CLINICAL STUDY PROTOCOL

Title:	A double-blind, randomized, placebo-controlled study to assess the safety and efficacy of nebulized PC945 when added to systemic antifungal therapy for the treatment of refractory invasive pulmonary aspergillosis (OPERA-T Study)
Short Title:	Safety and efficacy of PC945 in combination with other antifungal therapy for the treatment of refractory invasive pulmonary aspergillosis
Protocol Number:	PC_ASP_006
Original Protocol Date:	14 September 2021
Amendment 1	16 March 2022
Amendment 2	21 February 2024
Amendment 3	10 June 2024
Amendment 4	30 October 2024
Amendment 5	29 September 2025
IND number:	146173
NCT number:	NCT05238116
EudraCT number: (former application number prior to CTR transition)	2021-004554-32
EU CT number:	2024-511281-36
Phase:	3
Compound Identifier:	PC945
Sponsor:	Pulmocide Ltd. 44 Southampton Buildings London, WC2A 1AP

Company
Pulmocide Ltd.

SPONSOR SIGNATURE PAGE

INVESTIGATOR SIGNATURE PAGE

Protocol Title:	A double-blind, randomized, placebo-controlled study to assess the safety and efficacy of nebulized PC945 when added to systemic antifungal therapy for the treatment of refractory invasive pulmonary aspergillosis (OPERA-T Study)
Protocol Number:	PC_ASP_006
Original Protocol Date:	14 September 2021
Amendment 1	16 March 2022
Amendment 2	21 February 2024
Amendment 3	10 June 2024
Amendment 4	30 October 2024
Amendment 5	29 September 2025

I agree to conduct the study in accordance with the requirements of this protocol, the Study Reference and Pharmacy Manuals, and with the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (2013) including all amendments.

Investigator Name and Qualifications: _____

Investigator Signature	Date
Investigator Affiliation	Site Number

PROTOCOL SUMMARY

Rationale

The low systemic bioavailability and high degree of lung penetration and retention of nebulized PC945 could make it a suitable antifungal agent to be used in combination with systemic antifungal therapy for the treatment of invasive pulmonary aspergillosis (IPA) in order to improve treatment success rates without increasing the safety risk. The main objective of this study is therefore to assess the efficacy, safety and tolerability of PC945 when administered in combination with systemic antifungal therapy for the treatment of refractory IPA.

Objectives

Primary Objective

To assess the efficacy of nebulized PC945 in combination with systemic antifungal therapy for the treatment of refractory IPA

Secondary Objective

To assess the safety and tolerability of nebulized PC945 in combination with systemic antifungal therapy for the treatment of refractory IPA

CCICCCICCICCI

Primary Efficacy Outcome

Day 84 favorable overall response: being alive and having a complete or partial overall response at Day 84, as assessed by the Data Review Committee (DRC)

Secondary Efficacy Outcomes

- Favorable overall response: having a favorable response at any time during the 84-day (12-week) treatment phase. This endpoint will be based upon observing a complete or partial response at any time during the 84-day (12-week) treatment phase where the survival component is not included as part of the response definition

- Time to favorable overall response: the time from randomization to the first favorable overall response at any time during the 84-day (12-week) treatment phase

- All-cause mortality

Safety and Tolerability Outcomes

The safety and tolerability outcomes, which will be detailed in the Statistical Analysis Plan, will include, but will not be limited to, the following:

- Adverse events, changes in vital signs, laboratory data, and electrocardiograms (ECGs)

Study Design

This Phase 3, double-blind, randomized, placebo-controlled, parallel-group, multi-center, international study will assess the efficacy, safety, and tolerability of nebulized PC945 when added to systemic antifungal therapy for the treatment of refractory IPA.


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI

Study Population

This study will randomize approximately 123 subjects diagnosed with refractory invasive pulmonary aspergillosis. CCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCICCI

Inclusion Criteria

Potential study subjects must satisfy all the following inclusion criteria to be eligible to enter the study:

1. Subject is ≥18 years
2. Subject has provided informed consent in accordance with local legislation and guidelines which includes permission to retrieve pre-specified data from their historic medical records
3. Subject is willing to perform and comply with the study visits, laboratory assessments, and other study-related procedures

CCICCI

6. Subject has proven or probable IPA according to the modified 2019 EORTC/MSGERC consensus definitions (Table 8 and Table 9 in Appendix 16.6.1). If the subject is a lung transplant recipient and the diagnosis of proven or probable IPA is not confirmed using the modified 2019 EORTC/MSGERC criteria, the diagnosis of proven or probable IPA can be confirmed using the 2010 ISHLT consensus statements for the definitions of infections in cardiothoracic transplant recipients (Table 10, Table 11 and Table 12 in Appendix 16.6.2)
7. Subject's IPA has failed to respond to adequate antifungal therapy CCICCICCI CCICCI

   CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
   CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
   CCICCICCICCICCICCI

   CCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCI
   CCICCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI

Exclusion Criteria

Potential study subjects must satisfy none of the Exclusion Criteria to be eligible to enter the study.

15. Subject with a known or suspected concomitant medical condition or post-surgery complication that, in the opinion of the Investigator, may jeopardize adherence to the protocol requirements or impede the accurate measurement of efficacy or may be an unacceptable additional risk to the subject should he/she participate in the study
16. Subject who has previously received PC945
17. Subject with a known history of allergy, hypersensitivity, or any previous serious reaction to any component of the PC945 or placebo formulations
18. Subject who has recently received, is receiving or due to receive at any time during the study, an investigational medicinal agent that does not have any regulatory-approved indications. Subjects who are participating in any other trials e.g., Observational, diagnostic or using medications with an approved indication may be allowed to participate after consultation with the sponsor on an individual basis
19. [Removed]

Study Assessments

Efficacy

Safety

- Adverse events, including serious adverse events (SAEs)

Statistical Methods

Sample Size Justification

Statistical Analysis


CCICCI

TABLE OF CONTENTS

ABBREVIATIONS

ABPA	Allergic Bronchopulmonary Aspergillosis
AE	Adverse Event
AUC	Area Under the Curve
$AUC_{0-\tau}$	Area Under the Curve from time 0 to t to end of the dosing interval
AxMP	Auxiliary Medicinal Products
BAL	Bronchoalveolar Lavage
Bio-Rad Platelia	Bio-Rad Platelia Aspergillus enzyme immunoassay
CI	Confidence Interval
CL/F	Apparent clearance
C_{max}	Maximum observed plasma Concentration
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTIS	European Medicine Agency's Clinical Trial Information System
C_{trough}	Trough concentration
CYP	Cytochrome
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic Acid
DRC	Data Review Committee
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELF	Epithelial Lining Fluid
ELISA	Enzyme-Linked Immunosorbent Assay
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume over one second
FiO2	Fraction of inspired Oxygen
GCP	Good Clinical Practice
GVHD	Graft-Versus-Host Disease
HSCT	Hematopoietic Stem Cell Transplantation
HRCT	High Resolution Computed Tomography
IA	Invasive Aspergillosis
IB	Investigator's Brochure
IC50	50% maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IMMY LFA wACR	IMMY sōna Aspergillus Galactomannan Lateral Flow Assay with an automated cube reader
IP	Investigational Product
IPA	Invasive Pulmonary Aspergillosis

IRB	Institutional Review Board
IRIS	Immune Reconstitution Inflammatory Syndrome
ISHLT	International Society for Heart and Lung Transplantation
ITT	Intent To Treat
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency (of the UK)
MIC	Minimum Inhibitory Concentration
MIC_{90}	Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms. (90^{th} percentile MIC value)
miRNA	Micro Ribonucleic Acid
mITT	Modified Intention To Treat
MSc	Member State concerned
MSGERC	Mycoses Study Group Education and Research Consortium
ODI	Optical Density Index
PaO2	Partial pressure of Oxygen
PCR	Polymerase Chain Reaction
Ph. Eur.	European Pharmacopeia
PK	Pharmacokinetics
PV	Pharmacovigilance
qPCR	quantitative Polymerase Chain Reaction
REC	Research Ethics Committee
Ro	Accumulation ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard Of Care
SSRC	Sample Size Recalculation
STAT	Signal Transducer and Activator of Transcription
SUSAR	Suspected Unexpected Serious Adverse Reaction
T_{max}	Time to maximum concentration
$t_{1/2}$	Half-life
USP-NF	United States Pharmacopeia-National Formulary
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

The incidence of fungal infections and diseases has increased substantially over the past two decades and invasive forms are a leading cause of morbidity and mortality, especially among immune-suppressed patients. Aspergillosis (infection caused by the *Aspergillus* species of fungi) results in a range of disorders either directly from the infection, or by triggering an allergic response. *Aspergillus* can infect a variety of organs, though the respiratory system is the site most commonly involved.

Fungal spores are ubiquitous in the environment and the small size of *Aspergillus* spores facilitates inhalation and deposition in the distal airways [Fairs, 2012; Pasupneti, 2017]. In healthy individuals the spores are cleared by a combination of mucociliary action and phagocytosis by macrophages and neutrophils. However, in patients with impaired mucociliary function, retained mucus or compromised airways, inhaled spores can persist and spread within the airways [Takazono, 2017]. Corticosteroids or immunosuppressant therapies may also be a risk factor for aspergillosis if they impair macrophage and/or neutrophil function. The temperature and moist environment in the airways provide ideal conditions for germination and the establishment of infection [Takazono, 2017].

Invasive aspergillosis (IA) occurs in 4% of patients undergoing remission induction chemotherapy for hematological malignancies, in 9% allogeneic hematological stem cell transplant recipients [Van de Peppel, 2018] and in 2-8% of lung transplant recipients [Samanta, 2020; Baker, 2020; Ullmann, 2018], despite the use of antifungal prophylaxis in these patient groups. The incidence is lower in other solid organ transplant recipients such as those who have received hepatic, cardiac, pancreatic or renal transplants [Ullmann, 2018]. Invasive aspergillosis also occurs in patients treated with prolonged high dose corticosteroids, or other immunosuppressant, those with chronic obstructive pulmonary disease, lung cancer, hepatic cirrhosis or critically ill patients requiring admission to intensive care following influenza or of the coronavirus disease (COVID-19) infections [Ullmann, 2018; Verweij, 2020; Williams, 2007; Thompson, 2020].

Aspergillus is a particularly important opportunistic infection in lung transplant recipients [Pasupneti, 2017; Husain, 2019]. Post-transplant immunosuppressive therapy facilitates progression of infection by impairing the required immune response to prevent tissue invasive disease. *Aspergillus* colonization or infection occurs post-lung transplant in approximately 30-50% of patients [Solé, 2005; Husain, 2016], but is more common in patients transplanted for cystic fibrosis, who are often colonized with the organism pre-transplant [Husain, 2016; Nunley, 2002] Tissue-invasive infection occurs in the first-year post-transplant in 2-8% of patients [Samanta, 2020; Baker, 2020; Ullmann, 2018]. In the first 3 months post-transplant this presents as infection at the bronchial anastomotic site or as a more widespread tracheobronchitis which may result in tracheal stenosis, necrosis, rupture of the anastomosis, bronchial abscess or pneumothorax [Pasupneti, 2017;

Nunley, 2002]. *Aspergillus* pneumonia can occur at any time post-transplant. *Aspergillus* colonization is also associated with an increased risk of bronchiolitis obliterans syndrome.


CCICCI
CCICCI
CCICCI
CCICCI

1.1.2. Non-clinical Studies

A summary of the non-clinical studies is provided below. Please refer to the IB for more information.


CCICCI
CCICCI
CCICCI
CCICCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI


CCICCI
CCICCI
CCICCI
CCICCI

1.1.4. Study Conduct

This study will be conducted in accordance with the requirements of the Clinical Study Protocol; all supporting study procedure manuals; and in accordance with the Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013); the International Council on Harmonization harmonized tripartite guideline regarding Good Clinical Practice (E6 R2, November 2016); the EU Clinical Trials Regulation 536/2014 and Good Clinical Practice (2005/28/EC) where applicable; the US 21 Code of Federal Regulations where applicable; including any amendments to these regulations; and applicable local laws and regulations.

1.2. Rationale

CCI CCICCICCICCI

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI The main objective of this study is therefore to assess the efficacy, safety and tolerability of PC945 when administered in combination with systemic antifungal therapy for the treatment of refractory IPA.

1.2.2. Rationale for the Study Population

1.2.2.1. Subjects with Invasive Pulmonary Aspergillosis

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI


CCICCI
CCICCI
CCICCI
CCICCI


CCI
CCI
CCI
CCI


CCICCI
CCICCI
CCICCI
CCICCI


CCI
CCI
CCI

1.3. Potential Risks and Benefits to Human Subjects

The safety pharmacology and toxicology observations generated from the preclinical studies of PC945 indicate that the risks associated with its administration at the proposed clinical doses are likely to be minimal. Following inhaled delivery, PC945 plasma concentrations are hundreds to thousands fold lower than concentrations targeted for treatment or prophylaxis with systemically administered azoles.

Given that no safety alerts have been identified at the time of protocol finalization, no stopping criteria for PC945 are specified in this protocol. If any safety-related issues arise and in the opinion of the Investigator further dosing could put the subject at risk, subjects may be withdrawn from dosing. The Investigator may discuss any issues with the Sponsor before withdrawing a subject from dosing provided that this does not delay any medical decisions, in particular, in the event of an emergency situation.

The potency of PC945 against a range of *Aspergillus* species, which is the fungal organism most commonly associated with post lung transplant colonization and invasive pulmonary disease, has been demonstrated. The clinical dose selected for this study is expected to exceed the MIC_{90} for the most common *Aspergillus* strains. In addition to receiving nebulized PC945 or matching placebo, all subjects will also be treated with background

SOC antifungal therapy which may be adjusted by the Investigator based on the clinical response of the subject. Therefore, no subject will go untreated in this study.

2. OBJECTIVES

2.1. Primary Objective

To assess the efficacy of nebulized PC945 in combination with systemic antifungal therapy for the treatment of refractory IPA.

2.2. Safety Objective

To assess the safety and tolerability of nebulized PC945 in combination with systemic antifungal therapy for the treatment of refractory IPA.

3. ENDPOINTS

3.1. Primary Efficacy Outcome

Day 84 favorable overall response: being alive and having a complete or partial overall response at Day 84, as assessed by the DRC.

3.2. Secondary Efficacy Outcomes

- Favorable overall response: having a favorable response at any time during the 84-day (12-week) treatment phase. This endpoint will be based upon observing a complete or partial response at any time during the 84-day (12-week) treatment phase where the survival component is not included as part of the response definition.
- Time to favorable overall response: the time from randomization to the first favorable overall response at any time during the 84-day (12-week) treatment phase

- All-cause mortality

3.3. Exploratory Efficacy Outcomes

3.4. Safety and Tolerability Outcomes

The safety and tolerability outcomes, which will be detailed in the Statistical Analysis Plan, will include, but will not be limited to, the following:

- Adverse events, changes in vital signs, laboratory data, and ECGs

4. STUDY DESIGN

4.1. Summary of Study Design


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI

4.1.2. Randomization and Blinding

This is a randomized, double-blind, active-controlled, two-arm, parallel-group study. Subjects who have met all of the inclusion criteria and none of the exclusion criteria will be allocated to one of two strata, those with a high risk and those with a low risk of mortality. Subjects will be allocated to PC945 or placebo in a 2:1 ratio using permuted blocks within strata. Randomization will be conducted using an interactive web response system (IWRS) system.

The high-risk stratum will include subjects with any of one the following underlying diseases:

- Active malignancy at study entry
- Acute leukemia
- Recipient of an allogeneic HSCT
- Absolute neutrophil count <500 cells/µL for >10 consecutive days
- Corticosteroid use >0.3 mg/kg prednisone equivalent >3 consecutive weeks in the 60 days preceding the diagnosis of IPA
- Second lung transplant
- Signs of organ rejection

The low-risk stratum will include all other subjects.

The Investigator, the Sponsor, its designees, and the subject will not know the allocation of study treatment. [redacted] In addition, whenever study drug is administered in the clinic or in hospital for inpatient subjects, study medication will be prepared and administered to the subject by a nurse, pharmacist, or other designated person who will not have any influence on the safety and efficacy assessments. Similarly, such a nurse, pharmacist, or designated person will perform the drug accountability checks on dispensed and returned vials. These site personnel will be called the 'unblinded' site personnel. Each site will develop a Site Blinding Plan which will outline the site's specific strategy for maintaining the study blind.

4.1.2.1. Emergency Unblinding

Under usual conditions the study blind will not be broken until all subjects have completed the study and the database is locked. In other conditions, the blind should only be broken in cases of emergency where knowledge of the study treatment allocation would dictate the treatment of a subject. In these instances, the Investigator may elect to unblind a subject's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. The Investigator may discuss the particulars of the case with

the Medical Monitor. Once the decision to unblind a subject's treatment assignment has been made the designated study site personnel may break the treatment code for that subject by accessing the Web-based response system via password-protected access. The reason for breaking the code must be recorded in the subject's source documents.

4.1.3. Duration of Subject Participation

The total duration of subject participation from Day 1 (day of first dose of study drug) will be 112 days (16 weeks) divided into two periods: the Treatment Phase will last 84 days (12 weeks) from randomization and the Safety Follow-up Phase will last 28 days (4 weeks) from Day 84 to Day 112. The Day 112 visit is the last visit in the study.

4.2. Stopping Rules

4.2.1. Study Stopping Rules

Since no significant or known safety risks have been identified for nebulized PC945 based on the available preclinical and clinical safety data, no pre-specified safety stopping rules have been defined for this study. However, the safety of the subjects will be monitored on an ongoing basis in a blinded manner by the Investigator and the safety data will be reviewed regularly in a blinded manner by the Sponsor's and Clinical Research Organization's (CRO's) designated Medical Monitor(s). In addition, unblinded safety reviews will be performed by the DSMB. Refer to Section 10 for more information on subject withdrawal.

The study will be stopped at any time if an unfavorable risk-benefit assessment is reached based on an ongoing assessment of data from new nonclinical studies, from ongoing clinical studies, and from adverse drug reaction reports received from the Specials Program. A variety of reasons may lead either the Sponsor or a regulatory agency to terminate the study early, in which case all subjects would be withdrawn from the study.

4.2.2. Rules for Withdrawal of Subjects from the Study

The study has no stopping rules that will require withdrawing individual subjects from the study. Please refer to Section 10.2 for the Subject Withdrawal Criteria.

5. STUDY POPULATION

The eligibility criteria for enrolling subjects in this study are provided in Sections 5.1, 5.2, and 5.3. If there is any query relating to the inclusion or exclusion criteria described in these sections, the Investigator will discuss these with the Sponsor medical representative before enrolling a subject in the study. All subjects enrolled in the study must fully satisfy all eligibility criteria.

5.1. Number of subjects

This study will randomize approximately 123 subjects diagnosed with refractory IPA. CCI [redacted]

5.2. Inclusion criteria

Potential study subjects must satisfy all the following inclusion criteria to be eligible to enter the study:

1. Subject is ≥18 years
2. Subject has provided informed consent in accordance with local legislation and guidelines which includes permission to retrieve pre-specified data from their historic medical records
3. Subject is willing to perform and comply with the study visits, laboratory assessments, and other study-related procedures

[redacted]

6. Subject has proven or probable IPA according to the modified 2019 EORTC/MSGERC consensus definitions (Table 8 and Table 9 in Appendix 16.6.1). If the subject is a lung transplant recipient and the diagnosis of proven or probable IPA is not confirmed using the modified 2019 EORTC/MSGERC criteria, the diagnosis of proven or probable IPA can be confirmed using the 2010 ISHLT consensus statements for the definitions of infections in cardiothoracic transplant recipients (Table 10, Table 11, and Table 12 in Appendix 16.6.2)
7. Subject's IPA has failed to respond to adequate antifungal therapy [redacted]


CCI
CCI
CCI
CCI


CCICCI
CCICCI
CCICCI
CCICCI

5.3. Exclusion criteria

Potential study subjects must satisfy none of the Exclusion Criteria to be eligible to enter the study.

15. Subject with a known or suspected concomitant medical condition or post-surgery complication that, in the opinion of the Investigator, may jeopardize adherence to the protocol requirements or impede the accurate measurement of efficacy or may be an unacceptable additional risk to the subject should he/she participate in the study
16. Subject who has previously received PC945
17. Subject with a known history of allergy, hypersensitivity, or any previous serious reaction to any component of the PC945 or placebo formulations
18. Subject who has recently received, is receiving or due to receive at any time during the study, an investigational medicinal agent that does not have any regulatory-approved indications. Subjects who are participating in any other trials e.g., Observational, diagnostic or using medications with an approved indication may be allowed to participate after consultation with the sponsor on an individual basis
19. [Removed]

6. STUDY ASSESSMENTS AND PROCEDURES

CCICCICCICCICCICCICCI

6.1. Screening

The subject will be given the patient information to read and asked to sign the informed consent form (ICF). No study-specific assessments may be performed prior to the subject signing the study ICF.

Once informed consent has been obtained, the following screening information must be collected prior to randomization:


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI


CCICCI
CCICCI
CCICCI
CCICCI


CCI
CCI
CCI
CCI


CCICCI
CCICCI
CCICCI
CCICCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI

The Early Termination Visit is only required for subjects who completely withdraw consent for participation in the study and in such cases this visit should be conducted on the day of withdrawal or as soon as possible after the last dose of the blinded study medication. The Early Termination Visit is not appropriate for subjects who discontinue the blinded study medication, or decline specific assessments but otherwise continue in the study (including for safety follow-up).

6.5. Phone Contacts (Days 7, 21, 35, 49, 63, and 77)

Phone visits will be conducted at Days 7, 21, 35, 49, 63, and 77 with visit windows of +/- 3 days. If the subject is hospitalized, these visits may be performed at the bedside and by reviewing the subject charts.

At these study visits, the following information will be collected from the subject or from the subject's charts and will be recorded in the eCRF:

6.6. Day 112 Safety Follow-up Visit

A Safety Follow-up Visit will be conducted at Day 112. A visit window of +7 days is permitted.

At the Day 112 Visit, the following procedures will be performed:


CCI
CCI
CCI
CCI

6.8. Safety Assessments

Safety procedures will be conducted according to the Table of Events Schedule (Appendix 16.1).

All AEs (refer to Section 11.1 for definition of AEs) observed during the study must be recorded as such in the subject eCRF and reported to the Sponsor on the SAE Reporting Form (refer to Section 11.2 for recording and reporting procedures).

6.8.1. Vital Signs

The following vital signs will be recorded at the Baseline/Day 1 visit (pre-first dose of study drug) and at the Day 14, Day 28, Day 42, Day 56, Day 70, Day 84/Early Termination, and Day 112 Safety Follow-Up Visits:

- CCICCICCICCICCICCICCICCICCI
- CCICCICCICCICCICCICCICCICCICCICCI
- CCICCICCICCICCICCICCICCICCICCICCICCICCICCI
- CCICCICCICCICCICCICCICCICCICCICCI
- CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
  CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
  CCICCICCICCICCICCICCI

6.8.2. Brief Lung/Respiratory Exam

A brief lung or respiratory exam must be performed post study drug administration for all subjects at Baseline/Day 1 (post first dose of study drug), 14, 28, 42, 56, 70, and 84 visits as well as at the safety follow-up visit at Day 112. CCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCICCI

- CCICCICCICCICCICCICCICCICCICCICCICCICCICCI
- CCICCI
- CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCI
- CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCI(CCI

CCICCI
CCICCI


CCI
CCI
CCI
CCI

[redacted]

6.8.5.3. Additional Exploratory Laboratory Analyses

[redacted]

6.8.6. Pregnancy Testing

As part of the screening process, a urine pregnancy test performed either at the bedside or by the local laboratory or a serum pregnancy test performed by the local laboratory will be used to confirm that a female subject of childbearing potential is not pregnant at the time of randomization. At the Day 112 Safety Follow-Up Visit or at the Early Termination Visit, a serum pregnancy test will be performed on female subjects by the central laboratory.

6.8.7. Data Capture and Sample Collection for Drug-Drug Interactions

[redacted]

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCI

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCI

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI

6.8.8. Data Safety Monitoring Board

An unblinded independent DSMB, the members of which will not serve as Investigators on the study nor on the DRC, will monitor the safety of the trial subjects. Members of the DSMB will be independent of the Sponsor and the Investigators. A DSMB Charter, which the Sponsor and the DSMB members will approve, will describe the Committee's membership, operations, and frequency of meetings. The DSMB Chairperson will review SAEs and all-cause mortality at regular intervals to be defined by the Charter; the full committee will review all-cause mortality, AEs, SAEs, and other safety data at scheduled meetings.

In addition, the DSMB will also participate in the unblinded interim analysis only for the purpose of a sample size recalculation. The DSMB will use the results of the interim analysis and the associated conditional power to recommend, in a blinded manner, whether an increase in the sample size is needed. Other than the recommended sample size, no other information will be communicated from the DSMB to the sponsor.

The DSMB will be requested to avoid conducting a review of comparative efficacy for the purpose of closing the trial early for a finding of efficacy.

CCICCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI


CCICCI
CCICCI
CCICCI
CCICCI


CCI
CCI
CCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCI
CCI
CCI
CCI

6.9.6. Data Capture on Rescue Antifungal Treatment

Data on any rescue antifungal medication initiated for the treatment of fungal disease will be recorded in the eCRF and provided to the DRC. Rescue antifungal medication is defined as either the switching of the SOC antifungal agent(s) to a new agent or the addition of another SOC antifungal agent.

6.9.7. Data Capture on Mortality

Data on mortality (date and cause of death) including autopsy information where available and status of underlying disease will be collected in the eCRF and provided to the DRC. A vital records search will be conducted for all subjects with incomplete survival data at Day 84.

6.9.8. Data Review Committee

A blinded independent DRC, the members of which will not serve as Investigators on the study, will adjudicate the following:

- Confirmation of proven or probable IPA at randomization [retrospectively, for the purpose of statistical analyses and not for study qualification])
- Confirmation of refractoriness at Baseline/Day 1 (day of first dose of study drug [retrospectively, for the purpose of statistical analyses and not for study qualification])
- Overall response to treatment with study medication and SOC antifungal therapy at Day 42, at Day 84, and at the safety follow-up Day 112 visit using available clinical, mycological, and radiological data
- Assessment of the mycological response
- Occurrence of relapse of IPA at any time in the study (including weeks 12-16) in subjects with a DRC-confirmed favorable overall response during the 12-week treatment phase

Additional details will be provided in the DRC Charter.

6.10. Pharmacokinetic Procedures

The following samples will be collected for PC945 PK analyses in all subjects (refer to the Laboratory Manual for more details on the volume of blood needed for these samples):


CCICCI
CCICCI
CCICCI
CCICCI

6.11. Health Care Resource Utilization Data

Health care resource utilization information for the duration of the subject's participation in the study will be collected from the subject's chart and will be recorded in the eCRF at the final visit (i.e., either at the Day 112 or at the Early Termination Visit). These data may be used for future healthcare resource utilization and pharmaco-economic analyses. If these analyses are conducted, the data will be summarized in a separate report outside of the Clinical Study Report. In addition to the information collected on bronchoscopies and radiological procedures (for example chest CT scan), the following information regarding hospitalizations will be collected:

- Date of admission, date of discharge and reason for each hospital admission (including the hospitalization for a transplant procedure prior to enrollment)
- Number and duration of, and reason for, ICU admissions

- Number of, and reason for, bronchoscopies
- Number of, and reason for, CT chest scans (excluding the HRCT/regular CT scans required by the protocol)
- Use of rescue antifungal medication (reason for use and name and duration for each medication)
- Duration of parenteral antifungal treatment

7. LIFESTYLE AND/OR DIETARY RESTRICTIONS

The protocol does not require any specific lifestyle or dietary restrictions.

8. STUDY MEDICATION AND STANDARD OF CARE REFERENCE MEDICATION

8.1. Description of Study Medication

The Sponsor will be responsible for the supply of the IP/placebo for this study. A description of the study medication is provided in Table 6.

Table 6 Physical Description of IP and Placebo

8.2. Dosage

8.2.1. Dose Adjustments of Study Medication

Dose adjustments of study medication will only be permitted for a suspected drug-related AE or poor tolerability (refer to the Pharmacy Manual). If the dose of study medication needs to be reduced for any of these reasons, the frequency of the dose should be reduced CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCI

If the level of an immunosuppressant or other medication is found to be outside the target therapeutic range and a drug-drug interaction with study medication is suspected, the dose of study medication may not be changed. Only the dose or choice of the SOC antifungal agent, the immunosuppressant or other medication may be changed. Please refer to Section 6.8.7 for instructions on the need to a draw a blood sample for PK analysis if a study drug related DDI is suspected.

If adjustment to the original dose is being considered, please discuss with the study Medical Monitor.

8.3. Dose Rationale

Please refer to Section 1.2.2 of the protocol for the dose rationale.

8.4. Packaging and Labeling

Manufacturing and packaging of the study medication will be in accordance with applicable current Good Manufacturing Practice and the product will meet applicable criteria for use in humans. Labeling of study medication will follow applicable local or regional regulations.

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI

No medication can be relabeled without prior approval from the Sponsor.

8.5. Preparation and Administration

CCI

CCI

8.6. Handling and Storage

The Investigator's unblinded designee will verify and acknowledge receipt of the blinded investigational product. All study medication must be stored in a secure area with access limited to the Investigator's authorized unblinded site staff. Investigational product must be stored under appropriate conditions in accordance with the information provided in the Pharmacy Manual and on the label. Further information on the handling and storage requirements of the study medication is provided in the Pharmacy Manual.

No subject other than those enrolled in this study shall take study medication designated for this clinical trial. Study medication may not be utilized for any laboratory or animal research.

8.8. Drug Accountability

Drug accountability for study medication will be performed at the Day 14, 28, 42, 56, 70, and 84/Early Termination Visits by the designated unblinded staff not involved in other clinical assessments. Subjects will be instructed to bring all used and unused study CCICCICCI to each outpatient study visit (Day 14, 28, 42, 56, 70, and 84/Early Termination Visits) CCICCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCI All non-dispensed study medication and returned used CCICCICCICCICCI will be retained at the site for the unblinded Study Monitor's verification unless it contravenes local site policy. Please refer to the Pharmacy Manual for more information on drug accountability procedures,

Drug accountability for the dispensed, administered and returned SOC anti-mold medications is not required by the protocol, unless this is specifically required by local regulations.

8.9. Assessment of Compliance

Compliance will be assessed for all subjects to confirm that the subject is taking study medication according to the protocol instructions. Compliance will be assessed at each phone contact and in-person visit following the Baseline/Day 1 Visit (day of first dose of study drug) and will be recorded in the eCRF. All subjects will be given a subject diary to record the dates and times that study medication were taken, and if SOC mold-active medication for IPA treatment were taken or if any doses were missed and the reason for missing the dose.

For study medication, compliance will be assessed by the designated site staff considering all available information including subject diary, quantity of dispensed and returned used CCICCICCI based on the study medication dose and duration of treatment. Accountability of the used CCICCICCICCICCI must only be performed by the designated unblinded site staff. For subjects admitted to hospital, compliance of study medication will be assessed by reviewing the dispensing/administration information in the subject's charts (date of administration, time of administration, and dose taken).

For the SOC antifungal IPA treatment, compliance will be assessed by reviewing the subject diaries and by enquiring if any doses were missed by the subject and the reason for the missed dose(s). For subjects admitted to hospital, compliance will be assessed by reviewing the dispensing/administration information in the subject's charts (medication name, date of administration, and dose).

8.10. Treatment of Overdose of Study Medication

The Investigator is responsible for ensuring that subjects only receive the protocol-stipulated dose of study medication. If a subject receives a dose of study medication greater than the dose specified in the protocol for a single administration or greater than the dose specified for a 24-hour period, this must be reported to the Sponsor and recorded in the eCRF.

Subjects exposed to higher than proposed study medication doses should be observed and supported appropriately and managed using the clinical judgment of the Investigator.

Please refer to Section 11.3.3 for information on the considerations for expedited reporting following an overdose of study medication.

8.11. Occupational Safety

There are no specific occupational safety precautions for PC945.

9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Concomitant medications taken within 14 days prior to screening and/or during the study will be recorded in the subject's eCRF. The Investigator may also report other medications in the eCRF if relevant to the subject's participation in the trial. The Investigator should be informed as soon as possible about any new medication taken by a subject from the time of screening until the completion of the Early Termination or Day 112 Safety Follow-Up Visit.

9.1. Permitted Medications

Use of SOC non-mold active prophylaxis or treatment medications against yeast infections [redacted] bacterial infections (e.g., *Pseudomonas*) or viral infections (e.g., cytomegalovirus) are permitted. These medications must be recorded as concomitant medications in the eCRF.

After randomization, inhaled medications other than blinded study medication should be avoided. If an inhaled medication must be used, it must be administered approximately 60 minutes before or approximately 90 minutes after the administration of study medication.

While an inhaled bronchodilator may be used given the background medical history of the subject it may not be administered immediately prior to the administration of study medication.

If a subject develops bronchospasm after the administration of the blinded study medication, an inhaled bronchodilator may be used as soon as is clinically indicated in the opinion of the Investigator.

If the *Aspergillus* infection fails to respond or progresses during the study, and "rescue antifungal therapy" is required, the systemic mold-active SOC antifungal therapy may be changed, or additional mold-active antifungal therapy commenced as medically indicated while blinded nebulized study drug treatment continues at the Investigator's discretion. The requirement for rescue mold active antifungal therapy will be counted as a failure in the primary analysis and will also be evaluated as an exploratory endpoint.

If the systemic SOC mold active antifungal therapy results in side effects or drug-drug-interactions, the systemic mold active antifungal therapy can be changed as medically indicated while nebulized study drug treatment continues at the Investigator's discretion. [redacted]

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCI

No specific assessment has been conducted to determine if the co-administration of PC945 and a COVID-19 vaccine would lead to a DDI. Similarly, no specific assessment has been conducted to assess whether the safety and tolerability profile of PC945 could worsen or amplify any negative safety and tolerability effects of a COVID-19 vaccine, or vice versa. CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
Similarly, since the mechanism of action of PC945 does not involve stimulation of the immune system, the safety and tolerability profile of PC945 is not expected to worsen or aggravate that of a COVID-19 vaccine. Therefore, no specific instructions are being provided to separate the administration of PC945 and a concomitant COVID-19 vaccination. If administered during the study, an authorized or approved COVID-19 vaccine will be considered as a concomitant medication and should be reported.

9.2. Contraception

Female subjects of childbearing potential and male subjects with a female partner of childbearing potential must agree to either remain abstinent (see below) or use highly effective contraception throughout the study and until 30 days, after the last dose of study medication or of SOC mold-active treatment (or for 5 half-lives for those SOC antifungal agents with a long half-life whichever is longer). For the definition of a female subject of childbearing potential, please refer to Appendix 16.7.4. CCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCI

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCI

Contraception should include at least one highly effective method as follows:

Highly effective methods:

- Abstinence (only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, i.e.,

throughout the study and until 30 days after the last dose of study medication or of SOC mold-active treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject); OR

- Combined oral, vaginal ring or patch contraceptives, taken as directed for at least 30 days prior to screening; OR
- Contraceptive implant (Norplant®) implanted at least 90 days prior to screening; OR
- Injectable contraception (e.g., medroxyprogesterone acetate injection) given at least 14 days prior to screening; OR
- Intrauterine device or intrauterine system; OR
- Vasectomy (with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate) where the vasectomized male is the sole partner for the female study subject; OR
- Tubal ligation.

If subjects cannot access or use a highly effective method, a combination of male condom with either a cervical cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable **but are not considered highly effective birth control methods**. In such cases the Investigator must document the reason why highly effective methods cannot be used and discuss the risks involved as well as alternative contraceptive requirements with the subject.

The following forms of contraception are not permissible as the sole method of contraception for this study:

- A single barrier method of contraception (male condom, female condom, cervical cap, diaphragm, contraceptive sponge)
- Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactational amenorrhea method

9.3. Prohibited Medications

The following medications may not be used during the study:

- Nebulized amphotericin B
- Any investigational agent or any investigational antifungal agent, including an approved antifungal medication administered via an unapproved route

- After randomization, use of other inhaled medications should be avoided. If an inhaled medication must be used, it must be administered approximately 60 minutes before or approximately 90 minutes after the administration of study medication
- While an inhaled bronchodilator may be used given the background medical history of the subject it may not be administered immediately prior to the administration of study medication
- If a subject develops bronchospasm after the administration of the blinded study medication, an inhaled bronchodilator may be used as soon as is clinically indicated in the opinion of the Investigator

For SOC antifungal medications, the Investigator should follow the approved product labels of the respective medication with regards to which other medications are contra-indicated.

10. SUBJECT COMPLETION AND WITHDRAWAL

10.1. Subject Completion

A subject will be considered to have completed the study if he or she has completed assessments up to and including the Day 112 Safety Follow-Up Visit or if he or she has died during the study. The Investigator or designee will record in the eCRF whether the subject completed the study and whether the subject completed the 84-day (12-week) study medication treatment regimen.

10.2. Subject Withdrawal

Within the provisions of informed consent and good clinical judgment with respect to the subject's safety, every attempt should be made to have subjects complete both treatment (through Day 84) and follow up (through Day 112) parts of the study. Subjects will be informed that they are free to withdraw from the study at any time.

It is important that the Investigator documents information explaining why a subject withdraws or is discontinued from study treatment. This information, together with AEs occurring at those times, may help inform the cause-specific reasons for why some subjects remain on the assigned treatment while others do not.

The Investigator will immediately inform the Medical Monitor of early treatment discontinuation due to subject's withdrawal from the study.

Note that if a subject requires "rescue" antifungal treatment with a systemic antifungal agent at any time in the study, this will not automatically require that the subject be withdrawn from the study nor will the administration of IP need to be stopped. In general, all subjects should be followed as closely as possible to the study schedule of assessment if

they consent to do so regardless of whether or not they are willing or able to take their blinded study medication through Day 84 (Week 12).

10.2.1. Subject Withdrawal from Study

In accordance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, and the U.S. FDA regulations, a subject has the right to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution.

Although subjects are not obliged to give their reason for withdrawing consent, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subjects' rights. Reasons for withdrawal of consent, when provided by the subject, will be recorded in the eCRF. The Investigator will immediately inform the Medical Monitor of the decision of a subject to withdraw consent for study participation.

If a subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws entirely from the study, they may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

The Investigator may withdraw a subject from the study for any of the following reasons:

- Withdrawal of consent
- Lost to follow-up
- The Investigator or Sponsor determines that a subject's continued participation in all aspects of the study (including passive safety follow-up) would not be in the best medical interest of the subject
- The Sponsor closes the study

All subjects withdrawn early from further study prior to Day 84 will be required to complete the Day 84/Early Termination Visit on the day of withdrawal or as soon as possible after the last dose of the blinded study medication. Subjects withdrawn from the study for any reason will not be replaced.

For subjects that withdraw after Day 84 or are lost to follow-up, every reasonable effort will be made to contact a subject who fails to attend a Study Visit, or does not respond by telephone, in order to ensure that the subject is in satisfactory health.

Site personnel, or an independent third party, will attempt to collect the vital status of all subjects randomized, including those who did not receive any doses of study medication, in accordance with applicable laws and regulations. This may include collection of private information through interaction (e.g. follow-up scans, physical exams etc.) or from the subject's medical records based on subject's consent for continued collection of data based on non-interventional procedures to support safety follow-up. Public sources may be consulted, if permitted under applicable laws, for vital status information. If vital status is

determined as deceased, this will be documented, and the subject will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

10.2.2. Subject Discontinuation from Study Medication

The Investigator and/or the Sponsor Medical Monitor may exercise his or her medical judgment to terminate a subject's study treatment because of clinically significant changes in any clinical or laboratory parameter however those subjects should remain attending all study visits through Day 112.

Every reasonable effort must be made by study personnel to keep subjects on study treatment. However, study medication may be discontinued for any of the reasons below. Subjects who discontinue from study medication should be encouraged to complete all study visits per protocol while observing the following principles:

- ECG assessments that would be performed at pre- or post-study drug dose timings can be performed as a single assessment on the day of the visit when there is no 'dose'
- PK samples should continue to be collected at study visits per the planned protocol schedule for all subjects regardless of any early treatment discontinuation. Note that when there is no study drug dosing, a single PK blood draw is required at study visits per the protocol schedule.
- Antifungal SOC dosing diary and compliance should be completed through Day 112 visit

In addition to the scheduled protocol visits, subjects who have been discontinued from study medication may also undergo additional medical follow-up at the discretion of the Investigator. Subjects discontinued from the administration of study medication for any reason will not be replaced.

The following may cause the subject to be discontinued from further study medication administration:

- Adverse events that the Investigator considers to be related to study medication and that also meet one of the following criteria:
    - Is serious or severe
    - Is otherwise clinically significant (e.g., allergic reaction)
    - Unacceptable tolerability of the study medication
    - Death
- Suspected drug-drug interaction
- Progressive disease or significant clinical progression at an earlier time point, if judged by the Investigator to be in the subject's best interests

- Clinically significant intercurrent illness that could compromise the safety of the subject or the scientific value of the study
- Significant deviation from the protocol on the part of the subject that would lead to a medically unacceptable risk to the subject or compromise the scientific value of the study
- Requirement to use contraindicated medication that could compromise the safety of the subject
- Termination of the study by Pulmocide Limited
- Subject becomes pregnant (subject to be followed until delivery or termination of pregnancy. In the case of a live birth, subject will be followed for 30 days after the live birth)

In the event that a subject discontinues from study medication and also does not agree to follow the study schedule and/or declines some or all study assessments or procedures per the protocol schedule, site staff should seek agreement from the subject for safety follow-up. Collection of data available per routine care should be reported in eCRFs per the protocol schedule. In such cases, off-schedule or missed procedures (i.e., due to the subject declining them) will not be recorded as a deviation to the protocol.

10.3. Treatment After the End of the Study

Given that PC945 is still an investigational product, it will not be made available to trial subjects following their completion of the study.

10.4. Screen Failures

Rescreening of subjects will be permitted under certain circumstances. Please refer to Section 6.1.1.

The following data on screen failures will be entered in the eCRF:

- Visit Date
- Informed Consent
- Inclusion/exclusion criteria
- Demography
- Adverse events (if applicable, Section 11.2.1)

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1. Definition of an Adverse Event

An AE is defined as: "Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment" (ICH Guideline "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" E2A). An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes:

- Any new medical condition, sign or symptom, or newly diagnosed event that occurs during the AE reporting period (Section 11.2.1), including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period
- A previous condition that has worsened in severity or frequency or changed in character during the AE reporting period
- Complications that occur as a result of protocol-mandated interventions. An AE can arise from any use of the investigational drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose

For the purposes of this protocol, events that are not considered AEs include:

- Worsening of the study condition (IPA) unless a serious criterion is met. (Note that symptoms of worsening IPA are captured in study efficacy assessments)
- Anticipated fluctuating signs or symptoms of a pre-existing medical condition including the anticipated toxicities or adverse drug reactions related to the pharmacotherapy for the underlying condition (e.g., nausea and vomiting or mucositis related to chemotherapy, tremor in a subject with Parkinson's Disease; migraine episodes) that have not worsened in severity or frequency or changed in character during the AE reporting period
- Anticipated fluctuating signs or symptoms related to the immediate posttransplant procedure (where applicable) unless the Investigator believes that the event is related to the study medication or the event meets any of the criteria for a SAE (Section 11.1.3)
- Recognized complications of the organ or hematopoietic stem cell transplant procedure, if applicable, (such as pain, delayed wound healing, hemorrhage, hemothorax, pneumothorax, cardiac tamponade, pulmonary artery thrombosis, pulmonary edema, pericarditis, the requirement for re-intubation, arterial and venous thrombosis and stenosis, biliary disorders, fluid collections, and graft

rejection, etcetera) unless the Investigator believes that the event is related to the study medication or the event meets any of the criteria for a SAE (Section 11.1.3)

- Surgeries or medical procedures – the medical condition (new or worsened) that led to the surgery or medical procedure would be the reported AE (e.g., for appendicitis resulting in appendectomy, appendicitis would be reported as the AE)
- Overdose without clinical signs or symptoms
- Pregnancy (Section 11.4)

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs or vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs if they meet the definition of an AE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and worsen following the start of the study will be reported as AEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied (IPA) or that are associated with the underlying disease (for example the underlying malignancy or the underlying disease which led to the solid organ transplant, etc.), unless judged by the Investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

11.1.1. Adverse drug reaction

An adverse drug reaction is any AE where the causal relationship between the medicinal product and the AE is at least reasonably possible (i.e., a relationship cannot be ruled out).

11.1.2. Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., the IB for unauthorized IP, or summary of product characteristics or package insert/prescribing information for an authorized product).

11.1.3. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening

(The subject was at immediate 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)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is Medically Important*

*Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not reach the above definition but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an accident and emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A subject is classified as having undergone an inpatient hospitalization if they are admitted to the hospital overnight. Outpatient visits or short visits to the emergency room (less than 24 hours) do not meet this criterion.

For the purposes of this protocol, events that are not considered SAEs include:

- Hospitalization for a previously planned post-transplant bronchoscopy unless associated with an adverse event
- Hospitalization for a previously planned therapy (e.g., chemotherapy) or surgery associated with a condition present prior to informed consent signature that has not worsened during the AE reporting period

11.1.4. Definition of a Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is an AE that is believed to be related (possibly, probably or definitely related) to an investigational medicinal product and is both unexpected (i.e., the nature or severity is not expected from the information provided in the IB) and serious.

11.2. Procedures for Eliciting, Recording, and Reporting Adverse Events

11.2.1. Adverse Event Reporting Period

All AEs, including SAEs and other events for expedited reporting (Section 11.3), regardless of seriousness, severity, or presumed relationship to study drug, must be recorded in the source documents and in the eCRF according to the following reporting periods:

- From signing of informed consent until randomization: only AEs occurring as a result of the screening process (procedures) will be recorded (for subjects who are randomized, any clinically relevant or significant observations occurring not as a result of the screening process after the subject has signed consent but prior to randomization will be recorded on the medical history page of the eCRF).

- From randomization until 30 days following the last dose of study medication or the subject's last AE assessment in the study (last subject visit), whichever occurs later: all adverse events will be recorded (unless the AE, or SAE, is considered related to the study medication, which then requires that the AE be reported, regardless of the amount of time that has passed since receiving the last dose of study medication).

During the study, all AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 10.2).

Any AEs (including SAEs) that are unresolved at the subject's last AE assessment in the study (last subject's visit in the study) are followed up by the Investigator for as long as medically indicated and pertinent details recorded in the eCRF as applicable until database lock. After database lock, the Investigator may provide the final outcome for the event, including any additional clinically significant information regarding the AE or SAE, to the Sponsor on the paper Reporting Form as medically indicated. The Sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

11.2.2. Eliciting Adverse Events

Information on AEs and SAEs will be elicited at each AE assessment time point specified in the Time and Events Schedule (Section 16.1) by asking the subject an open-ended question such as: "Since you were last asked, have you felt unwell or different from usual in any way?" The subject may report AEs spontaneously at any time.

11.2.3. Adverse Events of Special Interest

Adverse events of special interest will include the signs and symptoms of drug-induced bronchospasm following the administration of IP. Please refer to Section 6.8.3, Assessing for Adverse Events of Special Interest, for more information.

Adverse Events of Special Interest, including non-serious events, are to be reported using the SAE Report form. All fields are to be completed including the narrative description section. Non-serious Adverse Events of Special Interest are to be reported within two weeks of investigational site awareness. Adverse Events of Special Interest will be reported to the pharmacovigilance (PV) provider as per Section 11.2.6 – Recording Adverse Events.

Follow-up information for non-serious Adverse Events of Special Interest must also be reported to Pulmocide or designee on the SAE Report Form and entered into the eCRF within two weeks of the site's awareness of the new information.

11.2.4. Assessing the Severity of AEs

AEs will be graded by the Investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Section 16.3). Where an adverse event is not represented in this reference toxicity grading table, the assessment of severity grade will be made by the Investigator using the following general categorical descriptors:

- Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities
- Moderate: Sufficient discomfort is present to cause interference with normal activity
- Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities

The term "severe" is often used to describe the intensity of a specific event; the event itself, however, may be of relatively minor medical significance, such as severe headache. Severe is not the same as serious, which is a regulatory definition (Section 11.1.3).

11.2.5. Assessing Relatedness or Attribution

The Investigator will also assess the relationship between the AE and the study medication according to the following criteria:

- Not related: The event is related to an etiology other than to PC945 medication (the alternative etiology must be documented in the study subject's medical record)
- Related: There is a temporal association between the event and the administration of study medication and there is a plausible mechanism for the event to be related to the investigational drug and causes other than the study product have been ruled out, and/or the event reappeared on re-exposure to the investigational drug. Conditions that may be considered a result of the lack of efficacy of the study drug are not considered adverse events, and they will be captured during the assessment of fungal disease or colonization.

11.2.6. Recording Adverse Events

All AEs and SAEs, whether spontaneously reported by the subject or elicited or noted by study staff, will be recorded in the subject's medical record and reported on the appropriate AE page of the eCRF per Section 11.1 and Section 11.2 In addition, a SAE Report Form must be completed per the instructions provided to report each SAE and AESI.

All AEs should be recorded using the words of the subject (verbatim term) to describe the AE, with two exceptions: if the verbatim term is vague or ambiguous (e.g., cramps), the study staff should try to obtain clarification by asking a follow-up question (e.g., what kind of cramps?) and record the words the subject used to clarify the event (e.g., menstrual cramps, calf muscle cramps).

If the subject reports a group of symptoms and the Investigator is comfortable with a unifying diagnosis, the diagnosis should be recorded (e.g., rhinopharyngitis instead of runny nose, cough, sore throat, and sneezing). At a minimum, the following information should be captured for each AE:

- Date of onset and resolution
- Outcome

- Severity
- Seriousness
- Relatedness to study medication
- Action taken with study medication
- Treatments administered

Any treatment administered as a result of an AE should be recorded on the Concomitant Medication eCRF.

11.3. Serious Adverse Events Reporting

11.3.1. Serious Adverse Events Notification

The Investigator has the obligation to report each SAE to Pulmocide or designee within 24 hours of knowledge of the occurrence. This includes SAEs that occur within 30 days after the last dose of study medication. Additionally, if the Investigator learns of any SAE that occurred after the Follow-up Period for which there is a reasonable possibility of relatedness to the study medication (as defined in Section 11.2.5), that event must be reported within 24 hours. Study reference manuals will contain the contact details of the Sponsor or designated safety representative(s) as well as the information on where and how to submit the SAE Report Form.

Serious Adverse Events must be reported by entering the SAE information into the eCRF and by completing the SAE Report Form per instructions provided. If the event meets serious criteria and it is not possible to access the eCRF, the SAE Report Form must still be provided within 24 hours of the site's awareness. The SAE information must be entered into the eCRF as soon as the eCRF system becomes accessible.

Cause of death is required whenever known. If an autopsy was performed, an autopsy report should be provided. Death should be reported as an outcome and not as an event.

The following information related to the SAE must be collected:

- Subject identification (subject study number, year of birth, gender, and race or ethnicity)
- Date of first study treatment dose
- Date and amount of last study treatment dose
- Whether the subject was taking study treatment at the time of the SAE
- Date, duration/end date, diagnosis or description of SAE
- Events and symptoms leading up to the SAE
- Action taken, including whether subject was withdrawn from study
- Study treatment status (e.g., no change, interrupted, discontinued, dose changed)

- Concomitant therapy (including doses, routes, and regimens)
- Pertinent laboratory data
- Medical history (including time on study prior to AE and history that might be related to the AE)
- Severity of AE
- Investigator's assessment of the relationship of the AE to study treatment
- Outcome of the AE

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Follow-up information for SAEs must also be reported to Pulmocide or designee on the SAE Report Form and entered into the eCRF within 24 hours of the site's awareness of the new information.

11.3.2. Serious Adverse Events Expedited Reporting

The Sponsor or the sponsor's designee will report all SUSARs or other expedited safety reports to the applicable Regulatory Authorities. All SUSARs will be reported to regulatory authorities unblinded and in accordance with local laws and regulations (e.g., EU Clinical Trials Regulation 536/2014). Investigators will be notified of all SUSARs or other expedited safety reports. The Investigator (or Sponsor where required) must report SUSARs or other expedited safety reports to the appropriate IRB/REC that approved the protocol unless otherwise required and documented by the IRB/REC.

11.3.3. Other Events to be Considered for Expedited Reporting

Other safety events that may require expedited reporting and/or an evaluation of safety include, but are not limited to:

- Suspected abuse or misuse of the study medication
- Overdose of the study medication if associated with clinical signs or symptoms

- Inadvertent or accidental exposure to the study medication
- Medication or dosing error involving the study medication

Other safety events should be recorded in the subject eCRF and source documents. Any safety event meeting the above criteria should be recorded on an SAE Report Form and reported to the PV provider as per Section 11.3.1.

11.4. Procedures for Reporting Pregnancy Exposure and Birth Events

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication.

All initial reports of pregnancy from randomization to 30 days after last dose of study medication or of pregnancy in female partners of male subjects, must be reported to the Sponsor's pharmacovigilance provider by the study site personnel within 24 hours of their knowledge of the event using a pregnancy notification form (as per Section 11.3.1). The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. In the case of a live birth, additional follow-up will be conducted at 30 days after birth. Elective abortions without complications should not be handled as AEs. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Report Form. Consent to obtain follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be included in the subject informed consent form and in a pregnant partner informed consent form. Pregnancy must be reported by entering the pregnancy information on the paper Pregnancy Report form and should be followed until outcome is known. The outcome of pregnancy should also be reported on a follow-up Pregnancy Report form. Any subject who becomes pregnant during the study must be promptly withdrawn from study treatment but should continue follow-up as described previously in Section 10.2.2. Any male subject whose partner becomes pregnant during the study will not need to stop taking the study medication.

12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

This section presents the key elements of the planned statistical analysis of the data resulting from this trial. Additional detail will be provided in a Statistical Analysis Plan (SAP).

All deviations from the protocol or SAP will be documented in the final study report.

12.1. Study Design Considerations

12.1.1. Sample Size Justification

12.2. Data Analysis Considerations

12.2.1. Analysis Populations

12.2.1.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will be defined as all randomized subjects.

12.2.1.2. Modified Intention-to-Treat Population

The modified intention-to-treat (mITT) population will be defined as randomized subjects who have DRC-confirmed refractory, proven or probable IPA and who have received at least one dose of blinded study medication. Consistent with ICH E9 this will be the primary analysis population for efficacy (i.e., full analysis set). Analyses for efficacy will be based on the randomized treatment assigned.

12.2.1.3. Safety Population

The Safety population will be defined as all randomized subjects who receive at least one dose of study medication. Analyses of safety will be based upon the actual treatment received.

12.2.1.4. PK Population

The PK population will be defined as all subjects who receive at least one dose of IP and have concentration-time data available.

12.2.2. Treatment Comparisons

CCI

12.2.3. Key Elements of Analysis Plan

12.2.3.1. Primary Efficacy Analyses

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCI

12.2.3.2. Secondary Efficacy Analyses

12.2.3.3. Evaluation of the Secondary Efficacy Outcomes

CCI

12.2.3.4. Exploratory Efficacy Analyses

CCICCI

[redacted]

12.2.3.5. Subgroup Analyses

The primary, secondary, and exploratory efficacy outcomes will be summarized descriptively by the following subgroups (mITT population):

- [redacted]
- High risk vs low risk subjects (Section 4.1.2) for the definition of high vs low risk subjects)
- [redacted]
- [redacted]
- [redacted]

CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI
CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI

12.2.3.6. Evaluation of Safety and Tolerability

CCI

CCI

12.2.3.7. Pharmacokinetic Analyses

CCI

[redacted]

12.2.3.8. Interim Analysis

[redacted]

An unblinded independent DSMB will periodically review the accumulating study data to assess safety of the trial participants. The primary function of the DSMB will be to monitor safety. [redacted]. The DSMB will not conduct a review of comparative efficacy for the purpose of closing the trial early for a finding of efficacy. [redacted]

12.2.4. Missing Data

In general, missing data will not be imputed. For the primary and secondary analyses, the method for incorporating subjects with incomplete data is described in Sections 12.2.3.1 and 12.2.3.2, respectively.

13. STUDY ADMINISTRATION

13.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Before initiation of a study site, the Sponsor will obtain approval from the appropriate regulatory agency to conduct the study in accordance with the International Council of Harmonization–Good Clinical Practice (ICH-GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

Specific to the European Region (EU):

In accordance with the Clinical Trials Regulation No 536/2014, Article 2.2 (8), (April 2014), the authorised SOC used in accordance with their marketing authorisations within the protocol are categorized and referenced in the EU as Auxiliary Medicinal Products (AxMPs).

The study will be conducted in accordance with ICH-GCP, all applicable subject privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki 2013, including, but not limited to:

- An Independent Ethics Committee (IEC)/IRB review and approval of study protocol and any subsequent amendments and all ICFs or other information given to the subject
- Subject informed consent
- Investigator reporting requirements

The Sponsor will provide full details of the above procedures, either verbally, in writing, or both.

Informed consent must be obtained from each subject before participation in the study. Written or electronic informed consent will be collected (informed consent by electronic means –only if permitted according to national law) following a review of the subject information by the potential subject and a discussion between the subject and the Investigator or suitably qualified designee. The study may be discussed with potential subjects and informed consent provided after the initial diagnosis of IPA is made and before response to SOC antifungal therapy has been assessed. However, informed consent (written or electronic), when permissible according to national law) must be obtained prior to the initiation of any study specific screening procedures. If a subject is unable to provide written informed consent, the subject's legally acceptable representative (i.e., acceptable to ICH and local law, as applicable) may provide written consent, as approved according to institution-specific guidelines. The ICF must be signed and dated by the subject, or the subject's legally acceptable representative, prior to study participation. A copy of the ICF must be provided to the subject or the subject's legally acceptable representative.

The Investigator will cooperate with all regulatory inspections and will notify the Sponsor as soon as they are aware of an inspection which may involve this study. With the exception of statutory regulatory authority inspections, the Sponsor will be consulted in the event of inspection of a clinical site by an outside authority before the Inspectors are permitted access to any of the study records or the study areas.

13.2. Study Monitoring

In accordance with applicable regulations, ICH-GCP, the monitoring plan and the Sponsor's and/or delegate procedures, monitors will contact the site before the start of the study to review with the site staff the protocol, study requirements, and their

responsibilities to satisfy regulatory, ethical, and the Sponsor's requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The Sponsor and or delegated monitors will perform risk-based monitoring during the conduct of the study to ensure that:

- The data are authentic, accurate and complete
- The subject's safety and rights are being protected
- The study is conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP and all applicable regulatory requirements

As described in FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, the Sponsor may consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites if planned on-site monitoring visits are no longer possible (FDA Guidance, 2021).

13.2.1. Access to Source Data

The Investigator and the head of the medical institution (where applicable) agree to allow the monitor, Sponsor-appointed auditors and regulatory inspectors direct access to all consented subjects' relevant and original source documents.

13.2.2. Data Handling and Record Keeping

Following closure of the study, the Investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

The Sponsor will inform the Investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, the Sponsor standard operating procedures and/or institutional requirements.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archiving of records at an off-site facility or transfer of ownership of the records in the event that the Investigator is no longer associated with the site.

Local laws related to data protection will be followed.

13.3. Data Management

For this study, subject data will be collected using an eCRF and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with the applicable Sponsor and their study representative's standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization [WHO] drug dictionary).

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor or designee will:

a. Ensure and document that the electronic data processing system(s) conforms to the Sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation)

b. Maintain standard operating procedures for using these systems

c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail)

d. Maintain a security system that prevents unauthorized access to the data, and policies to describe measures implemented in case of a data security breach

e. Maintain a list of the individuals who are authorized to make data changes

f. Maintain adequate backup of the data

g. Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing)

Training on the use of the electronic data collection system will be provided to all relevant study site staff.

13.4. Insurance, Indemnity, and Finance

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

The Sponsor will indemnify all Investigators participating in this study against future claims by study subjects who were administered study medication; the terms of this will be

detailed within a separate letter of indemnification. The indemnity will only apply where all study procedures have been carried out according to this protocol.

The financial aspects of the study are addressed in a separate agreement.

13.5. Study Administration During the COVID-19 Public Health Emergency

The FDA issued guidance in March 2020 (updated 30 August 2021) providing general considerations to assist Sponsors in assuring the safety of trial subjects, maintaining compliance with GCP, and minimizing risks to trial integrity for the duration of the COVID-19 public health emergency (FDA Guidance, 2021).

In the event that an unexpected and extenuating situation develops which may have an impact on study conduct (e.g., a public health emergency such as a pandemic disease), certain protocol deviations (e.g., administering the study drug or adhering to protocol-mandated visits and laboratory/diagnostic testing) may be unavoidable. In this situation, the Investigator must inform the Sponsor that the subject may not meet pre-specified protocol requirements.

In the above situation, the Sponsor should evaluate whether alternative methods for performing safety assessments (e.g., phone contact, virtual visit, and alternative location for assessment, including local labs or imaging centers) could be implemented and if they would be sufficient to assure the safety of subjects. They will also consider if alternative secure delivery methods are required to deliver PC945 to the subjects. The Sponsor will determine if a protocol amendment is required to implement the alternative methods.

Furthermore, the Sponsor will determine if in-person visits are necessary to fully assure the safety of subjects enrolled in the trial (for example to carry out procedures to assess subject safety or to ensure safe use of the study drugs); in making the decision to continue administration of the study drugs, the Sponsor and the Investigator should discuss and consider whether the safety of trial subjects can be assured with the implementation of the altered safety monitoring approach.

14. PUBLICATION

Following completion of the study, the data from the entire study or from subsets of the study will be considered for reporting at a scientific meeting or for publication in a scientific journal, in which case the Sponsor will be responsible for these activities and will work with the Investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues.

To comply with data disclosure transparency requirements and/or regulations, a description of the clinical trial and results will be registered in applicable government registry databases (e.g., ClinicalTrials.gov, EudraCT).

15. REFERENCES

Austin JH, Muller NL, Friedman PJ, *et al*. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology Aug 1996; 200(2):327–31

Baker A, Maziarz E, Arnold C, Johnson M, Workman A, Reynolds J, et al. Invasive Fungal Infection After Lung Transplantation: Epidemiology in the Setting of Antifungal Prophylaxis. Clinical Infectious Diseases 2020. DOI: 10.1093/cid/ciz156

CANCIDAS® Drug Label Information. Cancidas (caspofungin acetate) Updated October 11, 2024. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3bad23a6-09a6-4194-9182-093ed61bc71c

Colley T, Alanio A, Kelly S, et al. In vitro and in vivo antifungal profile of a novel and long-acting inhaled azole, PC945, on Aspergillus fumigatus infection. Antimicrob Agents Chemother 2017;61:e02280–16. https://doi.org/10.1128/AAC.02280-16

Colley T, Sehra G, Daly L, *et al.* Antifungal synergy of a topical triazole, PC945, with a systemic triazole against respiratory Aspergillus fumigatus infection. Sci Rep. 2019;9:9482. https://doi.org/10.1038/s41598-019-45890-w

Cornely OA, Kontoyiannis DP. How to prophylax against invasive fungal infections in adult ALL? An unmet need. Mycoses. 2018 Sep;61(9):646-9

Cornely OA, Hoenigl M, Lass-Florl A *et al*. Defining Breakthrough Invasive Fungal Infection– Position Paper of the Mycoses Study Group Education and Research Consortium (MSG-ERC) and the European Confederation of Medical Mycology (ECMM); Mycoses. 2019 Sep; 62(9): 716–729

CRESEMBA® (isavuconazonium sulfate) drug label information updated April 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f7f73b8-586a-4df0-935f-fecd4696c16c

Crooks V, Waller S, Smith T, Hahn TJ. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991 Jul;46(4):M139-44. Doi: 10.1093/geronj/46.4.m139. PMID: 2071835

Daly L, Lucas KA, Colley T, Strong P, Rapeport G, Ito K. Synergic anti-fungal activity of topical PC945, a novel inhaled azole, with systemic echinocandin on Aspergillus fumigatus in vitro human alveoli model. AAAM2020, Lugano, 2020, Abstract 33. https://aaam2020.org/wp-content/uploads/2020/03/Poster-33.pdf

Donnelly JP, Chen SC, Kauffman CA, *et al*. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020 Sep; 71(6): 1367-1376. https://doi.org/10.1093/cid/ciz1008 (published online in 2019)

Drew R, Ashley E, Benjamin Jr D, Davis R, Palmer S, Perfect J. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. Transplantation 2004;27;77(2):232–7

Eigl S et al: Influence of mould-active antifungal treatment on the performance of the Aspergillus-specific bronchoalveolar lavage fluid lateral-flow device test; International Journal of Antimicrobial Agents; 4 6(2015) 4-01-405

Fairs A, Agbetile J, Bourne M *et al*. Isolation of Aspergillus fumigatus from sputum is associated with elevated airborne levels in homes of patients with asthma. Indoor Air. 2012 Nov; 23(4): 275–84

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency; Guidance for Industry, Investigators, and Institutional Review Boards. FDA. 30 August 2021

FDA Guidance on Qualification of Biomarker — Galactomannan in studies of treatments of invasive Aspergillosis: (www.fda.gov/media/94480/download)

Hoenigl M et al. Sensitivity of galactomannan enzyme immunoassay for diagnosing breakthrough invasive aspergillosis under antifungal prophylaxis and empirical therapy. Mycoses 2013;56:471e6

Hollen PJ, Gralla RJ, Kris MG, *et al*. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Psychometric assessment of the Lung Cancer Symptom Scale. Cancer. 1994 Apr 15;73(8):2087–98

Husain S, Mooney ML, Danziger-Iaskov L *et al*. A 2010 working formulation for the standardization of definitions of infections in cardiothoracic transplant recipients. Journal of Heart and Lung Transplantation. ISHLT Consensus Statements. 2011 April; Vol 30, No 4

Husain S, Sole A, Alexander B, *et al.* The 2015 International Society for Heart and Lung Transplantation Guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients: Executive summary. Journal of Heart Lung Transplant 2016;35(3):261–82

Husain S, Camargo JF. Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019 Sep; 33(9): e13544

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 09 Nov 2016

Jones R & Neef N. Interpretation and prediction of inhaled drug particle accumulation in the lung and its associated toxicity, Xenobiotica 2012;42:1,86–93. DOI:10.3109/00498254.2011.632827

Kimura G, Nakaoki T, Colley T *et al*. *In Vivo* Biomarker Analysis of the Effects of Intranasally Dosed PC945, a Novel Antifungal Triazole, on Aspergillus fumigatus

Infection in Immunocompromised Mice. Antimicrob Agents Chemother. 2017;61:(9) e00124-17; DOI: 10.1128/AAC.00124–17

Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Critical Care Medicine. 1985;13(10);818–829

Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. Eur Respir Rev 2011; 20(121): 156–174

Lawrence J, Hung J. Estimation and confidence intervals after adjusting the maximum information. Biometrical J. 2003; 45(2);143–152

Lewis R, Cahyame-Zuniga L, Laventakos, K, *et al*. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. Mycoses, 2013, 56, 638–645

Maertens J, Glasmacher A, Herbrecht R *et al.* Caspofungin Combination Therapy Study Group. Multicenter, noncomparative study of caspofungin in combination with other antifungals as salvage therapy in adults with invasive aspergillosis. Cancer 2006:107(12);2888-2897

Maertens JA, Raad II, Marr KA *et al*. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016 Feb; 387(10020): 760-9

Marr KA *et al*. Antifungal therapy decreases sensitivity of the Aspergillus galactomannan enzyme immunoassay. Clin Infect Dis 2005;40:1762-9

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med 2011;30(28):3267-84 (published online in 2010)

MHRA 2014. www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials

Martinu T, Koutsokera A, Benden C *et al*. International Society for Heart and Lung Transplantation consensus statement for the standardization of bronchoalveolar lavage in lung transplantation. J Heart Lung Transplant. 2020 Jul;39(11):1171-1190

Meersseman W, Vandeasteele SJ, Wilmer A, Verbeken E, Peetermans W, Van Wijngaerden E. Invasive aspergillosis in critically ill patients without malignancy. Am J Respir Crit Care Med 2004 Sep;170 (6):621-625

Nunley D, Gal A, Vega J, e*t al*. Saprophytic fungal infections and complications involving the bronchial anastomosis following human lung transplantation. Chest 2002;122(4):1185–91

O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. West J Med. 1991; 155:384-387

Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109

Pasupneti S, Manouvakhova O, Nicolls M, Hsu J. Aspergillus-related pulmonary diseases in lung transplantation. Med Mycol 2017;55(1):96–102

Patterson TF, Thompson III GR, Denning DW *et al*. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2016 Aug 15;63(4):e1-60

POSACONAZOL® Drug Label Information. Updated May 13, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4032672e-1bb0-427d-a3b3-09cda4beaf34

Recommendations related to contraception and pregnancy testing in clinical trials, HMA Clinical Trial Coordination Group (CTCG), version 1.2, 07 Mar 2024. https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTCG/2024_HMA_CTCG_Contraception_guidance_Version_1.2__March_2024.pdf

Samanta P, Clancy CJ, Marini RV et al. Isavuconazole is as effective as and better tolerated than voriconazole for antifungal prophylaxis in lung transplant recipients; Clin Infect Dis. 2020 May 28;ciaa652. doi:10.1093/cid/ciaa652

Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. Journal of Clinical Oncology. 1984 Mar;2(3):187–93

Segal BH, Herbrecht R, Stevens DA *et al.* Defining Responses to Therapy and Study Outcomes in Clinical Trials of Invasive Fungal Diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria; Clin Infect Dis. 2008 Sep;47(5): 674-683

Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801-810

Solé A, Morant P, Salavert M *et al*. Aspergillus infections in lung transplant recipients: risk factors and outcome. Clin Microbiol Infect 2005;11(5):359–65

Summary of Product Characteristics, Posaconazole. https://www.ema.europa.eu/en/documents/product-information/noxafil-epar-product-information_en.pdf

Takazono T, Sheppard DC. Aspergillus in chronic lung disease: Modeling what goes on in the airways. Med Mycol. 2017 Jan; 55(1): 39-47

Teasdale G. Glasgow Coma Scale: Do it this way. Institute of Neurological Sciences NHS Greater Glasgow and Clyde. 2015.

Thompson GR, Cornely OA, Pappas PG *et al*. Invasive aspergillosis as an under-recognized superinfection in COVID-19. In Open forum infectious diseases 2020 Jul (Vol. 7, No. 7, p. ofaa242). US: Oxford University Press

Ullmann AJ, Aguado JM, Srikan-Akdagli S *et al*. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018 May; 24 Suppl 1: e1-e38

Van de Peppel RJ, Visser LG, Dekkers OM, de Boer MGJ. The burden of Invasive Aspergillosis in patients with haematological malignancy: A meta-analysis and systematic review. J Infec. 2018 Jun; 76(6): 550-562

Verweij PE, Rijnders BJA, Bruggemann RJM *et al.* Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Medicine 2020;46:1524–1535. https://doi.org/10.1007/s00134-020-06091-6

Walsh TJ, Raad I, Patterson TF *et al.* Treatment of Invasive Aspergillosis with Posaconazole in Patients Who Are Refractory to or Intolerant of Conventional Therapy: An Externally Controlled Trial. CID 2007 Jan; 44(1):2-12

Williams J, Lim R, Tambyah P. Invasive aspergillosis associated with bevacizumab, a vascular endothelial growth factor inhibitor. Int J Infect Dis. 2007 Nov; 11(6): 549-50

Wingard JR, Ribaud P, Schlamm HT, Herbrecht R. Changes in causes of death over time after treatment for invasive aspergillosis. Cancer; 2008 Apr; 112: 2309-2312

Zilberberg MD, Nathanson BH, Harrington R, Spalding JR, Shorr AF. Epidemiology and outcomes of hospitalizations with invasive aspergillosis in the United States, 2009–2013. Clinical Infectious Diseases. 2018 Aug 16;67(5):727-35

16. APPENDICES PROVIDED FOR STUDY PC_ASP_006


CCICCI
CCICCI


CCICCI
CCICCI
CCICCI


CCICCI
CCICCI


CCICCI
CCICCI

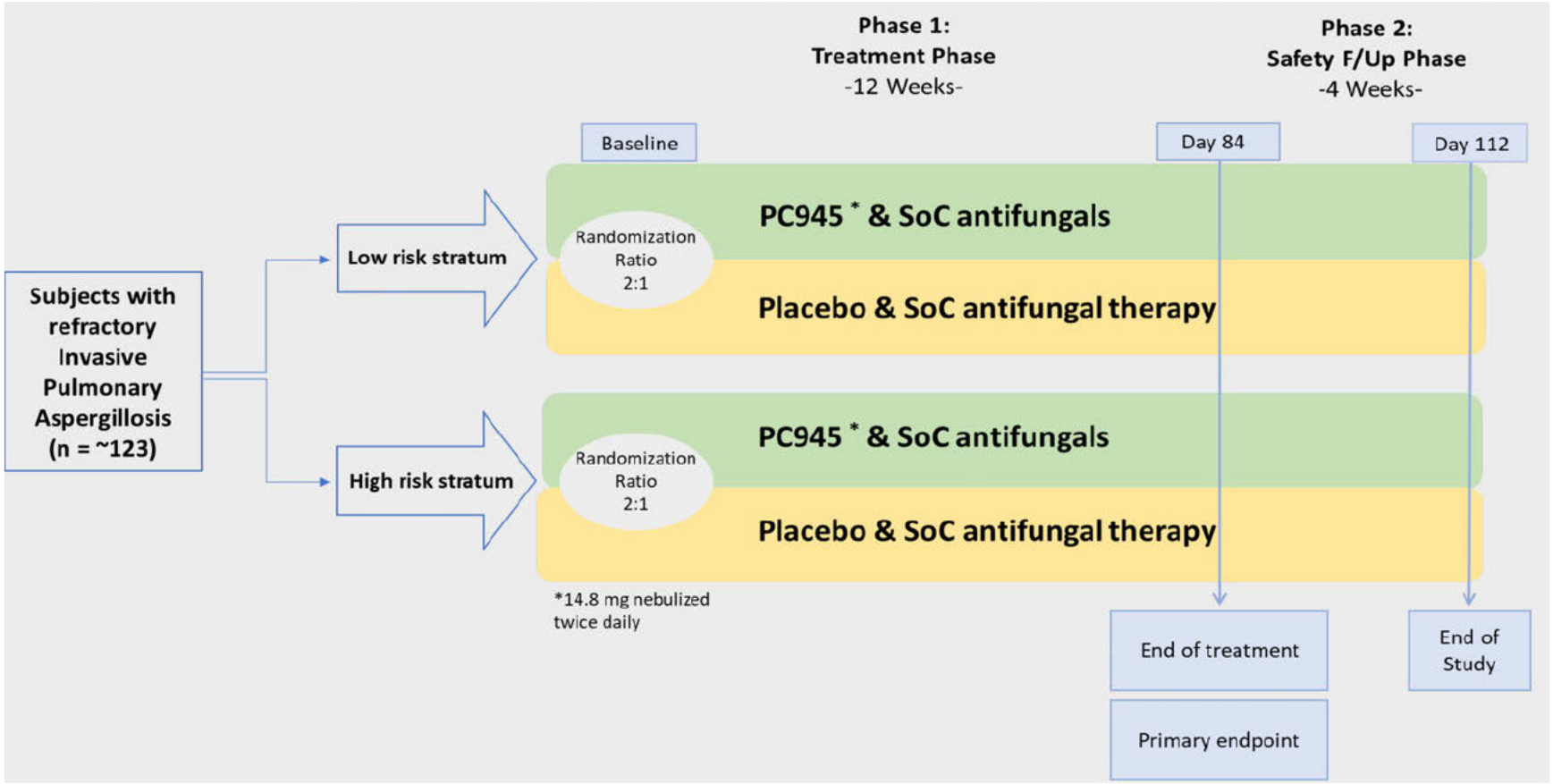

CCICCI
CCICCI
CCICCI


CCICCCICCCICCI

16.2. Appendix 2: Study Diagram

The study diagram is presented in Figure 4.

Figure 4: Study Diagram



16.3. Appendix 3: Common Terminology Criteria for Adverse Events, Version 5

Access the following link for CTCAE version 5.0:

https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v5-5x7.pdf

16.4. Appendix 4: Clinical Laboratory Assessments

Serum chemistry panel	Hematology
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase (AST) Bilirubin (total) Bilirubin (direct) Blood urea nitrogen Calcium Chloride Creatinine (with eGFR) Gamma-glutamyl transferase (GGT) Glucose (random/non-fasting) Phosphorous/inorganic phosphate Lipase Magnesium Potassium Sodium Total protein Uric acid	White blood cell count (WBC) Red blood cell count (RBC) Reticulocyte count Hemoglobin Hematocrit (Packed Cell Volume) Mean cell volume (MCV) Mean cell hemoglobin (MCH) Mean cell hemoglobin concentration (MCHC) Platelet count Full differential WBC (% and absolute numbers)
	Urinalysis
	Microscopic examination Specific gravity pH Protein Glucose Ketones Blood Urine Pregnancy Test (if indicated)
Pregnancy Tests	**Other**
Serum pregnancy test (if indicated)	[redacted]

16.5. Appendix 5: Listing of Additional Exploratory Laboratory Analyses [redacted]

Serum chemistry panel	Hematology
N/A	N/A
	Urinalysis
	N/A
	Other
	[redacted]

16.6. Appendix 6: Diagnostic Criteria for Invasive Pulmonary Aspergillosis and for Refractoriness and Overall or Mycological Response

16.6.1. Modified 2019 EORTC/MSGERC consensus definitions (Donnelly 2020) for Inclusion Criterion 6

Table 8 Criteria for Proven Invasive Pulmonary Aspergillosis - 2019 EORTC/MSGERC Consensus Definitions (Donnelly 2020)

Proven Invasive Pulmonary Aspergillosis	
Microscopy analysis (needle aspiration or biopsy of respiratory or pulmonary tissue obtained from a sterile procedure, excluding BAL fluid)	Histopathologic, cytopathologic, or evidence or direct microscopy examination in which hyphae morphologically consistent with *Aspergillus* spp. are observed together with associated tissue damage
	OR:
Culture (respiratory or pulmonary tissue obtained from a clinically or radiologically abnormal site consistent with an infectious disease process using a sterile procedure, excluding BAL fluid)	Positive culture for *Aspergillus* spp.
	OR:
Tissue nucleic acid diagnosis	Positive for *Aspergillus* spp. by PCR combined with DNA sequencing

Table 9 Criteria for Probable Invasive Pulmonary Aspergillosis – Modified 2019 EORTC/MSGERC Consensus Definitions (Donnelly 2020)

		Probable Invasive Pulmonary Aspergillosis
Host factors		At least one of the following: - ANC <500 cells/µL for >10 days and temporally related to the onset of IPA; - Hematologic malignancy (refers to an active malignancy, in receipt of treatment for this malignancy, and those in remission within the past 5 years) - Receipt of an allogeneic stem cell transplant - Receipt of a solid organ transplant - Prolonged use of corticosteroids at a dose of ≥0.3 mg/kg prednisone equivalent for ≥3 weeks in the 60 days preceding the diagnosis of IPA - Treatment with other recognized T-cell immunosuppressants during the 90 days preceding the diagnosis of IPA (such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte specific monoclonal antibodies, immunosuppressive nucleoside analogues) - Treatment with recognized B-cell immunosuppressants during the 90 days preceding the diagnosis of IPA (such as Bruton's tyrosine kinase inhibitors, e.g., ibrutinib) - Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency) - Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids.
		AND:
Clinical Features	**CT Scan**	Pulmonary aspergillosis with the presence of at least 1 of the following 4 patterns on CT: - Dense, well-circumscribed lesions(s) with or without a halo sign; OR - Air crescent sign; OR - Cavity; OR - Wedge-shaped and segmental or lobar consolidation
		OR:
	Bronchoscopy	The presence of tracheobronchitis or anastomotic infection seen on bronchoscopy: - tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar
		AND:
Mycological evidence	**Culture**	At least 1 positive culture for *Aspergillus* spp. (sputum, BAL, bronchial brushings, or aspirate)
		OR:

Microscopy detections of fungal elements	Indicating presence of *Aspergillus* spp. (sputum, BAL, bronchial brushings, or aspirate)
	OR:
Galactomannan antigen – ELISA[a, b]	Any 1 of the following: Serum: - Single serum or plasma: CCICCI ODI for subjects with a breakthrough infection i.e., while receiving mold-active prophylaxis or treatment or within 7 days of discontinuing mold-active prophylaxis or treatment) - Two separate serum samples with values each CCI ODI (not applicable for subjects with a breakthrough infection) BAL fluid: - Single BAL fluid sample CCICCI ODI for subjects with a breakthrough infection i.e., while receiving mold-active prophylaxis or treatment or within 7 days of discontinuing mold-active prophylaxis or treatment) Combination of serum or BAL fluid: - Single serum or plasma: CCICCICCICCI ODI (not applicable for subjects with a breakthrough infection)
	OR:
***Aspergillus* spp. PCR**	Any 1 of the following: Plasma, serum, or whole blood: - 2 or more consecutive positive PCR tests (taken on separate days) BAL fluid: - 2 or more duplicate PCR tests positive (from the same sample) Combination or plasma/serum/whole blood and BAL: - At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid

[a] Using the Bio-Rad Platelia *Aspergillus* enzyme immunoassay

[b] The VirCell VirClia *Aspergillus* chemiluminescent immunoassay may be used instead of the BioRad Platelia assay in exceptional cases with prior written approval from the Sponsor. According to the manufacturer of the VirClia assay, an index value >0.2 is considered a positive result.

16.6.2. 2010 ISHLT Consensus Statements for Inclusion Criterion 6 (adapted for IPA in Lung Transplant Recipients)

Table 10: *Aspergillus* Fungal Pneumonia in Cardiothoracic Transplant (Husain 2011, adapted)

Syndrome[a]	Signs/symptoms	Radiology	Laboratory
Pneumonia **Proven:** Histology (biopsy showing histologic evidence of parenchymal invasion by fungal hyphae) or positive culture from sterile tissue *ALONE*; *OR* with sign/symptoms + radiology + laboratory **Probable:** Sign/symptoms + radiology + laboratory + negative histology	At least one of the following: • Fever >38°C *OR* hypothermia <36.5°C with no other recognized cause • Leukopenia (<4,000 WBC/mm^3) *OR* leukocytosis (≥12,000 WBC/mm^3) • New onset of purulent sputum *OR* • Change in character *OR* quantity of sputum *OR* respiratory secretions suctioned • New-onset or worsening cough, dyspnea, tachypnea, or pleural rub, rales or bronchial breath sounds • Worsening gas exchange (O_2 desaturation, PaO_2/ FiO_2 ≤240, increased oxygen requirements or increased ventilation demand) • Pleural effusion	Chest radiograph with: • New or progressive and • persistent infiltrate • Consolidation • Cavitation • Nodules *OR* CT scan with at least one of the following[b]: • New or progressive and • persistent infiltrate • Consolidation • Cavitation • Nodules	Single positive culture for *Aspergillus* BAL/blood *OR* single positive PCR for *Aspergillus* BAL/blood *OR* positive galactomannan by ELISA[c, d] (CCI ODI) in the BAL *OR* at least TWO positive sputum cultures/PCRs of *Aspergillus*

[a] In the absence of biopsy categorize as probable: In the presence of histologic findings of both acute rejection and fungal invasion it should be classified as acute rejection with proven fungal infection.
[b] The presence of mosaic appearance and ground-glass opacity may represent development of bronchiolitis obliterans syndrome or obliterative bronchiolitis.
[c] ELISA assay required is Bio-Rad Platelia Aspergillus enzyme immunoassay
[d] The VirCell VirClia *Aspergillus* chemiluminescent immunoassay may be used instead of the BioRad Platelia assay in exceptional cases with prior written approval from the Sponsor. According to the manufacturer of the VirClia assay, an index value CCI is considered a positive result.

Table 11: *Aspergillus* Tracheobronchitis in Cardiothoracic Transplant (Husain 2011, adapted)

Syndrome[a]	Signs/symptoms	Radiology	Laboratory
Tracheobronchitis **Proven:** Histology (biopsy showing histologic evidence of invasion by fungal hyphae) or positive culture from sterile tissue *ALONE*; *OR* with sign/symptoms + radiology + laboratory **Probable:** Sign/symptoms + radiology + laboratory + negative histology	At least one of the following: • New-onset of purulent sputum *OR* change in character *OR* quantity of sputum /respiratory secretions suctioned • New-onset or worsening cough, dyspnea, tachypnea or bronchial breath sounds *AND* one or more endobronchial lesions (erythema, ulceration, necrosis and pseudomembrane formation including at the site endobronchial stent) without an alternative diagnosis and without evidence of invasive parenchymal disease	Chest radiograph without: • New or progressive and • persistent infiltrate • Consolidation • Cavitation • Nodules *OR* CT scan without: • New or progressive and • persistent infiltrate • Consolidation • Cavitation • Nodules	Single positive culture for *Aspergillus* BAL *OR* single positive PCR for *Aspergillus* BAL *OR* positive galactomannan by ELISA[b, c] (CCI) in the BAL *OR* at least TWO positive sputum cultures/PCRs of *Aspergillus*

The presence of mosaic appearance and ground-glass opacity may represent development of bronchiolitis obliterans syndrome or obliterative bronchiolitis.

[a] In the absence of biopsy categorized as probable: In the presence of histologic findings of both acute rejection and fungal invasion it should be classified as acute rejection with proven fungal infection.

[b] ELISA assay required is Bio-Rad Platelia Aspergillus enzyme immunoassay

[c] The VirCell VirClia *Aspergillus* chemiluminescent immunoassay may be used instead of the BioRad Platelia assay in exceptional cases with prior written approval from the Sponsor. According to the manufacturer of the VirClia assay, an index value CCIis considered a positive result.

Table 12: *Aspergillus* Bronchial Anastomotic Infection in Lung Transplant Recipients (Husain 2011, adapted)

Syndrome[a]	Signs/symptoms	Radiology	Laboratory
Bronchial anastomotic infection **Proven:** Histology (biopsy showing histologic evidence of invasion by fungal hyphae) or positive culture from sterile tissue *ALONE*; *OR* with sign/symptoms + radiology + laboratory **Probable:** Sign/symptoms + radiology + laboratory + negative histology	At least one of the following: • New onset of purulent sputum OR change in character OR quantity of sputum OR respiratory secretions suctioned • New-onset or worsening cough, dyspnea, tachypnea or bronchial breath sounds *AND* endobronchial lesions restricted to the site of anastomosis without clinical or histologic involvement of other parts of bronchial tree or lung parenchyma	Chest radiograph without: • New or progressive and • persistent infiltrate • Consolidation • Cavitation • Nodules *OR* CT scan without: • New or progressive and • persistent infiltrate • Consolidation • Cavitation • Nodules	Single positive culture for *Aspergillus* in BAL *OR* single positive PCR for *Aspergillus* in BAL *OR* positive galactomannan by ELISA[b, c] CCI) in the BAL *OR* at least TWO positive sputum cultures/PCRs of *Aspergillus*

[a] In the absence of biopsy categorize as probable: In the presence of histologic findings of both acute rejection and fungal invasion it should be classified as acute rejection with proven fungal infection.

[b] ELISA assay required is Bio-Rad Platelia Aspergillus enzyme immunoassay

[c] The VirCell VirClia *Aspergillus* chemiluminescent immunoassay may be used instead of the BioRad Platelia assay in exceptional cases with prior written approval from the Sponsor. According to the manufacturer of the VirClia assay, an index value CCI is considered a positive result.

16.6.3. Assessment of Overall Response

Table 13: Classification and Criteria for the Assessment of Overall Response (adapted from Segal, 2008)

	Complete	Partial	Stable	Worsening of Disease	Not Applicable
Survival status	Alive	Alive	Alive	Alive	
	AND	AND	AND	AND	
Clinical or Bronchoscopy (where applicable)	Resolution of all symptoms and signs attributable to IPA	Improvement of symptoms and signs attributable to IPA with no worsening of any signs and symptoms and no new symptoms attributable to IPA noted [1, 2]	Minor or no improvement in attributable symptoms and signs of disease	Worsening clinical symptoms or signs of disease	No attributable signs and symptoms present at baseline and no symptoms attributable to IA developed post baseline; or Unable to determine due to missing data
	OR	OR	OR	OR	OR
	Complete resolution of IPA-attributable abnormalities on bronchoscopy	Significant improvement of IPA-attributable abnormalities on bronchoscopy	Minor or no improvement of IPA-attributable abnormalities on bronchoscopy	Worsening of IPA-attributable abnormalities on bronchoscopy	Unable to determine due to missing data
	AND	AND	AND	AND	

Radiological	Resolution of radiological lesion(s); persistence of only a scar or postoperative changes	At least 25% reduction in diameter of radiological lesion(s) [1]	Radiological stabilization (defined as a 0%–25% reduction in the diameter of the lesion)	New sites of disease or radiological worsening of pre-existing lesions	No post-baseline radiology available for subject with baseline evidence of radiological disease (unless the assessment was not clinically indicated), or Unable to determine due to missing data; or Subject has anastomotic or tracheobronchial disease with no abnormalities visible on CT scan or chest X-ray attributable to IPA
	AND	AND	OR	OR	
Mycological[7]	Documented clearance of infected sites (i.e., culture or galactomannan[5,6,7] or PCR negative) that are accessible to repeated sampling (e.g., blood, sputum or BAL fluid/brushings/histology)[4]	Documented clearance of infected sites (i.e., culture or galactomannan[5,6,7] or PCR negative) that are accessible to repeated sampling (e.g., blood, sputum or BAL fluid/brushings/ histology)[3, 4]	Persistent detection of *Aspergillus* spp. (e.g., culture, blood or BAL fluid galactomannan positive by ELISA[5] CCI CCICCICCI CCICCICCI CCICCICCICCI ODI) or *Aspergillus* PCR positive (blood, BAL fluid, or sputum) or histological presence of invasive hyphae in infected sites)	Persistent detection of *Aspergillus* spp. (e.g., culture, blood or BAL fluid galactomannan positive by ELISA[5] CCI CCICCICCICCI CCICCICCICCI CCICCI DI) or *Aspergillus* PCR positive (blood, BAL fluid, or sputum) or histological presence of invasive hyphae in infected sites)	No mycological evidence available at baseline; or Unable to determine due to missing data[4]

1. Clear evidence of a radiological response (reduction in diameter by at least 25% with no new sites of disease) should be given more weight than subjective, nonspecific, or difficult-to-quantify symptoms or signs of disease. Thus, in the scenario of fungal pneumonia, we suggest that radiological improvement with persistence of fever or cough should be scored as a partial response.
2. Because radiological improvement often lags behind clinical improvement, radiological stabilization (0-25% reduction in the diameter of the lesion) and resolution of all attributable symptoms and signs of disease can also be equated with a partial response.
3. Cases of radiological stabilization with a biopsy of an infected site (e.g., lung biopsy) showing no evidence of hyphae and negative culture results can be equated with a partial response
4. If mycology data or information are missing due to further diagnostic testing not being clinically indicated and not missing due to other reasons, eradication will be presumed
5. Using the Bio-Rad Platelia *Aspergillus* galactomannan enzyme immunoassay
6. Using the VirCell VirClia *Aspergillus* galactomannan chemiluminescent immunoassay
7. Using the IMMY sōna *Aspergillus* galactomannan Lateral Flow Assay with an automated cube reader
8. While a positive galactomannan can be used to confirm that the subject's refractory clinical state is due to persistent Aspergillus infection, in situations where the galactomannan has decreased meaningfully but remains positive, Investigators should use clinical judgement (e.g., consider obtaining additional serum or BAL galactomannan levels of possible) to determine whether the subject remains appropriate for admission into the study and wherever possible should discuss the case with the sponsor's Medical Monitor prior to randomization.

16.6.4. Definition of Adequate Antifungal Therapy

Prior to randomization subjects must have been treated with any one, or combination, of the medications below for at least 7 (for progressive disease) to 14 (for stable disease) days to be considered refractory to treatment. Adequate antifungal therapy is defined as mold-active treatment at the approved dose(s). For certain triazole medications, it is recommended that drug levels are obtained when clinically indicated and/or as per local (country/site) usual practice, while following the recommendations within the ESCMID-ECMM-ERS guideline for the diagnosis and management of *Aspergillus* diseases (Ullmann, 2018).

16.6.5. Removed

Table 15: [Table 15 was removed]

This page remains blank.

16.7. Appendix 7: Eligibility Assessment References

16.7.1. Karnofsky Score

The Karnofsky Performance Scale Index allows subjects to be classified as to their functional impairment. The lower the Karnofsky score, the worse the survival for most serious illnesses [Crooks, 1991, Hollen, 1994; O'Toole, 1991; Oxford Textbook of palliative medicine, 1993; Schag, 1984].

Table 16: Karnofsky Performance Status Scale Definitions Rating Criteria (%)

Able to carry on normal activity and to work; no special care needed	100	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

16.7.2. Modified APACHE II Calculator

Acute Physiological And Chronic Health Evaluation (APACHE) II Calculation Worksheet (Knaus, 1985)

POINT SCORE → *Choose worst value in past 24 h*		4	3	2	1	0	1	2	3	4	SCORE
Glasgow Coma Scale		Score = 15 minus actual GCS									
Temperature (°C)		≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9	
MAP (mmHg)		≥160	130-159	110-129		70-109		50-69		≤49	
Heart Rate		≥180	140-179	110-139		70-109		55-69	40-54	≤39	
Respiratory Rate		≥50	35-49		25-34	12-24	10-11	6-9		≤5	
Oxygenation: [Alveolar-Arterial Oxygen Gradient (A-aDO_2)] ($A\text{-}aDO_2 = (FiO_2 \times 710) - (PCO_2 \times 1.25) - PO_2$)						FiO_2 =		PCO_2 =		PO_2 =	
If FiO_2 ≥0.5 record A-aDO_2		≥500	350-499	200-349		<200					
If FiO_2 <0.5: a PaO_2	OR					>70	61-70		55-60	<55	
b. Oxygen Saturation (%)						≥92	88-91		85-87	<85	
Arterial pH (OR if not available)		≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15	
Serum HCO_3 (venous mmol/L) (not preferred)		≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15	
Serum Na (mmol/L)		≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110	
Serum K (mmol/L)		≥7.0	6.0-6.9		5.5-5.9	3.5-5.4	3.0-3.4	2.5-2.9		<2.5	
Serum Creatinine (mg/dL)	Score double if patient has acute renal failure	≥3.5	2.0-3.4	1.5-1.9		0.6-1.4		<0.6			
Hematocrit (%)		≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20	
WBC (10^9/L or /mm^3)		≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1	
Sum of the 12 individual Physiological Variable points:											
Age Score: <44 years = 0 points; 45-54 years = 2 points; 55-64 years = 3 points; 65-74 years = 5 points; ≥75 years = 6 points:											
Chronic Health Points - If the patient has a history of severe organ system insufficiency (see below) or is immunocompromised assign points as follows: a) For nonoperative or emergency postoperative pt -- 5 points, or b) For elective postoperative pt -- 2 points											
TOTAL APACHE-II Score											

GLASGOW COMA SCALE (Teasdale, 2015)		
Parameter	**Response**	**Points Assigned (please circle)**
Eyes Open	Spontaneously	4
	To verbal command	3
	To pain	2
	No eye opening	1
	Not testable*	NT
Best Motor Response	Obeys command	6
	To painful stimulus:	
	Localizes pain	5
	Withdrawal from pain	4
	Flexion to pain	3
	Extension to pain	2
	No motor response	1
	Not testable*	NT
Best Verbal Response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1
	Not testable / intubated*	NT
	TOTAL GCS =	

* Individual components may be not testable due to any of the following (note this is not a comprehensive list):
- Eye: local injury and/or edema
- Verbal: intubation
- All (eye, verbal, motor): sedation paralysis, and ventilation eliminating all responses.

CHRONIC HEALTH DEFINITIONS
Organ insufficiency or immuno-compromised state evident prior to this hospital admission and are consistent with the following criteria:

LIVER: Biopsy-proven cirrhosis and documented portal hypertension; prior episodes of upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma

CARDIOVASCULAR: New York Heart Association Class IV

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform activities of daily living or household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or ventilator dependency

RENAL: Receiving chronic dialysis

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection (i.e., immuno- suppressive treatment, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection (i.e., leukemia, lymphoma, AIDS)

16.7.3. qSOFA Score

Quick Sequential Organ Failure Assessment (qSOFA) Scores (Singer, 2016)

Assessment Criterion:	Score 0	Score 1
Respiratory rate	≤21/min	≥22/min
Altered mental status (mentation)	Absent	Present
Systolic blood pressure	>100 mmHg	≤100 mmHg

16.7.4. Definition of Women of Childbearing Potential

According to the Clinical Trials Coordination Group (CTCG) document on the recommendations related to contraception and pregnancy testing in clinical trials (Version 1,2; 07 March 2024), a woman is considered of childbearing potential (WOCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile.

Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCI
CCI
CCI
CCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI

16.10. Appendix 10: Protocol Amendment 2 – Summary and Rationale for Changes


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI

16.11. Appendix 11: Protocol Amendment 3 – Summary and Rationale for Changes


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI

16.12. Appendix 12: Protocol Amendment 4 – Summary and Rationale for Changes


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI

16.13. Appendix 13: Protocol Amendment 5 – Summary and Rationale for Changes


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCI
CCICCI
CCICCI
CCICCI


CCICCICCI