] receiving isavuconazole and 255 [98%] receiving voriconazole) had TEAEs; the most common were GI disorders (174 [68%] vs 180 [69%]) and infections (152 [59%] vs 158 [61%]). Proportions of participants with TEAEs by system organ class were similar overall. However, isavuconazole-treated participants had a lower frequency of hepatobiliary disorders (23 [9%] vs 42 [16%]; p=0.016), eye disorders (39 [15%] vs 69 [27%]; p=0.002), and skin or subcutaneous tissue disorders (86 [33%] vs 110 [42%]; p=0.037). Drug-related adverse events were reported in 109 (42%) participants receiving isavuconazole and 155 (60%) receiving voriconazole (p<0.001). The results of SECURE Study demonstrated that isavuconazole was noninferior to voriconazole, the current first-line therapy, for the treatment of IA. Isavuconazole was well tolerated and had fewer study intervention-related AEs compared with voriconazole.

VITAL study

VITAL study, NCT00634049, was an open-label study conducted to evaluate the efficacy and safety of isavuconazole in the treatment of IA in patients with renal impairment, and in patients with IFD caused by rare molds, yeasts, or dimorphic fungi.[30] Of the 24 participants enrolled in this study who were assessed by the DRC as having an *Aspergillus*-only infection (the mITT-*Aspergillus* population), 20 had renal impairment. All-cause mortality and overall response rates in this renally-impaired mITT-*Aspergillus* population were similar to those for non-renally-impaired participants in SECURE study.

Efficacy in renally-impaired participants was also demonstrated in a *post hoc* pooled analysis of IA participants with and without renal impairment who received isavuconazole in 2 Phase 3 studies. In the pooled analysis of IA participants from both mITT populations, all-cause mortality through Day 42 was 12.9% for renally-impaired participants and 18.8% for non-renally-impaired participants.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of isavuconazonium sulfate may be found in the LPD, which is the SRSD for this study.

2.3.1. Risk Assessment

Important Identified and Important Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Isavuconazonium sulfate		
Important identified and important potential risks for isavuconazole include the following: • Important identified risks: side-effects during the isavuconazole infusion (Infusion-related reactions) • Important potential risks: teratogenicity	The potential risks are based on product labeling for isavuconazole and are common with the triazole class.	Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5).
Study Procedures		
Participants will be expected to commit time and may experience some discomfort while undergoing study assessments.		

2.3.2. Benefit Assessment

For IA or other filamentous fungi infection, voriconazole approved for this indication and is the recommended first-line treatment. Relative to voriconazole, isavuconazole offers the following potential advantages as a treatment for IA:

- Clinical pharmacology
  - High bioavailability with bioequivalence on AUC enabling interchangeable IV and oral dosing, and absence of a food effect
  - Reduced PK variability, limiting the risk of sub-therapeutic and/or supra-therapeutic exposure
  - Lower risk for drug-drug interactions. Voriconazole is a strong inhibitor of CYP3A4 (10-fold increase in midazolam AUC),[31] whereas isavuconazole is a moderate inhibitor (2-fold increase in midazolam AUC). This is particularly relevant for patients who require treatment with immunosuppressants that are substrates of CYP3A4 (cyclosporine, sirolimus, tacrolimus)
  - No need for cyclodextrin in the intravenous formulation, enabling IV administration in patients with moderate or severe renal impairment, and patients with ESRD
  - Long half-life, enabling once-daily maintenance dosing with associated compliance benefits
- Efficacy
  - Noninferior efficacy versus voriconazole, with comparable outcomes for all-cause mortality through Day 42 and Day 84 across study populations and subgroups
  - Similar result versus voriconazole for the key secondary endpoint of overall response at EOT in Phase 3 study.
  - Activity against Mucorales which can mimic infection and has been reported as a cause of breakthrough infection[32]
- Safety
  - Lower incidence of study-drug-related TEAEs
  - Lower incidence of TEAEs leading to permanent drug discontinuation
  - Lower incidence of TEAEs in the following SOCs
    - Hepatobiliary
    - Eye

    - Skin
    - Cardiac
    - Psychiatric
  - Lower incidence of moderate/severe TEAEs in Hepatobiliary, Skin and Cardiac SOCs
  - Lower incidence of clinically significant transaminase elevations

For mucormycosis, the most relevant comparison is AmB. While a head-to-head comparison is not available, relative to historic data with AmB, isavuconazole offers the following potential advantages as a treatment of mucormycosis:

- Clinical pharmacology
  - IV and oral formulations that can be used for both acute and maintenance treatment
- Efficacy
  - Similar mortality outcomes as reported in the literature and the Fungiscope Registry, including outcomes in hematological malignancy and severe disease patients who are at greatest risk
- Safety
  - Uncommon infusion reactions
  - Avoidance of long-term nephrotoxic effects of AmB
  - Acceptable tolerability with prolonged treatment

2.3.3. Overall Benefit/Risk Conclusion

Participants may experience improvements during the study and will benefit from more intense monitoring and more frequent assessments compared to usual standard of care. Participants who continue to experience loss of efficacy will be able to switch to other available treatment options based on discussion with their treating physicians if the participants decide to discontinue from the study. Participants may benefit from contributing to the understanding of isavuconazole when treating IA and other filamentous fungi infection in adults. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with isavuconazole are justified by the anticipated benefits that may be afforded to participants with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi infections.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• 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 TEAEs by SOC and PT will be summarized without regard to adherence to the isavuconazole treatment and use of prohibited medication.
Secondary:	**Secondary:**	**Secondary:**
• 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.	• 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.
	Other secondary efficacy endpoints: • The percentage of all-cause mortality at Day 84 following primary treatment with isavuconazole.	• 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 *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.
• 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

Objectives	Endpoints	Estimands
• 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**
• 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 primary treatment with isavuconazole.	• The percentage of all-cause mortality on Day 42 and 84 will be estimated in participants with IM without regard to adherence to the isavuconazole treatment.
	• 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 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.
CCI [redacted]		

If the investigator judges an SAE to have a causal relationship with the IMP, the investigator must additionally report the event to Pfizer Safety as described in Section 10.3.3, Adverse Event Reporting section, even if that event is a component of the endpoint.

4. STUDY DESIGN

4.1. Overall 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.

Approximately 70 participants are planned to be enrolled (assigned to study intervention) in China and 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 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 examination and antigen test (for *Aspergillus* and *Mucorales* species, including 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.

The primary objective is to characterize the safety and tolerability of isavuconazole through observing the TEAEs.

For the clinical evaluation, investigators will need to review and evaluate the following: categorization of the diagnosis of IFD at enrollment (including data up to Day 7 as relevant); the participant's overall response, clinical, radiological and mycological responses at Day 42, at EOT and Day 84 (or Day 180 for participants with IM); and whether or not the participant has LRTD.

The details of the study treatment will be included in the Study Intervention section of the protocol (see Section 6.1.1).

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for Single Arm Design

The clinical data of isavuconazole in the Chinese population have been obtained from 46 Chinese participants including 36 healthy volunteers and 10 participants with IFD.

Given the rarity of IA and IM patients and the clinical benefit of isavuconazole (see Section 2.2 and 2.3), a single-arm study is planned. The study aims to collect timely and useful supportive evidence, in addition to the existing available data, to confirm the safety, efficacy, and PK profile for isavuconazole in Chinese participants. The proposed sample size provides an 86.6% probability to observe at least one participant experiencing an AE with an incidence of 3% or more.

4.2.2. Rationale for Population Selection

The target population for this study is Chinese participants with proven, probable, or possible IFD caused by *Aspergillus* species or other filamentous fungi.

The possible IFD definition is very strict to include only those cases with the appropriate host factors and with sufficient clinical evidence consistent with IFD but for which there was no mycological support. If excluding possible IFD, the number of candidates eligible for clinical studies of fungal pneumonia would reduce dramatically, making clinical trials nearly impossible to conduct.

All the possible participants are required to conduct further diagnostic tests (at least serum GM antigen for participants with IA) to further confirm IFD as “probable” or “proven” within 7 days after the first administration of study intervention. This effort aims to achieve greater emphasis on mycological evidence for the categories of proven and probable IFD, and allows the category of possible IFD to be reserved for clinical manifestations fully consistent with fungal etiology but for which there is no mycological evidence available, although a reasonable attempt has been made to exclude an alternative etiology.

4.3. Justification for Dose

Treatment of acute or refractory IFD caused by *Aspergillus* species, *Mucorales* species, and other filamentous fungi, remains associated with high mortality rates. Therefore, early adequate treatment is crucial in these life-threatening diseases. The dosing regimen for this study will be based on the approved dose for treatment of IA and IM in LPD. No dose adjustment is necessary in patients with renal impairment, including patients with ESRD. No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B).

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the trial.

A participant is considered to have completed the study if they have completed all periods of the study, including the last scheduled visit shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The investigator or qualified designee will assess and confirm that participants meet study eligibility criteria before they are enrolled into the study.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male and female Chinese participants aged ≥18 years at the timing of providing informed consent.

Disease Characteristics:

2. Participants must have proven, probable, or possible IFD caused by *Aspergillus* species, *Mucorales* species or other filamentous fungi, refer to the guidelines of EORTC/MSG (version 2019)[32] or EORTC/MSG ICU (version 2021)[34] (see Appendix 9, Section 10.9).

Weight:

3. Participants with a body weight >40 kg at screening

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Participants with either chronic aspergillosis, aspergilloma, or ABPA.

2. Advanced HIV infection with CD4 count < 200 or acquired immunodeficiency syndrome-defining condition.

3. Any known or suspected condition of the participant that may jeopardize adherence to the protocol requirements or impede the accurate measurement of efficacy, for example, neutropenia not expected to resolve, participants with fungal endocarditis, fungal osteomyelitis, fungal meningitis, or palliative therapy only for underlying condition.

4. Participants who are unlikely to survive 5 days or participants on mechanical ventilation.

5. Known history of allergy, hypersensitivity to, or any serious reaction to the azole class of antifungals or to any component of the study intervention.

6. Participants with severe hepatic impairment (Child-Pugh Class C) at the time of enrollment.

7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

8. Concomitant use of efavirenz, ritonavir, etravirine, rifampicin/rifampin, rifabutin, nafcillin, ketoconazole, or St. John's Wort in the 5 days prior to first administration of study intervention.

9. Participants who have been administered more than 4 cumulative days of itraconazole, voriconazole, or posaconazole, for any reason, within the 7 days prior to the first administration of study intervention.

    1) Participants with applicable host factors who develop new evidence of IFD while on prophylactic therapy, for at least 14 days, with either an AmB product or an echinocandin, will be eligible for enrollment.

    2) Prior use of fluconazole of any duration and for any reason will be eligible for enrollment.

Prior/Concurrent Clinical Study Experience:

10. Previous administration with an investigational product or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

11. Pregnant female participants; breastfeeding female participants; fertile male participants and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in Section 10.4.4 for the duration of the study and for at least 28 days after the last dose of study intervention.

Diagnostic Assessments:

12. Participants with familial short QT syndrome

Other Exclusion Criteria:

13. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and/or marketed product(s), medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to isavuconazole which is marketed in China.

6.1. Study Intervention(s) Administered

Table 2. Description of the Treatments to be Administered

Intervention Name	(Isavuconazonium sulfate)
ARM Name	NA. This is a single arm study, all enrolled participants will receive the study intervention.
Type	Drug
Dose Formulation	Isavuconazonium sulfate for injection (vial is for single use) Isavuconazonium sulfate capsules
Unit Dose Strength(s)	200 mg isavuconazole for injection per vial 100 mg isavuconazole per capsule
Dosage Level(s)	Refer to Table 3 as below
Route of Administration	Refer to Table 3 as below
IMP or NIMP/AxMP	IMP
IMP Source	The IMP will be provided centrally by the sponsor
Ancillary Supplies	In-line filters for dispensing IV formulation of Isavuconazonium sulfate Microporous membrane made of PES and with a pore size of 0.2 µm to 1.2 µm or equivalent
Packaging and Labeling	Study intervention will be provided in vials for injection and blister cards for capsule. Each vial or blister card will be labeled as required per country requirement. The product will be provided in open label.

Table 3. Dosage Regimen for Isavuconazole

	Loading Dose	**Maintenance Dose***
Isavuconazole for injection 200 mg isavuconazole per vial	1 reconstituted vial (200 mg) intravenously every 8 hours for 6 doses (48 hours)	1 reconstituted vial (200 mg) intravenously once daily
Isavuconazole Capsule 100 mg isavuconazole per capsule	2 capsules (200 mg) orally every 8 hours for 6 doses (48 hours)	2 capsules (200 mg) orally once daily

Table 3. Dosage Regimen for Isavuconazole

	Loading Dose	Maintenance Dose*

* Maintenance dose is administered from Day 3 to EOT (max. 84 days for participants with IA or other filamentous fungi infection, or up to 180 days for participants with IM)

6.1.1. Administration

An isavuconazole loading regimen will be administered during **the first 48 hours** followed by a maintenance dose from Day 3 to EOT:

- 0–48 hours: IV infusion of 200 mg isavuconazole (q8h [±2h] – 3 total infusions over a 24 hour period)

OR

- 0-48 hours: 200 mg isavuconazole (2 capsules with each containing 100 mg isavuconazole, q8h[±2h] – 3 total dosages over a 24 hour period) PO

From **Day 3 to EOT**, participants will receive:

- One IV infusion of 200 mg isavuconazole once daily

OR

- 200 mg isavuconazole (2 capsules with each containing 100 mg isavuconazole) PO once daily

The first maintenance dose (Day 3) is recommended to start 12 to 24 hours after the last loading dose. Subsequent doses will be administered daily.

The switch to oral therapy should be made as early as possible from Day 3 onwards.

Reasons for not switching to oral must be documented as source, eg, unable to swallow, gastric suction, concerns about adequate dosing. Participants who do not switch will remain on IV treatment.

Participants who switch from IV to oral therapy may switch back to IV therapy at any time during the course of the study if the investigator feels it is necessary, eg, in the participant's best interest or necessary for the appropriate clinical management of the participant.

With oral administration, participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing. Isavuconazole capsules can be taken with or without food. Participants will self-administer the IP at home except on days of scheduled clinic visits or during hospitalization, where the IP will be administered in the clinic or inpatient.

Isavuconazole for infusion must be administered through an in-line filter over a minimum of **1 hour**. The reconstituted vial must not be given as a bolus injection. Do not infuse isavuconazole with other IV medications.

IV medication may only be administered by trained and qualified healthcare professionals.

The route of administration, whether or not there has been a change, and reasons for the change in route of administration will be considered source data and will not be required to be reported to clinical database.

Stopping administration of study intervention ≥48 hours will be considered as cessation of study intervention. The reasons for cessation of study intervention will be recorded in the eCRF.

Participants will be treated until they reach a defined discontinuation criterion (see Section 7.1), up to a maximum of 84 days (up to 180 days for participants with IM).

Participants who are considered by the investigator to have experienced a successful overall outcome will continue treatment for a minimum of **7 days** after resolution of all clinical symptoms and physical findings. The maximum treatment period of 84 days (180 days for participants with IM) must not be exceeded.

Non-study systemic antifungal medication is only allowed after the Day 42 visit, unless the participant has failed treatment with study medication prior to the Day 42 visit.

Participants with a successful overall response at EOT (prior to Day 42) must return for Day 42 and Day 84 visits, even if they are no longer under study treatment. It is recommended to keep participants on study treatment up to Day 42 if the administration of systemic antifungals as prophylaxis is anticipated after the end of study treatment.

Participants with an unsuccessful overall response at EOT and requiring alternative systemic antifungal therapy will not be asked to return for Day 42 and/or Day 84 visits; however the survival status at these time points will be collected. A Follow-up visit will be performed 4 weeks (±7d) after last dose of isavuconazole administration.

6.1.1.1. Compatibility for the Injection Formulation

Isavuconazonium sulfate for injection should only be administered with the following diluents:

- 0.9% sodium chloride injection
- 5% dextrose injection

6.1.2. Medical Devices

1 The in-line filter with a microporous membrane pore size of 0.2 to 1.2 micron used for isavuconazole injection will be supplied. The manufacturer of in-line filter has not been decided when the protocol was developed.

2 Instructions for medical device use are provided in the IPM.

3 In-line filter medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (See Section 8.4.9).

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention. See the IPM or package insert for storage conditions of the study intervention once reconstituted and/or diluted.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study

interventions will be accounted for using a study intervention accountability form/record. All blister cards of study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. **Returned study intervention must not be redispensed to the participants.**

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor **within 1 business day** of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

The investigational product will be dispensed by pharmacist/site staff manually at each visit from Day 1 onwards until EOT. A qualified staff member will dispense the investigational product using unique container numbers in the vials or blister cards provided, in quantities appropriate in quantities appropriate according to the SoA. The site staff(s) will maintain the product in the vials or blister cards provided throughout the course of dosing and return the vials or blister cards to the site at the next study visit as appropriate.

See the IPM or package insert for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.3. Assignment to Study Intervention

6.3.1. Allocation to Investigational Product

This is an open-label, single arm study. The investigator's knowledge of the treatment must not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

6.4. Blinding

Not Applicable.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IPM. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the study intervention supplies. All study interventions will be accounted for using a drug accountability form/record.

All blister cards of study intervention and all unused products must be returned to the investigator by the participant at every visit and at the end of the trial.

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned capsules. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

All IV doses of study intervention will be administered by the appropriately designated study staff at the investigator site.

6.6. Dose Modification

No dose adjustment is required based on age and gender. No dose adjustment is necessary in participants with renal impairment. It is recommended that the standard loading dose and maintenance dose regimen be utilized in participants with mild to moderate hepatic disease.

Switching between the IV and oral formulations of isavuconazonium sulfate is acceptable as bioequivalence has been demonstrated. Loading dose is not required when switching between formulations. Adequate overage of drug supplies will be provided to allow such a switch from one formulation to other. Clinically retained quantities per the local requirement will be included.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any dose of isavuconazole greater than the recommended dose regimen (600 mg/day during loading and 200 mg/day during maintenance) within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.
5. Obtain a blood sample for PK analysis within 24 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor as needed based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4, Section 10.4).

All concomitant medications will be recorded in the participant's eCRF as follows:

- All T-cell or B-cell immunosuppressants, such as cyclosporine or tacrolimus, ibrutinib, given within 3 months prior to the first dose of study intervention
- All corticosteroids given within 4 weeks prior to the first dose of study intervention
- All systemic, oral, or topical antifungal, antiviral, and antibacterial agents administered within 4 weeks prior to the first dose of study intervention
- All other medications given within 2 weeks prior to the first dose of study intervention
- All medications taken during the treatment period
- All medications taken during the 4-week posttreatment period.

Treatment with anticancer agents, if clinically indicated, is generally acceptable, if assessment of study endpoints is expected to be feasible.

Concomitant administration of non-study systemic antifungals is prohibited from the first dose of study intervention through the last FU visit, with the following exceptions:

- Failures of study therapy
- Non-systemic antifungal medication (eg, inhaled antifungals and oral AmB) are allowed and can be administered at any time.
- If administration of systemic antifungals as secondary prophylaxis is anticipated following successful therapy with study intervention, participants should remain on study intervention through the Day 42 visit, ie, do not start any non-study systemic antifungal medication until after the Day 42 visit. Secondary prophylaxis for participants who are expected to receive additional courses of chemotherapeutic agents, undergo BMT/HSCT, or are anticipated to remain significantly immunosuppressed is acceptable after the Day 42 visit. Reasons for requiring secondary prophylaxis must be documented in the eCRF.

Table 4 lists the concomitant medications that are prohibited during treatment with study medication.

Prohibited concomitant medications should be stopped **5 days** prior to the first administration of study medication and should not be introduced until **2 weeks** after the last dose of study intervention.

Table 4. Prohibited Concomitant Medications

Prohibited Medication
Rifampin/Rifampicin
Rifabutin
Nafcillin
Efavirenz, Ritonavir (at doses >200 mg every 12 hours)
Etravirine
Ketoconazole
St. John's Wort

Table 5. Concomitant Medications to be Used with Caution

Medications Requiring Monitoring of Drug Levels, Monitoring for Drug Effect/Side Effects, Dose Adjustment
Midazolam
Cyclosporine
Tacrolimus
Sirolimus
Mycophenolate mofetil
Short-acting opiates (alfentanyl, fentanyl)
Other anticancer agents (daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan)

Table 5. Concomitant Medications to be Used with Caution

Medications Requiring Monitoring of Drug Levels, Monitoring for Drug Effect/Side Effects, Dose Adjustment
Aprepitant Other NNRTI (eg, nevaripine) Methadone Clarithromycin Prednisone Cyclophosphamide Metformin Digoxin Vinca alkaloids Dabigatran etexilate Lopinavir, Ritonavir Indinavir Saquinavir Fosamprenavir Atorvastatin and other statins Pioglitazone Colchicine Bupropion

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with isavuconazole, standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following.

- Premature withdraw from the study
- Has a successful overall outcome and has received a minimum of 7 days therapy after resolution of all clinical symptoms and physical findings of infection
- Has an unsuccessful overall outcome and requires alternative systemic antifungal therapy
- Completes 84 days of treatment (180 days for participants with IM, if applicable)
- Withdrawn from the study at investigator's or sponsor's discretion
- Intolerable AE
- Non-compliance
- Pregnancy

- Use of prohibited medication, including non-study systemic antifungal medication as described in Section 6.9.
- Intercurrent illness requiring a change in participant management
- ALT or AST ≥10×ULN

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for the following assessments. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

The EOT assessments should be completed prior to premature withdrawal from study medication and, whenever possible, the Follow-up visit should be performed in all participants who received at least one dose of study medication. Survival status at Day 42, Day 84, EOT and Follow-up will also be collected.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participant's own baseline measurement)is ≥0.4 mg/dL (or ≥35.4°µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum urea, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the

abnormal SCr. If ≥2 healthy participants are noted to have 2 consecutive SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study protocol, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 150 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.2. Efficacy Assessments

All efforts should be made to have EOT assessments performed in all participants. Participants with a successful overall outcome at EOT (prior to Day 42) must return for Day 42, Day 84, or other planned visits (eg, Day 126 and Day 168 for participants with IM) through EOT as specified in SoA, even if they are no longer receiving study intervention. If administration of systemic antifungals as prophylaxis is anticipated following successful therapy, participants should remain on study intervention through the Day 42 visit, ie, do not start any non-study systemic antifungal medication until after the Day 42 visit.

Secondary prophylaxis for participants who are expected to receive additional courses of chemotherapeutic agents, undergo BMT/HSCT, or are anticipated to remain significantly immunosuppressed is acceptable after the Day 42 visit. Reasons for requiring secondary prophylaxis must be documented in the eCRF.

Participants withdrawn from study intervention or with an unsuccessful overall outcome at EOT and requiring alternative systemic antifungal therapy will not be asked to return for subsequent visits, but will be required to return for the FU visit which is planned on 4 weeks after the last dose of study intervention; however, the survival status at the time points as specified in SoA will be collected (confirmation by phone contact is acceptable and will be documented in the eCRF).

8.2.1. Clinical Signs and Symptoms of Invasive Fungal Infection

Assessment of signs and symptoms of IFD (refer to Appendix 9, Section 10.9 for more detail) will be performed as specified in SoA. All changes in clinical symptoms and physical findings related to IFD will be recorded on the eCRF.

8.2.2. Radiological Assessment of Invasive Fungal Infection

Initial local radiologic assessment of IFD by CT scan (or HRCT) or MRI may be used to determine participant eligibility at Screening. Baseline radiological assessments of IFD by CT should be performed once the participant has completed the informed consent. However, assessments performed up to 7 days after the first administration of study intervention may be used to confirm the diagnosis of IFD. Out-of-window assessments may be considered as baseline assessments upon sponsor's (or designee) prior approval.

Radiological assessments should be made by CT (or HRCT) or MRI and all radiological images and local reports pertaining to IFD will be based on investigators' discretion.

8.2.3. GM Antigen

GM antigen will be tested at Screening. If clinically indicated, can be tested during Day 1 to Day 7, for participants with IA only. Assessments performed up to 7 days after the first administration of study intervention may be used to confirm the diagnosis of IFD. All the "possible" IFD participants are required to conduct further diagnostic tests (at least GM antigen for participants with IA) to further confirm IFD as "probable" or "proven" within 7 days after the first administration of study intervention. Criteria regarding interpretation of GM test results refer to Appendix 9, Section 10.9.

GM antigen result for eligibility at screening will be based on local lab test results.

In addition, samples obtained for GM antigen assay (or collected any time while participants with probable, proven or possible Aspergillus are still receiving study drug) will be shipped to a central laboratory. BAL for GM specimens may be processed locally, but an additional aliquot of BAL fluid will be collected for shipment to the central laboratory as well.

8.2.4. Bronchoscopic Assessment of Invasive Fungal Infection

If bronchoscopic assessments are clinically indicated, samples are to be obtained for the following tests: culture and histology/cytology. The culture and histology/cytology will be performed using local laboratories for eligibility assessment. If samples are obtained at baseline and up to Day 7, an additional sample will be stored for shipping to the central reference laboratory for mycological testing.

If BAL is sent for GM antigen testing, the results should be recorded in the eCRF. BAL for GM specimens will be processed locally.

8.2.5. Mycological Assessment of Invasive Fungal Infection

All mycological assessments will be based on results generated in the local laboratory to assess the participant's eligibility at screening and following mycological response. Pathogen isolates must be shipped to the central reference laboratory for confirmation of local mycological results.

Baseline mycological assessment (Screening through Day 7) of the participant's IFD status will be performed according to the microbiological manual or the best local practice using local laboratories, including obtaining suitable samples for fungal culture and isolation and/or biopsy/biological fluid samples from the infected site for histology/cytology. Day 42 and Day 84 assessments will be performed within ±7 days, as well as Day 126 and Day 168 for IM participants. EOT assessments will be performed within ±3 days.

Baseline and different (species level) pathogen isolates (defined as clinically significant isolates) will be stored and shipped to a central laboratory for isolation of fungal species and susceptibility testing.

If the identities of the pathogens differ between the central and local laboratories, the central laboratory results will take precedence over the local results for both eligibility and response evaluation purposes.

8.2.6. Neutropenic Status/Absolute Neutrophil Count

Neutropenic status will be recorded within 4 weeks prior to screening and up to the end of the study period. The presence or absence of neutropenia (defined as ANC $<0.5 \times 10^9$/L [$<500/mm^3$]) and subsequent persistence (ongoing) or resolution (2 consecutive ANC values $> 0.5 \times 10^9$/L on 2 separate days) will be reflected in the ANC values recorded in the eCRF. All ANCs performed (or calculated) at local laboratories during a neutropenic episode will be recorded in the eCRF along with the date drawn to include the values documenting the resolution. When differentials are not performed due to insufficient WBCs, the total WBCs will be recorded for that day in the eCRF.

8.2.7. Survival Status

Survival status will be recorded until the Follow-up visit and be evaluated through EOT in all participants, irrespective of when treatment was discontinued. Detailed requirement should be performed as specified in Section 1.3 SoA.

If the participant has died, the date and cause of death along with the reporting of SAE details will be recorded in the eCRF.

8.2.8. Investigator's Assessment of Overall Response

The investigator's assessment of overall response will be recorded at Day 42, EOT and Day 84. For participants who had an overall response of failure at EOT (prior to Day 42 visit), assessment of response is not required on Day 42 and Day 84.

The investigator will be asked to provide his/her opinion of the participant's response as follows:

Clinical Response (all non-radiological clinical symptoms and physical findings):

- Resolution of all attributable clinical symptoms and physical findings

  (ie, resolution of all clinical symptoms and physical findings of IFD present at baseline and/or resolution of those that appeared at a subsequent visit)

- Resolution of some attributable clinical symptoms and physical findings

  (ie, resolution of some but not all clinical symptoms and/or physical findings of IFD present at baseline and/or of those that appeared at a subsequent visit)

- No resolution of any attributable clinical symptoms and physical findings and/or worsening

  (ie, no resolution or worsening of any clinical symptoms and/or physical findings of IFD present at baseline and/or of those that appeared at a subsequent visit)

- Results not available/participant unevaluable

  (ie, visit and/or assessment of clinical symptoms and physical findings of IFD was not performed at any time point [Day 42, EOT or Day 84])

- No attributable signs and symptoms at screening

  (ie, no clinical symptoms or physical findings of IFD present at baseline)

Radiological Response:

- ≥ 90% improvement
- ≥ 50% to < 90% improvement
- ≥ 25% to < 50% improvement
- < 25 % improvement
- No signs on radiological images at screening (Proven IFD only)
- Results not available (ie, visit and/or radiological assessment was not performed at any time point [Day 42, EOT or Day 84])

Radiological assessments should be made by CT and all radiological images and local reports pertaining to IFD will be based on investigators' discretion.

Mycological Response:

- Eradication

  (eradication of the original causative organism cultured or identified by histology/cytology at baseline)

- Presumed eradication

  (missing documentation of the eradication of the original causative organism at baseline plus resolution of all or some clinical symptoms and physical findings of IFD present at baseline and/or of those that appeared at a subsequent visit)

- Persistence

  (persistence of the original causative organism cultured or identified by histology/cytology at baseline or emergence of a new causative organism)

- Presumed persistence

  (missing documentation of the persistence of the original causative organism at baseline plus no resolution or worsening of any clinical symptoms and physical findings of IFD present at baseline and/or of those that appeared at a subsequent visit)

- No mycological follow-up results available, for any reason

  (no diagnostic test done at any time point of assessment *[Day 42, EOT, Day 84, Day126, or Day 168]*)

- No mycological evidence at screening (up to Day 7)

  (any negative diagnostic test(s) obtained or not done at baseline [from screening up to Day 7 inclusive])

8.2.9. Definition of Response and Outcome

Table 6 defines a successful overall outcome.

Participants with no host factors, except for those with a proven IFD, will have an overall response of indeterminate, regardless of their respective clinical, radiological, and mycological response.

Participants not available for assessment, who are considered to have had an overall response of failure, or required alternative systemic antifungal therapy prior to Day 42 and/or Day 84 and/or EOT will be considered as having had an overall response of failure at Day 42 and/or Day 84 and/or EOT.

In addition, death of a participant will always be considered an overall response of failure for subsequent assessments.

Table 6. Definition of Successful Overall Response

	Clinical Response	Radiological Response	Mycological Response
Success	• Resolution of all attributable clinical symptoms and physical findings • Resolution of some attributable clinical symptoms and/or physical findings	• 90% improvement from screening • ≥50% – <90% improvement from screening • ≥25% - <50% improvement from screening[1] • No signs on radiological images at screening (Proven IFD only)	• Eradication • Presumed Eradication

Any one criterion from each response column is required to be considered to have an overall outcome of success.
1. At Day 42 for participants with proven or probable IFD. At Day 84, however, this would be considered unsuccessful.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

Physical examinations will be conducted at Screening and on Day 1, Days 42, 84, and EOT. At the Follow-up visit, physical examinations will only be performed in participants with abnormalities observed at the EOT visit. Physical exams should also be performed throughout the study when clinically indicated as determined by the investigator.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3, Section 10.3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

Assessments comprising blood pressure (SBP and DBP; mmHg), PR(bpm), RR(times per minute) and axillary, ear, or forehead BT(C°) will be made at Screening and visits as specified in SoA. If participants discontinue from study intervention prior to Day 7, Day 7 and Day 14 assessments on vital signs are not required. At the Follow-up visit, vital signs assessments will be performed only in participants with abnormalities observed at the previous visit.

On Day 1, vital signs will be measured within 1 hour before and 1 hour after the end of each dose of study intervention administration. From Day 7 onwards, vital signs will be measured once prior to study intervention administration.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3, Section 10.3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP and PR measurements should be preceded by at least 5 minutes of rest with the participant in a semisupine or sitting position, in a quiet setting without distractions.

Vital signs will be taken before blood collection for laboratory tests and consist of a single measurement of PR and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute apart). The average of the 3 BP readings will be recorded on the CRF.

8.3.2.2. Temperature and Respiratory Rate

Temperature and respiratory rate findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted.

8.3.3. Electrocardiograms

Twelve-lead ECG recordings will be obtained at Screening and will also be performed on Day 1, Days 14, 42, 84 and EOT, while the participant remains on study intervention. All participants will have an ECG at EOT.

Standard 12-lead ECGs should be collected on visits specified in the SoA using an ECG machine that automatically calculates the HR and measures PR, QT, QTc intervals and QRS complex. Each ECG recording is to be signed and dated by the investigator or his designee. Abnormalities, if not related to the underlying disease, must either be confirmed as clinically not significant or are to be repeated until they have returned to baseline levels. Abnormalities should not be reported as AEs on the AE page of the eCRF unless they result in a clinically relevant condition.

All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

If a) a post-dose corrected QT (QTc) interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7, Section 10.7.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2, Section 10.2 for the list of clinical safety laboratory tests to be performed and the SoA for timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, Section 10.2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5, Section 10.5 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 6, Section 10.6 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.5. Eye Examination

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 Day 14, 28, and 42 (also on visits as specified in SoA for participants with IM). An eye examination will be performed at the Follow-Up Visit only if abnormal at EOT. The examination will consist of visual acuity, confrontational visual field testing, and color perception testing. A qualified ophthalmologist will assess participants at Screening and through the study. Any abnormalities noted will be recorded in the eCRF.

8.3.6. Pregnancy Testing

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3.7. Other Assessment

8.3.7.1. Anti-infective 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 will be recorded in the appropriate section of the eCRF.

8.3.7.2. Non-Medication Procedures

All non-medication procedures (eg, radiation therapy), including all treatment for IFD (eg, surgery), associated with the participant's underlying disease received 2 weeks prior to the first administration of study intervention, during the study, and including the 4 weeks posttreatment period will be recorded in the appropriate section of the eCRF.

8.3.7.3. Hospitalization Status

Reason for hospitalization, date of admission, and date of discharge and will be recorded in the eCRF from screening up through the 4 weeks posttreatment period.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3, Section 10.3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally

authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant or legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

Note: **Death** is considered an outcome of an AE. Whenever possible the underlying cause of death should be reported as the AE

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider

the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3, Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact, etc.

- A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 5 terminal halflives after the last dose or until study end for devices, whichever is longer.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact, etc.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following DREs are common in participants with IFD independent of exposure to study intervention, can be serious/life-threatening, and are defined as endpoints in this protocol:

- Death;

Because this event is typically associated with the disease under study, it will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. This event will be recorded on the corresponding CRF page in the participant's CRF within 24 hours of being made aware of the event. These DREs will be monitored by a safety review team on a routine basis.

Note: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The AE leading to death is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant

OR

- The investigator considers that there is a reasonable possibility that the death was related to study intervention.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 8, Section 10.8.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.4.1 through 8.4.4 and Appendix 3, Section 10.3 of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 8, Section 10.8.

8.4.9.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1 The investigator notifies the sponsor by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2 The device deficiency must be recorded on the Medical Device Complaint form.

3 If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

4 If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.4.1.1). All relevant details related to the role of the device in the event must be included in the CT SAE Report Form as outlined in Sections 8.4.1.1 and 8.4.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility

to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

Blood samples of approximately 3 mL, to provide a minimum of 1.2 mL plasma, will be collected for measurement of plasma concentrations of isavuconazole as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Unless stated in Section 1.3.1, collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF/DCT). Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF/DCT).

Samples will be used to evaluate the PK of isavuconazole. Samples collected for analyses of isavuconazole (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of isavuconazole will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

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

9.1.1. Estimands

9.1.1.1. Estimand for treatment emergent adverse event (TEAE)

The incidence rates of TEAEs by SOC and PT will be summarized without regard to adherence to the isavuconazole treatment and use of prohibited medication.

9.1.1.2. Estimand for the all-cause mortality

The percentage of all-cause mortality on Day 42 and 84 will be estimated in participants with IFD caused by *Aspergillus* species and other filamentous fungi, or Mucormycosis without regard to adherence to the isavuconazole treatment.

9.1.1.3. Estimand for the overall, clinical, mycological, and radiological responses

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 Mucormycosis 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.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Defined Analysis Set	Description
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 participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
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.
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 Appendix 9, Section 10.9.
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.
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.
Safety Population	The safety population consists of all enrolled participants who receive at least 1 dose of study intervention.
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.

9.3. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. Efficacy Analyse

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

The key secondary efficacy endpoint of crude rate of all-cause mortality through Day 42 will be analyzed on the ITT population. Any death that occurs after first dose of study intervention through Day 42 will be included. A participant with the last known survival status before Day 42 or missing and the last assessment day before Day 42 will be treated as death. The 95% CI of the crude mortality rate will be calculated based on an exact binomial distribution.

The same analysis will be repeated for the mITT, myITT-IA, and myITT-IM populations.

All-cause mortality rate over time by Day 42 will also be estimated using the KM method. In the KM analysis, time to death will be observed until Day 84 for participants with IA and Day 180 for participants with IM.

The other secondary endpoint of the percentage of all-cause mortality through Day 84 will be summarized and analyzed similarly to the all-cause mortality through day 42.

The clinical, mycological, radiological, and overall response at EOT, Day 42 and Day 84 will be summarized. The 95% CIs of the response rates will be calculated based on an exact binomial distribution.

9.3.2. Safety Analyses

Safety variables will be summarized descriptively for the safety population. 95% CIs for the binary outcome of selected safety variables may be presented based on an exact binomial distribution.

The primary safety endpoint is the incidence rates of TEAEs by SOC and PT. A TEAE is defined as any AE that starts on or after the first administration of study intervention until 28 days after last dose of study intervention. Other key summaries of AEs include the summaries of

- TEAE related to study intervention
- Treatment-Emergent SAEs
- TEAE leading to discontinuation of study intervention
- TEAE leading to deaths
- All deaths

Vital signs will be listed and summarized by means and standard deviation (SD). Laboratory test values will be presented in change from baseline and shift tables and by individual listings with flagging of values outside the normal reference ranges. ECG findings will be presented by listings and frequency tables, as appropriate.

9.3.3. Other Analyses

9.3.3.1. Pharmacokinetic Analysis

PK analysis will be conducted using the PK concentration analysis set. Observed plasma concentrations of isavuconazole will be summarized for CCI using descriptive statistics in the overall study population. CCI

Summary statistics of isavuconazole plasma concentrations at specified sampling visits/timepoints will be reported in the CSR.

9.4. Interim Analyses

An interim analysis maybe performed to assess safety and efficacy after around 40% of the planned participants complete their study participation. The interim analysis conducted for internal reference to support compound development. The analysis methods in the interim report will follow the methods planned for the full study. As the study does not involve any statistical hypothesis testing of the key endpoints, there will be no adjustment of multiplicity or group sequential boundaries.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan will be documented. In addition, the analysis details will be documented and approved in the SAP.

9.5. Sample Size Determination

Initially approximately 56 participants were planned to be enrolled (assigned to study intervention) and approximately 53 participants were expected to be treated. With 53 treated participants, for AEs that are as common as 3% or more, there would have been a probability of 80% to observe at least 1 participant experiencing such AEs. The China regulatory agency suggested to expand the sample size. The sample size is modified to enroll approximately 70 participants, among which approximately 66 participants are expected to be treated. With 66 treated participants, for AEs that are as common as 3% or more, there is a probability of 86.6% to observe at least 1 participant experiencing such AEs.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant or their legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or their legally authorized representative must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or their legally authorized representative.

The participant or their legally authorized representative must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or their legally authorized representative is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their legally authorized representative must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by Pfizer.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered

closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

If the sponsor decides to terminate the study for a reason unrelated to the safety of study intervention, participants may continue to receive study intervention per the investigator's judgment and protocol-specified safety assessments will continue to be performed for these participants until the end of the study as defined in Section 4.4. The following non safety-related study procedures and assessments may be stopped upon written notification from the sponsor:

- Efficacy assessment refer to Section 8.2.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Use of Medical Records

In certain situations, sponsor review of redacted copies of participant medical records for IFD diagnosis may be performed, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or

understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA and Section 8.3.4 of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 7. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin RBC count Platelet count WBC count Total neutrophils (Abs) Lymphocytes (Abs)	BUN/Urea and creatinine CystatinC (at baseline) Sodium Potassium AST, ALT Total bilirubin Alkaline phosphatase	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	At screening: • FSH[b] • Pregnancy test (β-hCG)[c]

a. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
b. For confirmation of postmenopausal status only.
c. Local urine testing will be standard for the protocol unless serum testing is required by the protocol, local regulation or IRB/EC. Serum or urine βhCG for female participants of childbearing potential.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/selfharming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires in-participant hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-participant setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow up information and send an SAE follow up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 Days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) ***plus*** an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- The male participant should be advised of the benefit for a WOCBP partner using a highly effective method of contraception with a failure rate of <1% per year, as described in Section 10.4.4.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she (a) is not pregnant or breastfeeding; and (b) agrees not to donate eggs (ova, oocytes) for the purpose of reproduction 28 Days after the last dose of study intervention; and (c) at least 1 of the following conditions applies:

- Is not a WOCBP (see definition in Section 10.4.3).

  OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (failure rate of <1% per year) with low user dependency during the intervention period and agrees to use it for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study

intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential.

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

[redacted]

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral + barrier*

    - Intravaginal + barrier*

- Transdermal + barrier*

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral + barrier*
   - Injectable + barrier*

8. Sexual Abstinence

   Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: Kidney Safety Monitoring Guidelines

10.6.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. 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).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.6.2. Age-Specific Kidney Function Calculation Recommendations:

10.6.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

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	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
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	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021;385:1737-49.

10.6.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

KDIGO criteria grade (G)	Study Population	G1	G2	G3	G4	G5
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	Adult participants eGFR (mL/min/1.73m²)	≥90	≥60 to 89	30 to 59	15 to 29	<15

KDIGO albuminuria (A) criteria	A1	A2	A3
Albumin-to-creatinine ratio (ACR)	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as SAEs

• QTcF prolongation >500 ms.
• New STT changes suggestive of myocardial ischemia.
• Newonset LBBB (QRS complex >120 ms).
• Newonset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptomfree participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptomfree participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II seconddegree (Mobitz II) AV block.
- Complete (thirddegree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second or thirddegree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 3 (Section 10.3.2).
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition
• A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.8.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and will also capture the required information on the Medical Device Complaint form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for

recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3).

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency
• Follow-up applies to all participants, including those who discontinue study intervention. • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the CT SAE Report Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

10.8.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.4).

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.9. Appendix 9: Diagnosis Criterial for Proven, Probable, or Possible IFD Caused by *Aspergillus* Species, Mucorales Species or Other Filamentous Fungi

Proven Invasive Fungal Disease

Participants with a positive diagnostic test obtained prior to the first dose and up to 7 days after the first administration of study medication:

- Either histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy showing hyphal forms with evidence of associated tissue damage (either microscopically or as an infiltrate or lesion by imaging).

OR

- Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, eg, transbronchial biopsy, open-lung biopsy, or brain biopsy, excluding BAL fluid, a paranasol or mastoid sinus cavity specimen, and urine.

OR

- Blood culture that yields a mold (eg, *Fusarium* species) in the context of a compatible infectious disease process. In an immunocompetent host, a blood culture that yields *Aspergillus* species is to be considered a contaminant and the participant is not eligible for enrollment.

OR

- Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue.

Host factors (a) and clinical features (b) are not required for participants with proven IFD. However, if such host factors and clinical features are present at baseline, they will be recorded in the eCRF.

Probable Invasive Fungal Disease

	At least one host factor [a] as below
PLUS	**At least one clinical feature [b]** as below
PLUS	**At least one mycological criterion [c]** as below

a. HOST FACTORS:

- Either recently resolved or ongoing neutropenia (neutropenia defined as absolute neutrophil count (ANC) $<0.5 \times 10^9$/L [$< 500/mm^3$] for ≥10 days), temporally related to the onset of fungal disease

- hematologic malignancy
- receipt of an allogeneic hematopoietic stem cell transplant (HSCT) / bone marrow transplant (BMT)
- receipt of a solid organ transplant
- prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3mg/kg corticosteroids for ≥ 3 weeks in the past 60 days
- treatment with other recognized T-cell immunosuppressants (such as calcineurin inhibitors, tumor necrosis factors- α blockers, lymphocyte-specific monoclonal antibodies or immunosuppressive nucleoside analogs) during the past 90 days (participants whose underlying condition is rheumatologic in nature are not eligible for enrollment)
- treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib
- inherited severe immunodeficiency (eg, chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency)
- acure graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids
- chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis)
- Severe influenza (or other severe viral pneumonia, such as coronavirus disease 2019 [COVID-19]), liver disease, malnutrition, severe burns, diabetes

b. CLINICAL FEATURES:

Lower Respiratory Tract Disease (LRTD)

See Table 8 below for a summary of status of invasive fungal disease at baseline for participants with LRTD.

The medical history must be established to exclude alternative etiologies and to distinguish between an acute or subacute presentation rather than a chronic pulmonary infection. Onset of clinical symptoms and/or physical findings within approximately 2 weeks prior to the first administration of study medication defines an acute or subacute pulmonary infection.

Either the presence of at least one of the following signs on computed tomography (CT) scan or high resolution computed tomography (HRCT) or magnetic resonance imaging (MRI):

For pulmonary aspergillosis:

- Dense, well-circumscribed lesion(s) with or without a halo sign

- Wedge-shaped and segmental or lobar consolidation
- Air crescent sign
- Cavity.

For other pulmonary mold disease, a reverse halo sign is also included.

OR

Allogeneic BMT / HSCT or neutropenic participants who have non-specific focal infiltrates, confirmed by CT scan (or HRCT) or MRI, and have mycological evidence of disease will also be classified as probable. The presence of non-specific focal infiltrates or evidence of disease on plain chest X-ray must be confirmed by CT scan (or HRCT) or MRI within the 7 days after the first administration of study medication.

Non-Lower Respiratory Tract Disease (NLRTD)

See Table 9 below for a summary of status of invasive fungal disease at baseline for participants with NLRTD.

Sino-Nasal Infection:

- CT scan or MRI showing sinusitis **PLUS** at least one of the following:
  - Acute localized pain (including pain radiating to eye)
  - Nasal ulcer, black eschar
  - Extension from the paranasal sinus bony barriers, including into the orbit.

Central Nervous System Infection:

- At least one of the following:
  - Focal lesions on imaging, or
  - Meningeal enhancement on CT or MRI.

c. MYCOLOGICAL CRITERIA:
(cytology, direct microscopy, culture from non-sterile sites, antigen detection)

- Either sputum, bronchoalveolar lavage (BAL), bronchial brush samples, or sinus cavity specimen demonstrating the presence of fungal elements either by culture of a mold (eg, *Aspergillus* species) or detection by cytology or direct microscopy of hyphal forms
- Or for Aspergillosis specifically, GM antigen detected in plasma, serum, BAL, or CSF at least one of the following positive results is an acceptable mycological evidence for

enrollment as probable IFD, and it is recommended to refer to the guideline of EORTC/MSG (version 2019) or EORTC/MSG ICU (version 2021)[34, 35]:

- Single serum or plasma: ≥1.0;
- BAL fluid: ≥1.0
- Single serum or plasma: ≥ 0.7 and BAL fluid ≥ 0.8
- two consecutive values of either serum, plasma or BAL fluid between ≥ 0.5 to <1.0 (from two separate specimens of the same category)
- CSF: ≥ 1.0

- Or for *Aspergillus* species specifically, *Aspergillus* PCR at least one of the following:
  - plasma, serum, or whole blood 2 or more consecutive PCR tests positive
  - BAL fluid 2 or more duplicate PCR tests positive
  - At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid

Possible Invasive Fungal Disease

PLUS	**At least one host factor [a]** as above
	At least one clinical feature [b] as above

NOTE: Participants fulfilling the criteria for possible IFD as defined above will be eligible for enrollment; however, confirmatory CT scan, GM test, **in addition to**, acceptable mycological criteria as defined above is required within the 7 days after the first administration of study medication.

BAL PCR (only): two or more duplicate PCR tests positive (2 or more aliquots of the same sample) are allowed to enroll as probable IFD. Specimens for culture and histology/cytology must be obtained from the BAL during the same procedure and serum GM must still be obtained per protocol requirements.

Table 8. Status of Invasive Fungal Disease at Day 7 for Participants with Lower Respiratory Tract Disease (LRTD)

Host Factors	**Clinical Features** **"Lower Respiratory Tract Disease"**	**Mycological Criteria**			
		No positive culture		**Positive culture or microscopy (cytology/histology) of hyphal forms**	
		Serum testing negative for GM[2]	**Serum/plasma testing positive for GM[2] or Positive BAL GM[2]**	**Nonsterile site (i.e. sputum, BAL, or bronchial brushing specimen)**	**Sterile site (i.e. transbronchial biopsy or open lung biopsy) or with associated tissue damage**
Neutropenia (ANC < 0.5 x 10^9/L[<500/mm^3]) temporally related to the onset of fungal disease **OR** hematologic malignancy **OR** Receipt of an allogeneic hematopoietic stem cell transplant **OR** Receipt of a solid organ transplant **OR** prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3mg/kg corticosteroids for ≥ 3 weeks in the past 60 days. **OR** treatment with other recognized T-cell immunosuppressants (such as calcineurin inhibitors, tumor necrosis factors-α blochers, lymphocyte-	Presence of at least one imaging sign on CT scan (or HRCT) or MRI: - Dense, well-circumscribed lesion (s) with or without a halo sign - Wedge-shaped infiltrate and segmental or lobar consolidation - Air crescent sign - Cavity **OR** Presence of new "nonspecific" imaging findings on CT scan (or HRCT) or MRI[1] **OR** For other pulmonary mold disease, a reverse halo sign is also included	**Possible**	**Probable**		**Proven**

Table 8. Status of Invasive Fungal Disease at Day 7 for Participants with Lower Respiratory Tract Disease (LRTD)

Host Factors	Clinical Features "Lower Respiratory Tract Disease"	Mycological Criteria			
		No positive culture		Positive culture or microscopy (cytology/histology) of hyphal forms	
		Serum testing negative for GM[2]	Serum/plasma testing positive for GM[2] or Positive BAL GM[2]	Nonsterile site (i.e. sputum, BAL, or bronchial brushing specimen)	Sterile site (i.e. transbronchial biopsy or open lung biopsy) or with associated tissue damage
specific monoclonal antibodies or immunosuppressive nucleoside analogs) during the past 90 days **OR** treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib **OR** inherited severe immunodeficiency **OR** acure graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids **OR** chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis) **OR** Severe influenza (or other severe viral pneumonia, such as coronavirus disease 2019 [COVID-19]), liver disease, malnutrition, severe burns, diabetes					

1. Only allogeneic BMT / HSCT or neutropenic participants who have non-specific focal infiltrates, confirmed by CT scan (or HRCT) or MRI, and have mycological evidence of disease will be classified as probable.
2. Applicable to *Aspergillus* species only.

Table 9. Status of Invasive Fungal Disease at Day 7 for Participants with Non-Lower Respiratory Tract Disease (NLRTD)

Host Factors	Clinical Features	Mycological Criteria			
		No positive culture		Positive culture or microscopy (cytology/histology) of hyphal forms	
		Serum testing negative for GM[1]	Serum/plasma testing positive for GM[1] or Positive CSF GM[1]	Non-sterile site	Sterile site (i.e. brain biopsy or blood culture) or with associated tissue damage
Neutropenia (ANC < 0.5 x 10^9/L[<500/mm^3]) temporally related to the onset of fungal disease **OR** hematologic malignancy **OR** Receipt of an allogeneic hematopoietic stem cell transplant **OR** Receipt of a solid organ transplant **OR** prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3mg/kg corticosteroids for ≥ 3 weeks in the past 60 days. **OR** treatment with other recognized T-cell immunosuppressants (such as calcineurin inhibitors, tumor necrosis factors-α blochers, lymphocyte-specific monoclonal antibodies or immunosuppressive nucleoside analogs) during the past 90 days	**Sino-Nasal Infection** Imaging (CT or MRI) showing **sinusitis PLUS** at least one of the following: - Acute localized pain (including pain radiating to eye) - Nasal ulcer, black eschar - Extension from the paranasal sinus bony barriers, including into the orbit. **CNS infection** At least one of the following: - Focal lesions on imaging, or - Meningeal enhancement on CT or MRI.	**Possible**	**Probable**		**Proven**[2]

Table 9. Status of Invasive Fungal Disease at Day 7 for Participants with Non-Lower Respiratory Tract Disease (NLRTD)

Host Factors	Clinical Features	Mycological Criteria			
		No positive culture		Positive culture or microscopy (cytology/histology) of hyphal forms	
		Serum testing negative for GM[1]	Serum/plasma testing positive for GM[1] or Positive CSF GM[1]	Non-sterile site	Sterile site (i.e. brain biopsy or blood culture) or with associated tissue damage
OR treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib **OR** inherited severe immunodeficiency **OR** acure graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids **OR** chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis) **OR** Severe influenza (or other severe viral pneumonia, such as coronavirus disease 2019 [COVID-19]), liver disease, malnutrition, severe burns, diabetes					

1. Applicable to *Aspergillus* species only.
2. Blood cultures that yield a mold (eg, *Fusarium* species) in the context of a compatible infectious disease process. In an immunocompetent host, positive blood culture that yields *Aspergillus* species is to be considered a contaminant and is not eligible for enrollment.

Proven and Probable Mucormycosis

Mucormycosis will be proven by histopathology or growth from sterile body sites. Probable mucormycosis includes growth from respiratory specimens in patients with pneumonia and no alternative cause.

Onset of clinical symptoms and/or physical findings within approximately 2 weeks prior to the first administration of study medication defines an acute or subacute infection.

10.10. Appendix 10: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 1 (04 Nov 2022)

Overall Rationale for the Amendment: Clarifications for treatment duration and protocol required data for defined visits are added to study design. The protocol is updated to fit for microbiological assessment based on comments from Center for Drug Evaluation (CDE) and to keep consistency throughout the protocol.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 3. Objectives, Endpoints, and Estimands	Estimands updates to The incidence rates of TEAEs by SOC and PT will be summarized without regard to adherence to the isavuconazole treatment and use of prohibited medication.	Updated according to SciOps comment.	Substantial
Section 8.2.3. GM Antigen	Added statement: "In addition, samples obtained for GM antigen assay (or collected any time while participants with probable, proven or possible Aspergillus are still receiving study drug) will be shipped to a central laboratory. BAL for GM specimens may be processed locally, but an additional aliquot of BAL fluid will be collected for shipment to the central laboratory as well.	Added to enable evaluation of PK/PD for clinical isolates as required by HA. Mycological testing for eligibility will be based on the local lab. A central reference lab will be used for in-vitro testing and reporting.	Substantial
Section 8.2.4. Bronchoscopic Assessment of Invasive Fungal Infection	Clarified that the culture and histology/cytology will be performed using local laboratories for eligibility assessment. If samples are obtained at baseline and up to Day 7, an additional sample will be stored for shipping to the central reference laboratory for mycological testing.	Changes are made to add a central reference lab performing in-vitro PK/PD analysis per HA request.	Substantial
Section 8.2.5 Mycological Assessment of Invasive Fungal Infection	Updated text to clarify assessment for eligibility will be based on results generated in the local laboratory at screening and by the central lab for mycological response evaluation. Schedules and guidelines for local and center assessments are also updated.	Changes are made to enable evaluation of PK/PD for clinical isolates as required by HA. Mycological testing for eligibility will be based on the local lab. A central reference lab will be used for in-vitro testing and reporting.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 9.1.1. Estimands and Section 9.1.1. Estimand for treatment emergent adverse event (TEAE)	Added Section 9.1.1 Estimands and 9.1.1.1 Estimand for treatment emergent adverse event (TEAE): "The incidence rates of TEAEs by SOC and PT will be summarized without regard to adherence to the isavuconazole treatment and use of prohibited medication."	Updated according to SciOps comment.	Substantial
Section 1.1. Synopsis/ Section 4.1 Overall Design	Added statements: "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)." "For the clinical evaluation, investigators will need to review/evaluate the following: categorization of the diagnosis of IFD at enrollment (including data up to Day 7 as relevant); the participant's overall response, clinical, radiological and mycological responses at Day 42, at EOT and Day 84 (or Day 180 for participants with IM); and whether or not the participant has LRTD." (added in Section 4.1)	To clarify the study visit schedule should be followed during hospitalization, as well as in outpatient. Clarify that EOT may occur before the Day42 or Day84 visit. Clarify that the treatment assessment will be performed by the investigators.	Nonsubstantial
Section 1.1. Synopsis/ Section 4.1 Overall Design	Updated content: Original text: Participants fulfilling the criteria for "**possible**" IFD will be eligible for enrollment; efforts of further IFD classification as "**probable**" or "**proven**" by culture and histology/cytology antigen (*Aspergillus* species only) should be performed during the screening period. However, assessments performed up to 7 days after the first administration of study intervention may be used to confirm the diagnosis of IFD. Updated text:	To clarify the culture and histology/ cytology antigen testing are applicable for both *Aspergillus* species and *Mucorales* species.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	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 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.		
Section 1.1. Synopsis	Follow-up period in Study Arms and Duration is updated to 4 weeks ±7 days after last dose of study intervention.	To keep the consistency throughout the protocol.	Nonsubstantial
Section 1.1. Synopsis/ Section 5.1 Inclusion Criteria	Updated to add guidelines EORTC/MSG (version 2019) and EORTC/MSG ICU (version 2021) to Disease Characteristics. Text updated from "participants must have a body weight >40 kg at screening" to "participants with a body weight >40 kg at screening" in Section 5.1.	Added EORTC/MSG ICU (version 2021) guideline as reference for the diagnosis. alignment of wording between sections.	Nonsubstantial
Section 1.1. Synopsis/ Section 6.1.1 Administration	Added statements: "The switch to oral therapy should be made as early as possible from Day 3 onwards." "Participants will be treated until they reach a defined discontinuation criterion (see Section 7.1), up to a maximum of 84 days (up to 180 days for participants with IM)." "Participants who are considered by the investigator to have experienced a successful overall outcome will continue treatment for a minimum of 7 days after resolution of all clinical symptoms and physical findings. The maximum treatment period of 84 days (180 days for participants with IM) must not be exceeded." "Non-study systemic antifungal medication is only allowed after the Day 42 visit, unless the participant has	To clarify the discontinuation criteria should follow the specific section and to keep consistency throughout the protocol, also to clarify the treatment duration for a certain participant.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	failed treatment with study medication prior to the Day 42 visit."		
Section 1.3 Schedule of Activities	Visit Window for Day 84 and Post treatment follow is changed to ±7 days. Anti-infective history is specified to 4 weeks prior. Added data collection dates for assessments of physical examination (on Day 1), weight/height (on Day 42 and on EOT or discontinuation) and neutropenic status/ANC (at screening). Corresponding changes are made in section 8.2 and section 8.3 accordingly. For prior medication and pregnancy test footnotes 'c' and 'd' are added to the screening visit, respectively. For bronchoscopic assessment, footnote 'l' is removed and replaced with footnote 'o' for visits on Day 1, Day 2, Day 3, and Day 7. For mycological assessment, footnote 'l' is removed for all visits except for visits ongoing from Day 1, to Day 28. "EOT, Day 42, Day 84 and Follow-up assessments are required for all participants. Participants with a successful overall response are required to return for all three visits" and "A Follow-up visit will be performed 4 weeks (±7d) after last dose of isavuconazole administration." is added to footnote 'k'. Follow-up visit for assessment of Radiology assessment and Bronchoscopic assessment are removed.	Updated to keep consistency throughout the protocol.	Nonsubstantial
Section 1.3 Schedule of Activities/ Section 8.2.3. Serum GM Antigen	Footnote 'r' is added to the SoA, GM antigen assessment will be conducted at screening, and if clinically indicated, from Day 1 to Day 7 for participants with IA only. Updated Content Original text: Serum GM antigen will be drawn at Screening, and on Day 1, Day 3, Day 7, and through EOT, if clinically indicated, for participants with IA only. Updated text: GM antigen will be tested at Screening. If clinically indicated, it	Updated to keep consistency throughout the protocol in accordance to Section 8.2.3. and allow flexibility on the date of collection GM antigen from Day1 to Day7 according to the timepoint of baseline GM antigen testing.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	also can be tested during Day 1 to Day 7, for participants with IA only.		
Section 1.3.1. Pharmacokinetic Sampling Schema	Added "For IV infusion, if the PK sampling time window has overlap with next one due to infusion period, it is suggested to collect different PK sample according to their own time window, respectively, if possible." to footnote d.	To clarify the PK sample collection requirement for study implement convenience.	Nonsubstantial
Section 4.1 Overall Design	Section 6.1.1 was updated to Section 6.1.	To correct a reference error.	Nonsubstantial
Section 5 Study Population	Removed Pfizer, and contents about enrollment approval process from the review of eligibility criteria. Original text: Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled into the study. The enrollment approval process will be initiated for a participant after an informed consent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment approval will be based on review of CRF/system data. Updated text: The investigator or qualified designee will assess and confirm that participants meet study eligibility criteria before they are enrolled into the study.	Removed to align with the clinical practice in reviewing the participants' eligibility the enrollment.	Nonsubstantial
Section 5.2 Exclusion Criteria	Added "or vaccine" to bullet 10.	To keep consistent and in line with the template.	Nonsubstantial
Section 6. Study Intervention(s) and Concomitant Therapy	Specified study intervention refers isavuconazole which is marketed in China.	To keep consistent through the protocol.	Nonsubstantial
Section 6.1.1. Administration	Added statement: "Participants will self-administer the IP at home except on days of scheduled	To clarify the dosing instruction on the day of scheduled visit.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	clinic visits or during hospitalization, where the IP will be administered in the clinic or inpatient."		
Section 6.1.1 Administration	"Participants with a successful overall outcome at EOT (prior to Day 42) must return for Day 42 and Day 84 visits, even if they are no longer under study treatment. It is recommended to keep participants on study treatment up to Day 42 if the administration of systemic antifungals as prophylaxis is anticipated after the end of study treatment. Participants with an unsuccessful overall outcome at EOT and requiring alternative systemic antifungal therapy will not be asked to return for Day 42 and/or Day 84 visits; however the survival status at these time points will be collected. A Follow-up visit will be performed 4 weeks (±7d) after last dose of isavuconazole administration."	To clarify the study visit schedule arrangement in case a participant failed for the treatment.	Nonsubstantial
Section 6.1.1.1 Reconstitution Instructions for the Injection Formulation/ Section 6.1.1.2 Dilution and Preparation Instructions for the Injection Formulation	Both section were removed.	As the product is on market, the drug handling will follow the local package insert and/or IP manual for this study. Deleting 6.1.1.1 and 6.1.2.1 as site should refer to IPM for how to prepare IP. 6.2 also stated "See the IPM or package insert for instructions on how to prepare the study intervention for administration.	Nonsubstantial
Section 6.9. Prior and Concomitant Therapy	Added "B-Cell" and "ibrutinib"	Updates were made to reflect current practice in allowed and prohibited concomitant therapy.	Nonsubstantial
Section 7.1 Discontinuation of Study Intervention	Added "as described in Section 6.9"	To clarify the available reference.	Nonsubstantial
Section 7.1 Discontinuation of Study Intervention	Added Statements "The EOT assessments should be completed prior to premature	Added to clarify the requirements on visit schedule arrangement	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	withdrawal from study medication and, whenever possible, the Follow-up visit should be performed in all participants who received at least one dose of study medication. Survival status at Day 42, Day 84, EOT and Follow-up will also be collected."	and the data collection for participants who have premature withdrawal.	
Section 7.1.1. Potential Cases of Acute Kidney Injury / Section 8.4.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs	Added mandatory language of Section 7.1.1. Potential Cases of Acute Kidney Injury and Section 8.4.7 Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs	Protocol template update.	Nonsubstantial
Section 8.2.2. Radiological Assessment of Invasive Fungal Infection	Added "or MRI".	Added to allow radiological assessment by MRI, especially for participants categorized as Non-LRTD.	Nonsubstantial
Section 8.2.5. Mycological Assessment of Invasive Fungal Infection/ Section 8.2.8. Investigator's Assessment of Overall Response	Day 126 and Day 168 are added to the timepoints for Mycological assessments for IM participants	Keep consistency with SoA	Nonsubstantial
Section 8.2.3. Serum GM Antigen	Removed statement: "Outside of these time points, mycological assessments will be performed as clinically indicated and/or in line with standard clinical management. The results of all assessments performed during the study will be recorded on the eCRF ."	Removed redundant wording and keep consistency with SoA.	Nonsubstantial
Section 8.3.2 Vital Signs	Added "ear, or forehead"	Added to fit for the clinical practices at sites.	Nonsubstantial
Section 8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting/ Section 8.4.7.	Added text defining DRE and the conditions where Death will be reported as DRE instead of SAEs, which should be recorded and reported on corresponding CRF page.	Because IFD is serious/life-threatening, and death are defined as endpoints in this protocol. So it will not be captured as	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs		endpoints. But the cause of death should be reported as AE.	
Section 9.2 Analysis Sets	"GMc" is updated to "GM"	To correct a typo	Nonsubstantial
Section 10.9 Diagnosis Criterial for Proven, Probable, or Possible IFD Caused by Aspergillus Species, Mucorales Species or Other Filamentous Fungi	Added Statements to a. HOST FACTORS "- Receipt of a solid organ transplant; - acure graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids; - treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib" "- chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis) - Severe influenza, liver disease, malnutrition, severe burns, diabetes Added Statements to c. MYCOLOGICAL CRITERIA "and it is recommended to refer to the guideline of EORTC/MSG (version 2019) or EORTC/MSG ICU (version 2021)."	Added other possible host factors for potential participants, especially who may be recruited from ICU, etc.	Nonsubstantial
Table 8 Status of Invasive Fungal Disease at Day 7 for Participants with Lower Respiratory Tract Disease (LRTD)	Removed "or sinus cavity", "No host factor" and "Ineligible." Added statements: "**OR** Receipt of a solid organ transplant **OR** acure graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids OR treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib"	Corrected since the table is for LRTD category, and added applicable host factors for LRTD.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	"OR chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis) OR Severe influenza, liver disease, malnutrition, severe burns, diabetes"		
Table 9 Status of Invasive Fungal Disease at Day 7 for Participants with Non-Lower Respiratory Tract Disease (NLRTD)	Removed "No host factor" and "Ineligible. Added Statements: "**OR** Receipt of a solid organ transplant **OR** acure graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids OR treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib" "OR chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis) OR Severe influenza, liver disease, malnutrition, severe burns, diabetes"	Added applicable host factors for NLRTD.	Nonsubstantial

10.11. Appendix 11: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ABPA	allergic bronchopulmonary aspergillosis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AmB	amphotericin B
AML	acute myeloid/myelogenous leukemia
ANC	absolute neutrophil count
AUC	area under the curve
AV	atrioventricular
BAL	bronchoalveolar lavage
β-hCG	β-human chorionic gonadotropin
BLQ	below the limit of quantification
BP	blood pressure
bpm	beats per minute
BMT	bone marrow transplant/transplantation
BT	body temperature
[redacted]	
BUN	blood urea nitrogen
CDE	Center for Drug Evaluation
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence interval
CK	creatine kinase
C_{max}	maximum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSF	Cerebrospinal fluid
CSR	clinical study report
CT	computed tomography; clinical trial
DBP	diastolic blood pressure
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DRC	Data Review Committee
DRE	disease-related event
EC	ethics committee
ECG	electrocardiogram
EDB	exposure during breastfeeding

Abbreviation	Term
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EORTC/MSG	European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group
EOT	end of treatment
ESCMID/ECMM	European Society of Clinical Microbiology and Infectious Diseases/European Confederation of Medical Mycology
ESRD	end stage renal disease
FSH	follicle-stimulating hormone
FU	follow up
GGT	gamma-glutamyl transferase
GCP	Good Clinical Practice
GI	gastrointestinal
GM	galactomannan
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HRCT	high resolution computed tomography
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplantation
IA	invasive aspergillosis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IFD	invasive fungal disease
IM	invasive mucormycosis
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IPA	invasive pulmonary aspergillosis
IPAL	investigational product accountability log
IPM	investigational product manual
IRB	institutional review board

Abbreviation	Term
ITT	intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	intravenous
KM	Kaplan-Meier
LFT	liver function test
LPD	Local Product Document
LRTD	lower respiratory tract disease
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MIC	minimum inhibitory concentration
myITT	mycological intent-to-treat IA
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
NA	not applicable
NIMP	noninvestigational medicinal product
NLRTD	non-lower respiratory tract disease
PCD	primary completion date
PCR	Polymerase Chain Reaction
PD	pharmacodynamic(s)
PES	polyethersulfone
PI	principal investigator
PK	pharmacokinetic(s)
PO	by mouth; oral(ly)
popPK	population pharmacokinetic
PP	per protocol
PR	pulse rate
PT	prothrombin time [also used in the document as “preferred term”. Avoid use of the same abbreviation for 2 terms.]
PTA	probability of target attainment
PVC	premature ventricular complexes
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia’s formula
qual	qualitative
RA	regulatory agency
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SCr	Serum Creatinine

Abbreviation	Term
SD	standard deviation
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
t 1/2	half-life
TBili	total bilirubin
TEAE	treatment-emergent adverse event
CCI [redacted]	
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	Woman/ women of childbearing potential

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