CLINICAL STUDY PROTOCOL

Title:	A randomized controlled open-label study to assess the safety and tolerability of nebulized PC945 for prophylaxis or pre-emptive therapy against pulmonary aspergillosis in lung transplant recipients.
Short Title:	PC945 prophylaxis or pre-emptive therapy in lung transplant recipients
Protocol Number:	PC_ASP_007
Original Protocol Date:	06 April 2021
Amendment 1:	04 June 2021
Amendment 2:	11 August 2021
Amendment 3:	08 December 2021
Amendment 4:	17 April 2023
IND:	146173
Phase:	2
Compound Identifier:	PC945
Sponsor:	Pulmocide Ltd, 44 Southampton Buildings London, WC2A 1AP

Author	Department	Company
[redacted]	[redacted]	Pulmocide Ltd

Sponsor Signature Page

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A randomized controlled open-label study to assess the safety and tolerability of nebulized PC945 for prophylaxis or pre-emptive therapy against pulmonary aspergillosis in lung transplant recipients.

Protocol Number: PC_ASP_007

Original Protocol Date: 6 April 2021

Amendment 1: 04 June 2021

Amendment 2: 11 August 2021

Amendment 3: 08 December 2021

Amendment 4: 17 April 2023

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:

Protocol Amendment 4–Summary and Rationale for Changes


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PROTOCOL SUMMARY

Rationale

It is anticipated that the low systemic bioavailability and high degree of lung penetration and retention of nebulized PC945 could make it a suitable alternative to systemic antifungal agents as prophylaxis or as pre-emptive therapy to prevent pulmonary aspergillosis in lung transplant recipients. The objective of this study is therefore to assess the safety and tolerability of PC945 when administered as monotherapy prophylaxis or as pre-emptive therapy in lung transplant recipients. The observations from this study may help inform the design of future clinical trials aimed at confirming these findings.

Objectives

Primary Objective

To assess the safety and tolerability of inhaled PC945 when administered as anti-mold prophylaxis or as pre-emptive therapy to prevent pulmonary aspergillosis.

Exploratory Objective

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Pharmacokinetic Objective

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Endpoints

Primary Endpoint

Completion of 12 weeks of PC945 or initial standard of care (SoC) as anti-mold prophylaxis or as pre-emptive therapy.

Exploratory Safety and Tolerability Endpoints

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- Adverse events (AEs), adverse changes in vital signs, laboratory data, and electrocardiograms (ECGs)
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  - [redacted]

Exploratory Efficacy Endpoints

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- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Pharmacokinetics Assessments

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- [redacted]
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Study Design

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Study Population

The study will randomize approximately 100 subjects who have received a single or double lung transplant.

Inclusion Criteria

Potential study subjects must satisfy all of the following Inclusion Criteria to be eligible to enter the study:

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6a. Cohort 1 (*de novo* prophylaxis immediately post-transplant): subject must be ready to be randomized and start anti-mold prophylaxis within 72 hours of returning to the intensive care unit (ICU) after the transplant surgery

or

6b. In Cohort 2 (pre-emptive therapy): subject must meet all of the following:

- *Aspergillus* spp. colonization of the respiratory tract confirmed within 91 days (13 weeks) after a lung transplant. Colonization is defined according to the 2010 ISHLT Consensus Statement definition criteria for colonization and are included in the protocol (Section 5.2.1)
- Without evidence of pulmonary fungal disease
- Must be ready to start anti-mold medication within 96 hours after the positive culture(s), galactomannan or polymerase chain reaction (PCR) result(s) were reported

Exclusion Criteria

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

1. Subject who would normally receive CCICCICCICCI as the only mold active antifungal agent as initial SoC prophylaxis or pre-emptive therapy
2. Subject with a fungal disease requiring systemic antifungal treatment at the time of transplant
3. Subject has received a mold active antifungal agent post-transplant (Note: a subject who receives a mold active antifungal agent within 24 hours before, during, or after the transplant procedure will not be excluded if the mold active medication was stopped within 72 hours of returning to the ICU after the transplant surgery, or prior to randomization (whichever happens first)
4. Subject who has previously received PC945
5. Subject who is receiving, or who is due to receive at any time during the study, an investigational medicinal agent
6. Subject who is participating, or who is due to participate at any time during the study, in a therapeutic clinical trial. For any other trials (e.g. observational or using approved medication), consultation with Pulmocide and the medical monitor is required.
7. Subject has an endobronchial stent *in situ*
8. Subject with a known history of allergy, hypersensitivity, or any previous serious reaction to any component of the PC945 formulation.CCICCICCICCI CCICCI

9. Subject with an elevated alanine transaminase (ALT) or, aspartate transaminase (AST) ≥5 x the upper limit of normal (ULN)
10. Subject with any known history or current evidence of alcohol or drug abuse that, in the Investigator's opinion, would exclude the subject from participation in the study

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12. Subject's life expectancy is not expected to be sustained for the duration of the trial (16 weeks), in the opinion of the investigator

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Study Assessments

Safety

- Adverse events, including serious adverse events (SAEs)
- Adverse events of special interest (AESIs):
  - Pre- and post-dose bronchospasm assessment (spirometry)
  - Recording of symptoms and signs related to airway irritation
- Physical Examination
- Vital Signs
- 12-lead Electrocardiogram
- Clinical Laboratory Tests
  - Hematology
  - Clinical Chemistry
  - Urinalysis
- Data capture on DDIs and changes to antifungal and/or concomitant medications due to DDIs

Efficacy

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Pharmacokinetics

Statistical Methods

Sample Size

Approximately 100 subjects will be randomized.

Statistical Analysis

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ABBREVIATIONS

ABPA	Allergic Bronchopulmonary Aspergillosis
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC_{0-24}	Area under the curve from time 0 to 24 hours
AUC_{0-tau}	Area under the curve from time 0 to end of dosing interval
AUC_{ss}	Area under the curve at steady state
BAL	Bronchoalveolar lavage
BP	Blood pressure
C_{max}	Maximum observed plasma concentration
CI	Confidence interval
CL/F	Apparent clearance
CMV	Cytomegalovirus
CRF	Case report form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
CYP	Cytochrome
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DRC	Data Review Committee
eCRF	electronic Case Report Form
ECG	Electrocardiogram
eGFR	Estimated glomerular flow rate
ELF	Epithelial lining fluid
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume over 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
IC_{50}	50% maximal inhibitory concentration
ICU	Intensive care unit
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IRB	Institutional Review Board
ISHLT	International Society for Heart Lung Transplantation
IWRS	Interactive web response systems
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare Products Regulatory Agency of the UK
MIC90	Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms. (90% percentile MIC value)

NOAEL	No observed adverse effect level
PCR	Polymerase chain reaction
PK	Pharmacokinetic
qPCR	Quantitative polymerase chain reaction
REC	Research Ethics Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoC	Standard of Care
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TID	Three times daily
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
WBC	White blood cells
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Lung transplantation is an important treatment option to prolong survival and improve quality of life in patients with end-stage lung disease caused by a variety of disorders, such as chronic obstructive pulmonary disease, interstitial lung disease, cystic fibrosis, and alpha-1-antitrypsin deficiency [Bemiss B, 2014]. While the risk of organ rejection in subjects who have undergone a lung transplant is highest in the first year, advances in immunosuppression regimens have reduced rejection rates [Villalobos A, 2020], however their use increases the risk of opportunistic infections [Fishman J, 1998].

Fungal diseases are the most important of these opportunistic infections and are associated with high rates of morbidity and mortality [Mattner F, 2007]. *Aspergillus* species, most commonly *A. fumigatus*, are the most important of these opportunistic fungal infections [Bemiss B, 2014; Husain S, 2009; Solé A, 2005]. Lung transplant recipients are especially vulnerable to this pathogen, which is inhaled from the environment directly into the transplanted lungs, where the small size of the spores facilitates deposition in the distal airways [Pasupneti S, 2017]. Clearance of the spores is hampered by reduced mucociliary function, an impaired cough reflex following denervation of the lung during the transplant procedure, and loss of lymphatics [Bemiss B, 2014]. Post-transplant immunosuppressive therapy facilitates progression of the infection, limiting the immune function required to prevent tissue invasive disease.

Invasive fungal diseases occur in approximately 8 to 9% of post-lung transplant patients [Pappas PG, 2010; Samanta P, 2020; Baker A, 2020], but are more common in patients with cystic fibrosis, who are often colonized with the organism pre-transplant [Luong ML, 2014]. During the first 3 months post-transplant, colonization of the airways can lead to tissue-invasive infection [Bemiss B, 2014; Husain S, 2009; Nunley D, 2002]. 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. *Aspergillus* colonization is also associated with an increased risk of bronchiolitis obliterans syndrome [Weigt S, 2013]; an increased risk of late onset, extra-pulmonary invasive aspergillosis [Husain S, 2016]; and an increase in mortality [Solé A, 2005; Felton, 2012; Samanta P, 2020].

Together these risks have led to recommendations for post-transplant antifungal prophylaxis and early and frequent post-transplant surveillance bronchoscopies to detect and treat colonization and tissue-invasive disease as early as possible [Husain S, 2016; Nunley D, 2002; Silveira F, 2007; Geltner C, 2016; Remund K, 2009]. Despite bronchoscopic surveillance and widespread use of antifungals to treat *Aspergillus*-related disease, mortality in lung transplant recipients from these infections remains high [Denning, 2015].

There have been conflicting reports in the literature about whether the benefit of currently available antifungal prophylaxis therapies outweighs the risks. In a 2013 meta-analysis, it

was reported that prophylaxis did not significantly reduce the risk of *Aspergillus* colonization or of invasive pulmonary disease compared with no prophylaxis [Bhaskaran, 2013]. Furthermore, the widespread use of prophylactic antifungals is limited by the potential for side effects and drug-drug interactions [Villalobos A, 2020]. Nevertheless, due to the significant risks associated with fungal disease in this patient group, *de novo* or universal prophylaxis is still standard practice in many centers.

[redacted] Further details are provided in the current version of the Investigator's Brochure.

1.1.1. Description of the Investigational Product PC945

[redacted]

1.1.2. Non-clinical Studies

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

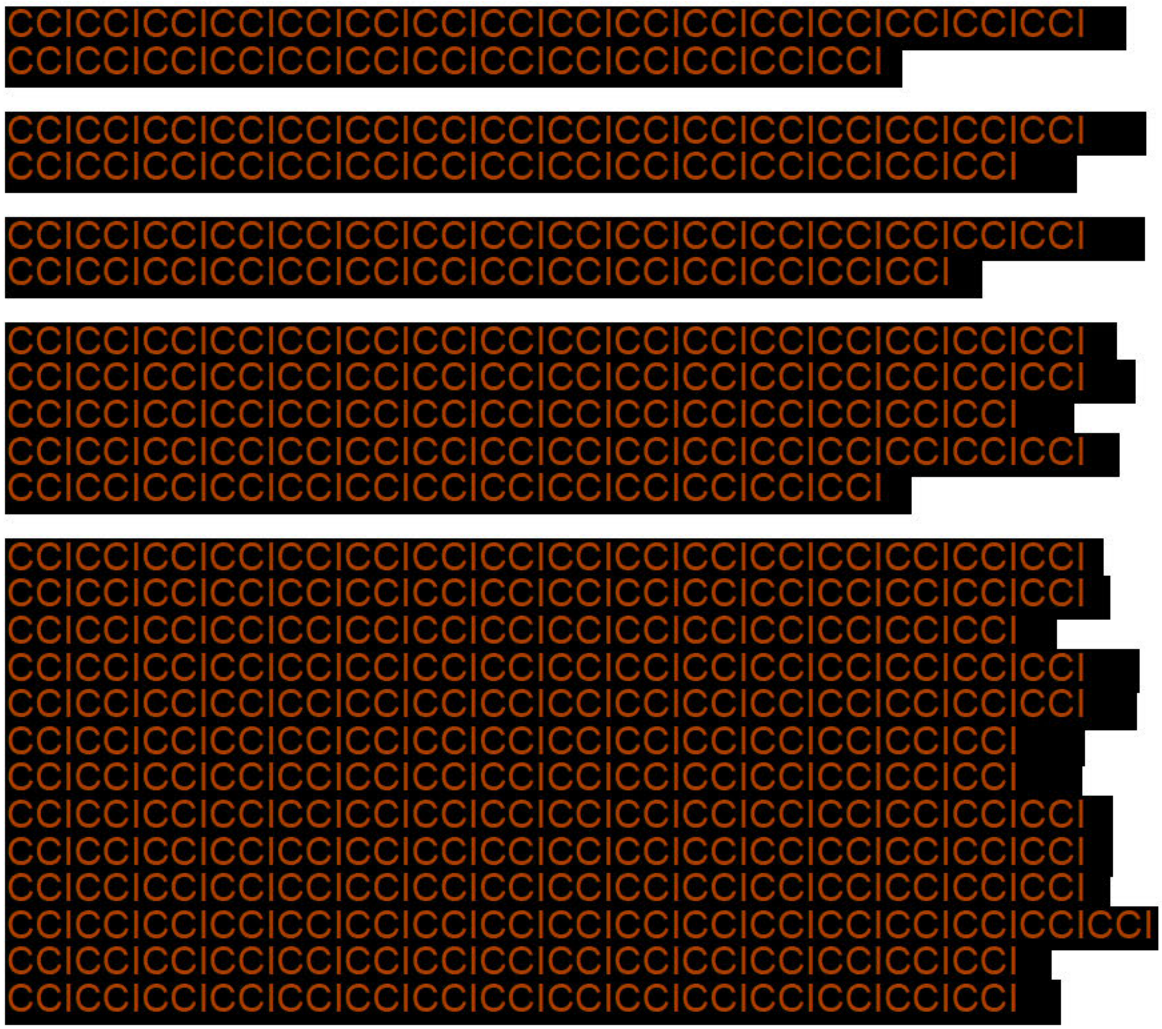
1.1.2.1. *In Vitro* Pharmacologic Effects

1.1.2.2. *In Vivo* Pharmacologic Effects

1.1.2.3. Safety Pharmacology

1.1.2.4. Toxicology

1.1.2.5. Pharmacokinetic Drug-Drug Interaction Potential



1.1.3. Clinical Studies

This section describes the available data from the Phase 1 and 2a clinical program.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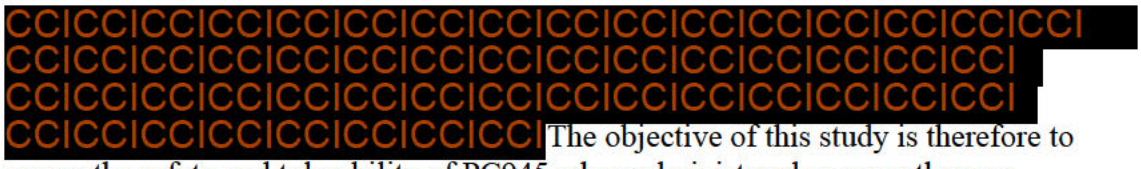
1.1.4. Study Conduct

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 European Union Directives for Clinical Trials (2001/20/EC) 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

1.2.1. Rationale for the Study



The objective of this study is therefore to assess the safety and tolerability of PC945 when administered as monotherapy prophylaxis or as pre-emptive therapy in lung transplant recipients. The observations from this study may help inform the design of future clinical trials aimed at confirming these findings.

1.2.2. Rationale for the Use of a Range of Standard of Care Anti-mold Agents as Standard of Care Prophylaxis or Pre-emptive Therapy in the Control Arm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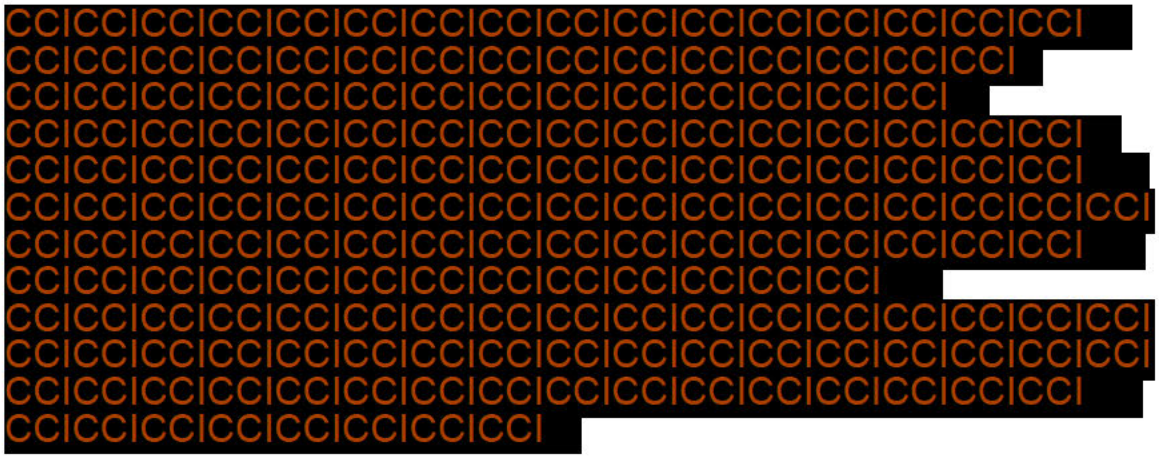
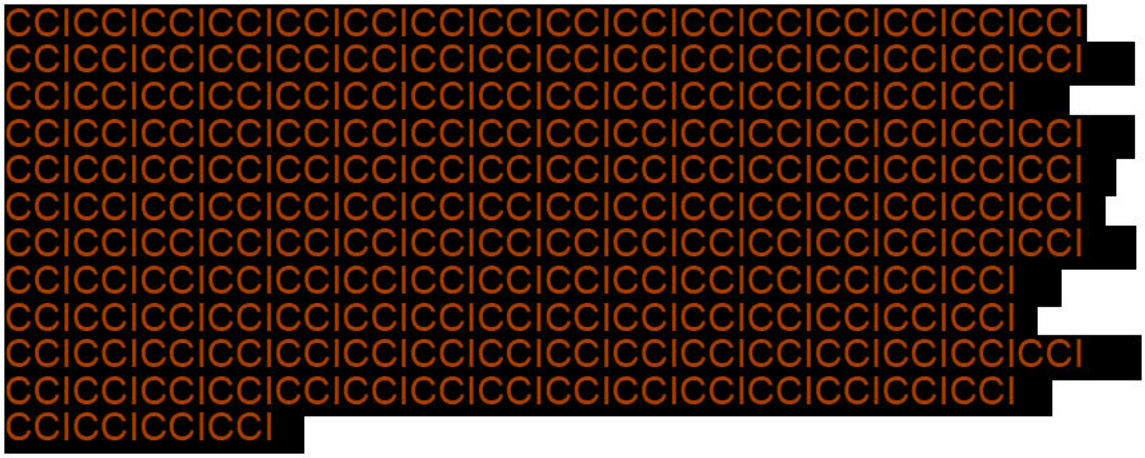
1.2.3. Rationale for Permitting Extended Anti-mold Prophylaxis and for Switching PC945 Subjects to SoC Anti-mold Prophylaxis in the Safety Follow-up Phase



1.2.4. Rationale for the Open-label Design



1.2.5. Rationale for the Dose of PC945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1.3. Potential Risks and Benefits to Human Subjects

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[redacted] 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 MIC90 for the most common *Aspergillus* strains. In the control arm, standard of care antifungal prophylaxis is permitted. In all subjects, if fungal disease is diagnosed rescue antifungal treatment may be initiated.

[redacted]

2. OBJECTIVES

2.1. Primary Objective

To assess the safety and tolerability of inhaled PC945 when administered as anti-mold prophylaxis or as pre-emptive therapy to prevent pulmonary aspergillosis.

2.2. Exploratory Objective

[redacted]

2.3. Pharmacokinetic Objective

[redacted]

3. ENDPOINTS

3.1. Primary Endpoint

- Completion of 12 weeks of PC945 or initial SoC as anti-mold prophylaxis or as pre-emptive therapy

3.2. Exploratory Safety and Tolerability Endpoints

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]

3.3. Exploratory Efficacy Endpoints

- [redacted]
  - [redacted]
  - [redacted]
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3.4. Pharmacokinetic Assessments

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4. STUDY DESIGN

4.1. Summary of Study Design

4.1.1. Study Design


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4.1.2. Randomization and Blinding

This is a randomized, active-controlled open-label two-arm study. Subjects who have met all of the inclusion criteria and none of the exclusion criteria will be enrolled into one of two cohorts (Cohorts 1 and 2). Within cohort, at the baseline visit, they will be randomized 2:1 (using permuted block randomization stratified by cohort) to either open-label nebulized PC945 or to SoC systemic mold-active antifungal

prophylaxis/pre-emptive therapy. Randomization will be conducted using an interactive web response system (IWRS) system.

[redacted] The Statistical Analysis Plan, the Blinding Plan and the Data Review Committee Charter will provide more information.

4.1.3. Duration of Subject Participation

The Prophylaxis or Pre-emptive Therapy Phase will last 12 weeks from randomization and will include 12 weeks of prophylaxis (Cohort 1) or pre-emptive therapy (Cohort 2). The Safety Follow-up Phase will last 4 weeks from Week 12 to Week 16. The Week 16 visit is the last visit in the study.

The frequency of the study visits and the procedures and data to be collected at these visits (detailed in Time and Events Schedule; Appendix 16.1) is intended to align with the standard of care management of lung transplant recipients so as to minimize placing additional burden on the subjects and to minimize having to perform additional investigations that would not normally be part of their routine care.

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 by the Investigator and the safety data will be reviewed regularly by the Sponsor's and Contract Research Organization (CRO)'s designated Medical Monitor. Refer to Section 10 for more information on subject withdrawal.

In addition, since the study is not powered for efficacy, no pre-specified stopping rules for efficacy have been defined.

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 individual subjects to be withdrawn from the study. Please refer to Section 10.2 for the Subject Withdrawal Criteria.

5. STUDY POPULATION

5.1. Number of Subjects

The study will randomize approximately 100 subjects.

5.2. Eligibility Criteria

5.2.1. 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 received either a single or double lung transplant but did not receive any other organ transplant (e.g., heart, kidney, etc.) at the time of the lung transplantation. History of prior organ transplant (>1 year) is acceptable

6a. Cohort 1 (*de novo* prophylaxis immediately post-transplant): subject must be ready to be randomized and start anti-mold prophylaxis within 72 hours of returning to the intensive care unit (ICU) after the transplant surgery

or

6b. In Cohort 2 (Pre-emptive therapy): subject must meet all the following:

i. *Aspergillus* spp. colonization of the respiratory tract confirmed within 91 days (13 weeks) after a lung transplant. Colonization is defined according to the 2010 ISHLT Consensus Statement as follows:

Laboratory–presence of:

- Single positive BAL culture for *Aspergillus* spp., OR
- Single positive BAL polymerase chain reaction (PCR) for *Aspergillus* spp., OR
- Positive BAL galactomannan >1.0, OR
- At least 2 positive sputum cultures or PCRs for *Aspergillus* spp.

Signs/symptoms:

- Absence of fever >38ºC or hypothermia <36.5ºC with no other recognized cause
- Absence of new-onset of purulent sputum, or change in character or quantity of sputum or respiratory secretions suctioned
- Absence of new-onset or worsening cough, dyspnea, tachypnea, or pleural rubs, rales or bronchial breath sounds, AND
- Normal appearing respiratory mucosa OR absence of endobronchial lesions including the anastomotic site and without clinical or histologic evidence of invasive parenchymal disease

Radiology:

- Chest radiograph or CT scan without:
  - New infiltrates
  - Progressive infiltrates (worsening of existing pulmonary infiltrates from the initial scan)
  - Persistent infiltrates (stable pulmonary infiltrates at two weeks after appropriate antibiotic therapy)
  - Consolidation
  - Cavitation
  - Nodules

ii. Without evidence of pulmonary fungal disease

iii. Must be ready to start anti-mold medication within 96 hours after the positive culture(s), galactomannan or PCR result(s) were reported

5.2.2. Exclusion Criteria

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

1. Subject who would normally receive CCICCICCICCI as the only mold active antifungal agent initial SoC prophylaxis or pre-emptive therapy
2. Subject with a fungal disease requiring systemic antifungal treatment at the time of transplant
3. Subject has received a mold active antifungal agent post-transplant (Note: a subject who receives a mold active antifungal agent within 24 hours before, during, or after the transplant procedure will not be excluded if the mold active medication was stopped within 72 hours of returning to the ICU after the transplant surgery, or prior to randomization (whichever happens first)
4. Subject who has previously received PC945

5. Subject who is receiving, or who is due to receive at any time during the study, an investigational medicinal agent
6. Subject who is participating, or who is due to participate at any time during the study, in a therapeutic clinical trial. For any other trials (e.g. observational or using approved medication), consultation with Pulmocide and the medical monitor is required.
7. Subject has an endobronchial stent *in situ*
8. Subject with a known history of allergy, hypersensitivity, or any previous serious reaction to any component of the PC945 formulation, azoles, CCICCICCI CCICCI
9. Subject with an elevated alanine transferase (ALT) or, aspartate transaminase (AST) ≥5 x upper limit of normal (ULN)
10. Subject with any known history or current evidence of alcohol or drug abuse that, in the Investigator's opinion, would exclude the subject from participation in the study

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12. Subject's life expectancy is not expected to be sustained for the duration of the trial (16 weeks) in the opinion of the investigator

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6. STUDY ASSESSMENTS AND PROCEDURES

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6.1. Screening/Baseline Visit


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6.1.1. Rescreening of Subjects

Subjects in either Cohort may be re-screened once and only if (1) anti-mold prophylaxis or pre-emptive therapy was not initiated post-transplant and (2) approved by the Sponsor's designated Medical Monitor. Rescreening may be permitted, for example, in a Cohort 1 subject if the subject fails screening and later becomes colonized with *Aspergillus* spp. (potentially eligible for Cohort 2), within 91 days (13 weeks) after transplant, and is without any evidence of pulmonary fungal disease, and providing no anti-mold prophylaxis had been initiated after the transplant procedure.

Re-screened subjects will be noted as previously screened and assigned a new subject number within IWRS system. If a subject is re-screened within 7 days of the initial screening, only the screening assessment(s) that failed the study entry criterion/criteria need to be repeated. If re-screening occurs more than 7 days after the initial screening, all screening assessments must be repeated.

6.1.2. Discharge

Discharge from hospital could occur at any point during the study as directed by institutional standard care.

All randomized subjects will receive an IRB/REC-approved emergency contact card once discharged from the hospital, which they must be instructed to carry with them for the duration of the study. Each card will carry the following information:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and site 24-hour contact telephone number
- Site number
- Subject number
- Any other information that is required

At discharge, all subjects must be trained on how to use and maintain the nebulizer device, on how to self-administer the PC945 nebulization, and on how to complete the subject diary.

If a subject in Cohort 2 has already been discharged from hospital at the time of randomization, then this patient training should be completed at the Day 1 visit.

Subjects will be instructed not to take their study medication (PC945 or their SoC anti-mold prophylaxis or pre-emptive therapy) at home in the mornings of scheduled visits which would occur at Week 2, 6 and 12/Early Termination Visits. At those visits, subjects will be instructed to bring their PC945 or SoC prophylaxis or pre-emptive therapy medication and nebulizer equipment to the site so that the morning doses can be administered at the site and coordinated with the applicable pre- and post-dose procedures.

6.2. Day 2

6.3. Study Safety Visits (Weeks 2, 6, and 12/Early Termination)


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6.4. Phone Contacts (Weeks 3, 4, 5, 7, 8, 9, 10, 11 and 14)

6.5. Week 16 Safety Follow-up Visit

6.6. Unscheduled Visit

[redacted]

6.7. Safety Procedures

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

6.7.1. Vital Signs (Baseline, D2, Weeks 2, 6, 12/Early Termination and Week 16)

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- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.7.2. Brief Lung/Respiratory Exam (Weeks 2, 6 and Unscheduled)

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.7.3. Assessing for Adverse Events of Special Interest–Signs and Symptoms of Drug-Induced Bronchospasm Including Pre- and Post-dose Spirometry

[redacted]

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[redacted]

6.7.4. Laboratory Assessments

6.7.4.1. Hematology, Clinical Chemistry and Urinalysis (Baseline and Weeks 2, 6, 12/Early Termination and Week 16)

[redacted]

[redacted]

[redacted]

6.7.4.2. Biomarker Analyses (Baseline and Weeks 2, 6, 12/Early Termination and Week 16 Visits)

[redacted]

6.7.4.3. Additional Exploratory Laboratory Analyses (Baseline and Week 12/Early Termination Visits)

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

6.7.5. Pregnancy Testing (Screening, Early Termination and Week 16 Visits)

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 the subject is not pregnant at the time of randomization. At the Week 16 visit or at the Early Termination Visit, a serum pregnancy test will be performed by the central laboratory.

6.7.6. Twelve-lead Electrocardiogram (Baseline-Day 1 and Weeks 2, 6, 12/Early Termination Visit and Week 16)

[redacted]

- [redacted]
- [redacted]

[redacted]

6.7.7. Data Capture for Drug-Drug Interactions

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

6.8. Efficacy Data Capture Procedures

6.8.1. Data Capture from Bronchoscopy (All Visits)

[redacted]

6.8.1.1. Anastomosis and tracheobronchial lesions

[redacted]

- [redacted]
- [redacted]

6.8.1.2. Bronchoalveolar lavage

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

6.8.1.3. Endobronchial Brushings

[redacted]

- [redacted]

- [redacted]
  - [redacted]
  - [redacted]

6.8.1.4. Endobronchial Biopsy

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

6.8.1.5. Transbronchial Biopsy

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

6.8.2. Data Capture on Chest Radiological Investigations (All Visits)

No chest radiological investigations, such as a chest X-ray or chest CT-scan, are required by the study protocol in addition to those ordinarily performed as part of the routine care of the subject. Any clinically significant observations from radiological investigations such as (but not limited to) chest X-rays or chest CT -scans performed as part of the subject's SoC will be entered as adverse events in the eCRF by the Investigator. Data collected from these radiological investigations related to the assessment of pulmonary or extra-pulmonary fungal infections conducted at any time while the subject is in the study will be provided to the DRC.

6.8.3. Data Capture on Rescue Antifungal Treatment (All Visits)

Data on any rescue antifungal medication initiated for the treatment of fungal disease, or for colonization will be recorded in the eCRF and provided to the DRC.

6.8.4. Data Capture on Mortality (All Visits)

Data on mortality (date and cause of death) will be collected in the eCRF and provided to the DRC. If an autopsy was performed, the autopsy report should be provided to the DRC if it is available.

6.8.5. Data Capture on the Clinical Symptoms and Signs of Pulmonary Fungal Disease, per ISHLT Criteria (All Visits)

The presence or absence of any of the following symptoms and signs, that according to the Investigator are attributed to a pulmonary fungal disease, and are collected as part of the SoC of each subject, will be recorded at each study visit and will be used by the DRC as part of their determination for whether a subject has developed pulmonary fungal disease:

- Fever >38°C (>100.4°F) or hypothermia <36.5°C (<97.7°F) with no other recognized cause
- Leukopenia (<4,000 White blood cells [WBC]/mm^3) or leukocytosis (>12,000 WBC/mm^3)
- New onset of purulent sputum
- 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

6.8.6. Data Review Committee

As part of the SoC, subjects will be monitored for the symptoms and signs and laboratory and radiological features of pulmonary fungal disease or colonization. The presence of post-randomization pulmonary fungal disease or colonization will be adjudicated in all subjects by a blinded independent DRC using the 2010 ISHLT consensus statements for the Standardization of Definitions of Infections in Cardiothoracic Transplant Recipients [Husain S, 2011]. In addition, for the Cohort 2 subjects for the purpose of the statistical analyses and not for study qualification, the DRC will also adjudicate the diagnosis of pulmonary *Aspergillus* spp. colonization made at screening using the 2010 ISHLT consensus statement.

Pulmonary fungal disease will be categorized by the DRC as bronchial anastomotic infection, tracheobronchitis, fungal pneumonia, and will be further categorized as proven or probable. The DRC will also assess outcome of colonization present before transplant in Cohort 1. The Data Review Committee Charter will describe the processes to be followed by the Committee, as well as the frequency of the review meetings. Where there

is discordance between the Investigator and the DRC as to whether a subject has developed pulmonary fungal disease or colonization, for the purposes of the exploratory efficacy analyses, the final assessment of the DRC will be used.

The following information may be provided to the DRC for all subjects:

- Clinical signs and symptoms attributed to the suspected fungal disease
- Bronchoscopy findings including (where available) images taken at bronchoscopy, local results of BAL cultures and galactomannan levels, quantitative PCR, cytology from BAL and/or endobronchial brushings, and PK and histology from endobronchial brushings, endobronchial biopsies and transbronchial biopsies (Section 6.8.1)
- Central Lab *Aspergillus* PCR in BAL when applicable
- Other radiological investigations (where available) for example, chest X-ray, chest MRI, and/or chest CT-scan (Section 6.8.2)
- Clinically significant or relevant local and central hematology laboratory data, for example WBC and differential counts (Section 6.7.4.1)
- Clinically significant or relevant local laboratory pulmonary microbiology and blood culture results and the results of tests for respiratory viral infections
- Local laboratory CRP levels (if available)
- Mortality data, autopsy report when applicable (Section 6.8.4)

The DRC will not be asked to adjudicate on non-fungal pulmonary infections nor on non-infectious post-transplant pulmonary or airway complications. Such events will be captured on the adverse event page of the eCRF and the relevant information will be provided to the DRC as part of the adjudication process for pulmonary fungal disease or colonization.

6.9. Pharmacokinetic Procedures

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]


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[redacted]

[redacted]

6.9.1. Pharmacokinetic Procedures in all PC945 Subjects (First 24 hours [Day 2], Weeks 2, 6, 12/Early Termination and Week 16)

[redacted]

6.9.2. Pharmacokinetic Procedures in the Enriched Pharmacokinetic Subgroup (First 24 hours [Day 2], Weeks 2, 6, 12/Early Termination and 16)

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

6.10. Health Care Resource Utilization Data (Week 16 or the Early Termination Visit)

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 Week 16 or 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 other 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 the transplant procedure)
- Number and duration of ICU admissions
- Number of, and reason for, bronchoscopies
- Number of, and reason for, CT chest scans
- Use of rescue anti-mold medication for mold colonization or fungal disease (name and duration of each medication)

7. LIFESTYLE AND/OR DIETARY RESTRICTIONS

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

8. INVESTIGATIONAL PRODUCT AND STANDARD OF CARE REFERENCE MEDICATION

8.1. Description of Investigational Product

[redacted].

8.2. Dosage

[redacted]

- [redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

8.2.1. Dose Adjustments of Investigational Product

[redacted]

[redacted]

8.3. Dose Rationale

Please refer to Section 1.2 of the protocol for the dose rationale.

8.4. Packaging and Labeling

Manufacture and packaging of the PC945 investigational study agent will be in accordance with applicable current Good Manufacturing Practice (GMP) and the product will meet applicable criteria for use in humans.

[redacted]

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

8.5. Preparation and Administration

8.6. Handling and Storage

The Investigator or designee will verify and acknowledge receipt of the investigational product (PC945). All PC945 and nebulizer supplies must be stored in a secure area with access limited to the Investigator and authorized 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 PC945 is provided in the Pharmacy Manual.

No subject other than those enrolled in this study shall take PC945 designated for this clinical trial. PC945 may not be utilized for any laboratory or animal research.

8.7. Standard of Care Reference Therapy

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8.8. Drug Accountability

Drug accountability for PC945 will be performed at the Weeks 2, 6 and 12/Early Termination Visits. CCICCICCICCICCICCICCICCICCICCI All PC945 dispensed to subjects must be accurately recorded on the Drug Accountability Record maintained at the study site. Subjects will be instructed to bring all used and unused PC945 CCI to each outpatient study visit (Weeks 2, 6 and 12/Early Termination Visits), together with the CCI of PC945 to be administered that morning at the site. All undispensed investigational product and returned used and CCICCICCICCI will be retained at the site for the Study Monitor's verification.

Drug accountability for the dispensed, administered and returned SoC anti-mold medications is not required by the protocol.

8.9. Assessment of Compliance

Compliance will be assessed for all subjects in each treatment group to confirm that the subject is taking PC945 according to the protocol instructions or is taking the SoC prophylaxis or pre-emptive therapy medication as per the Investigator's instructions. Compliance will be assessed by the designated site personnel at each in-hospital visit (Days 1 and 2) and at each phone contact or clinic visit (Weeks 2, 6 and 12/Early Termination), and will be recorded in the eCRF. At discharge from hospital, all subjects will be given a subject diary in order to record the date and time that either PC945 or SoC anti-mold medication was taken or if a dose was missed and the reason for missing the dose.

In each group, compliance will be assessed as follows:

- In the PC945 group:
  - While the subject is hospitalized compliance will be assessed by reviewing the dispensing/administration information in the subject's charts (date of administration, time of administration, and dose taken)
  - After the subject has been discharged compliance will be assessed by reviewing the subject diaries; by enquiring if any doses were missed by the subject and the reason for the missed dose(s); and by reviewing the quantity of dispensed and returned used and CCICCICCICCI the PC945 dose and duration of treatment
- For the SoC control arm:
  - While the subject is in hospital compliance will be assessed by reviewing the dispensing/administration information in the subject's charts (medication name, date of administration, and dose)
  - After the subject has been discharged 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)

8.10. Treatment of Investigational Product Overdose

The Investigator is responsible for ensuring that subjects only receive the protocol-stipulated dose of the PC945. If a subject receives a dose of PC945 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. Please refer to the Study Reference Manuals for instructions on how to report an overdose of PC945.

Subjects exposed to higher than proposed IP 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 PC945.

8.11. Occupational Safety

There are no specific occupational safety precautions for PC945.

9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

9.1. Permitted Medications

Use of standard of care non-mold active prophylaxis medication against yeast infections [redacted] bacterial infections (e.g., *Pseudomonas*) or viral infections (e.g., CMV) is permitted. These medications must be recorded as concomitant medications in the eCRF.

Note that a subject who received a mold active antifungal agent within 24 hours before, during, or after the transplant procedure must have stopped the mold active medication within - 72 hours of returning to the ICU after the transplant surgery, or prior to randomization (whichever happens first).

After randomization, use of inhaled medications other than for SoC mold prophylaxis/pre-emptive therapy or PC945 should be avoided. If an inhaled medication must be used, it must be administered at least 60 minutes before or 90 minutes after the administration of either PC945 or the inhaled SoC prophylaxis/pre-emptive therapy.

[redacted] if no prior bronchospasm was experienced by the subject unless it is part of the site's premedication protocol for [redacted] administration. If premedication with an inhaled bronchodilator is used, this information must be recorded in the eCRF. In PC945 subjects, a bronchodilator may not be administered immediately prior to the administration of PC945. If a subject develops acute bronchospasm either after the administration of either PC945 or the inhaled SoC prophylaxis/pre-emptive therapy, or any other time, an inhaled bronchodilator may be used as soon as is clinically indicated in the opinion of the investigator.

In either arm, the subject may receive rescue antifungal treatment if, for example, a subject develops proven or probable fungal disease as determined by the Investigator or if it was learned after randomization that the explanted or donor lung was subsequently found to be positive for a fungal organism and a systemic antifungal treatment is indicated. Similarly, rescue antifungal treatment may be administered in a Cohort 1 subject if the subject becomes colonized and treatment is considered clinically necessary by the Investigator. The reason for, and use of, antifungal medication for any of the above reasons must be recorded in the eCRF. In the PC945 arm, PC945 may be continued in addition to the rescue antifungal treatment at the discretion of the Investigator. However,

if [redacted] is required as part of the rescue antifungal regimen, then PC945 must be stopped when [redacted] starts.

Given the low systemic exposure following inhaled administration of PC945 at therapeutic doses, the risk of PC945 drug interactions is expected to be minimal (Section 1.1.2.5). Nevertheless, following the standard of care when antifungal medications are administered, caution should be used and where appropriate, drug levels should be monitored when PC945 is co-administered with medications that are metabolized by [redacted]

The Investigator should be informed as soon as possible about any additional medication taken by a subject from the time of screening until the completion of the follow-up visit. All relevant medications taken by the subject during the study must be recorded in the eCRF.

9.2. Contraception

All male and female subjects must use an acceptable effective form of contraception until 30 days after the last dose of PC945 or of SoC anti-mold prophylaxis or pre-emptive therapy. In the SoC arm, this is required because many of the SoC anti-mold medications have been shown to be teratogenic in rats and embryotoxic in rabbits at systemic exposures equal to those obtained in humans with therapeutic doses. [redacted]

Contraception should include one of the following:

- Placement of an intra-uterine device
- Placement of a hormone-releasing intra-uterine system
- Bilateral tubal occlusion
- Sterilization of the male partner (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
- Abstinence from heterosexual intercourse, due to hospital admission or where this is consistent with the preferred and usual lifestyle of the subject
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

The following forms of contraception are documented to have a failure rate of <1% per year but no drug-drug interaction studies have been completed and a reduction in efficacy cannot be ruled out. Therefore, if the following methods of contraception are used, they must be supplemented by the use of a male condom:

- Established use of a combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal or transdermal)
- Established use of a progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)

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

- Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactational amenorrhea method

9.3. Prohibited Medications

For subjects receiving PC945, concomitant mold active antifungal prophylaxis is not permitted as initial antifungal prophylaxis. Concomitant mold active antifungal agents are allowed only in the setting of subjects receiving PC945 that require rescue antifungal therapy to treat a new colonization or fungal disease and provided the Investigator deems the continuation of PC945 of benefit for the subject.

Any investigational medicinal agent is not permitted.

For subjects receiving SoC antifungal prophylaxis 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 Week 16/Safety Follow-up Visit. The Investigator or

designee will record in the eCRF whether the subject completed the study and whether the subject completed the 12-week PC945 or SoC prophylaxis/pre-emptive therapy.

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 week 12) and follow up parts of the study through Week 16. Subjects will be informed that they are free to withdraw from the study at any time.

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 week 16.

It is important that the Investigator collects information explaining why a subject discontinues, 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.

In general, all subjects should be followed as per the study schedule of assessment regardless of whether or not they are able to take their randomly assigned study treatment.

Note that if a subject in the PC945 arm requires treatment with a systemic antifungal agent during the Prophylaxis or Pre-emptive Therapy Phase, this will not automatically require that the subject be withdrawn from the study nor will the administration of PC945 need to be stopped.

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. Food and Drug Administration (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.

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 study follow-up would not be in the best medical interest of the subject
- The Sponsor closes the study

All subjects withdrawn prior to Week 12 will be required to complete the Week 12/Early Termination Visit on the day of withdrawal or as soon as possible after the last dose of PC945 or SoC antifungal prophylaxis, or pre-emptive therapy. Subjects withdrawn from the study for any reason will not be replaced.

For subjects that are withdrawn after week 12 or 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.

Survival status will be collected for subjects who withdraw from further study participation or in those lost to follow-up, where local law allows.

10.2.2. Subject Discontinuation from PC945 or Standard of Care Prophylaxis or Pre-emptive Therapy

Every reasonable effort must be made by study personnel to keep subjects on study treatment. However, PC945 or SoC prophylaxis or pre-emptive therapy may be discontinued for any of the reasons below. It is encouraged that subjects withdrawing from PC945 or SoC prophylaxis or pre-emptive therapy remain in the study to complete all study visits per protocol while observing the following principles:

- ECG and Spirometry assessments that would be performed at pre- or post- study drug dose timings can be performed as a single assessment when there is no 'dose'
- PK samples should continue to be collected per planned protocol schedule for all PC945 subjects regardless of any early treatment discontinuation.
- Antifungal SoC dosing diary and compliance should be completed through week 16 visit

In addition to the scheduled protocol visits, subjects who have been withdrawn from PC945 or SoC prophylaxis or pre-emptive therapy may also undergo additional medical follow-up at the discretion of the Investigator. Subjects withdrawn from the administration of PC945 or SoC prophylaxis or pre-emptive therapy for any reason will not be replaced.

Reasons that may cause the subject to be withdrawn from further PC945 or SoC prophylaxis or pre-emptive therapy include but are not limited to the following:

- Adverse events that the Investigator considers to be related to PC945 or SoC prophylaxis or pre-emptive therapy 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 IP
  - 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 protocol on the part of the subject that would lead to a medically unacceptable risk to the subject
- 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)

10.3. Treatment After the End of the Study

Given that PC945 is still an investigational agent, 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.

Data on screen failures will be collected in the eCRF as described in the Data Management Plan. For subjects who sign informed consent or for whom consent is provided by a Legally Authorized Representative, and who undergo screening procedures but who are not randomized, the reason for screen failure will be collected.

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 patient 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:

- Anticipated fluctuating signs or symptoms of a pre-existing medical condition (e.g., tremor in a patient 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
- Recognized complications of the lung transplant procedure (such as hemorrhage, hemothorax, pneumothorax, cardiac tamponade, pulmonary artery thrombosis, pulmonary edema, pericarditis or the requirement for re-intubation) unless the investigator believes that the event is related to the study medication (PC945) or the SoC anti-mold medication, but these events must be reported if they meet criteria for SAE
- 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 significantly 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, 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 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

An SAE 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 classed 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 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 the initiation of screening procedures until randomization: only AEs occurring as a result of the screening process will be recorded (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 is considered definitely, probably, or possibly 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 SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 10.2.1).

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 recorded in the eCRF 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 (Appendix 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

AEs of special interest will include the signs and symptoms of drug-induced bronchospasm following the administration of either nebulized PC945 or SoC anti-mold prophylaxis/pre-emptive therapy. Please refer to Section 6.7.2 Assessing for Adverse Events of Special Interest for more information.

Adverse Events of Special Interest will be reported to the PV provider as per Section 11.2.6-Recording Adverse Events.

11.2.4. Assessing the Severity of Adverse Events

AEs will be graded by the Investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Appendix 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 PC945 or SoC anti-mold medication according to the following criteria:

- Not related: The event is related to an etiology other than to PC945 or to SoC anti-mold 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 PC945 or of SoC anti-mold 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 on the appropriate AE page of the eCRF. In addition, the SAE Report Form must record each SAE.

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). As a minimum, the following information should be captured for each AE:

- Date of onset and resolution
- Outcome
- Severity
- Seriousness
- Relatedness to PC945 or to SoC anti-mold medication
- Action taken with PC945 or to SoC anti-mold medication

- Treatments administered

Any treatment administered as a result of an AE should be recorded on the Concomitant Medication case report form (CRF).

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 PC945 or SoC anti-mold 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 investigational drug (as defined in Section 11.2.5), that event must be reported within 24 hours. The Study reference manual 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 reporting form.

Serious Adverse Events must be reported by entering the SAE information into the eCRF. If the event meets serious criteria and it is not possible to access the eCRF, SAE reporting via a paper form will be required. In this situation, the Investigator must complete a paper copy of SAE report form, scan, and e-mail it to the contact provided in the Safety Management Plan. 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 must be handled in the same way and reported within the same time frame as the initial report.

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. 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/Research Ethics Committee (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 Investigational Product (IP)
- Overdose of the IP is associated with clinical signs or symptoms
- Inadvertent or accidental exposure to the IP
- Medication or dosing error involving the IP

Other safety events should be recorded in the subject CRF and source documents. Any safety event meeting the above criteria should be recorded on an SAE 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 PC945 or of SoC anti-mold medication in female subjects, 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 participant 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 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 either be reported by entering the pregnancy information into the eCRF or via paper reporting 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 10.2.1. 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

A Statistical Analysis Plan (SAP) will describe in detail the statistical analyses for the study. Any revisions to the SAP, and reasons for such revisions, will only be made prior to database lock. The final Clinical Study Report (CSR) will describe such revisions.

This section presents the basic elements of the SAP. Should the SAP and the methods described in this section of the protocol differ, the methods in the SAP shall prevail.

12.1. Study Design Considerations

12.1.1. Sample Size Assumptions

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 comprise all randomized subjects. Subjects should be followed for the entire 16 weeks of Phase 1 and Phase 2. A subject is considered randomized as soon as the IWRS assigns a treatment number. Analyses based upon the ITT population will be summarized by the randomized treatment.

12.2.1.2. Safety Population

The safety population will consist of all randomized patients who received at least one dose of PC945 or SoC anti-mold prophylaxis/pre-emptive therapy. Analyses based upon the safety population will be summarized by the treatment received.

12.2.2. Treatment Comparisons

[redacted]

12.2.3. Key Elements of Analysis Plan

12.2.3.1. Primary Analyses

[redacted]

12.2.3.2. Analyses of Safety and Efficacy Tolerability

[redacted]

[redacted]

[redacted]

[redacted]

12.2.3.3. Evaluation of Efficacy

[redacted]

12.2.3.4. Pharmacokinetic Analyses

12.2.4. Missing, Unused, and Spurious Data

Analyses will be based upon observed data. Reasons for missing data will be summarized.

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.

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 International Ethics Committee/IRB review and approval of study protocol and any subsequent amendments and all Informed consent forms 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.

Written or electronic informed consent must be obtained from each subject before participation in the study. Written or electronic informed consent may be provided by a Legally Authorized Representative. Written or electronic informed consent will be collected following a review of the subject information leaflet by the potential subject or Legally Authorized Representative and a discussion between the subject/Legally Authorized Representative and the Investigator or suitably qualified designee. The study may be discussed with potential subjects and informed consent provided while the subject is on the lung transplant waiting list. Written or electronic informed consent must be obtained prior to the initiation of any study-specific screening procedures.

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 CRF 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, 2021].

13.2.1. Access to Source Data

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor, Sponsor-appointed auditors and regulatory inspectors direct access to all relevant 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 (SOPs) and/or institutional requirements.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival 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 electronic CRF 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 SOPs 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
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 PC945; 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 participants, maintaining compliance with GCP, and minimizing risks to trial integrity for the duration of the COVID-19 public health emergency [FDA, 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 participants 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 may 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.

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16. APPENDICES PROVIDED FOR STUDY PC_ASP_007

16.1. Appendix 1: Time and Events Tables

The Time and Events table for Cohort 1 and Cohort 2 are presented in Table 3.


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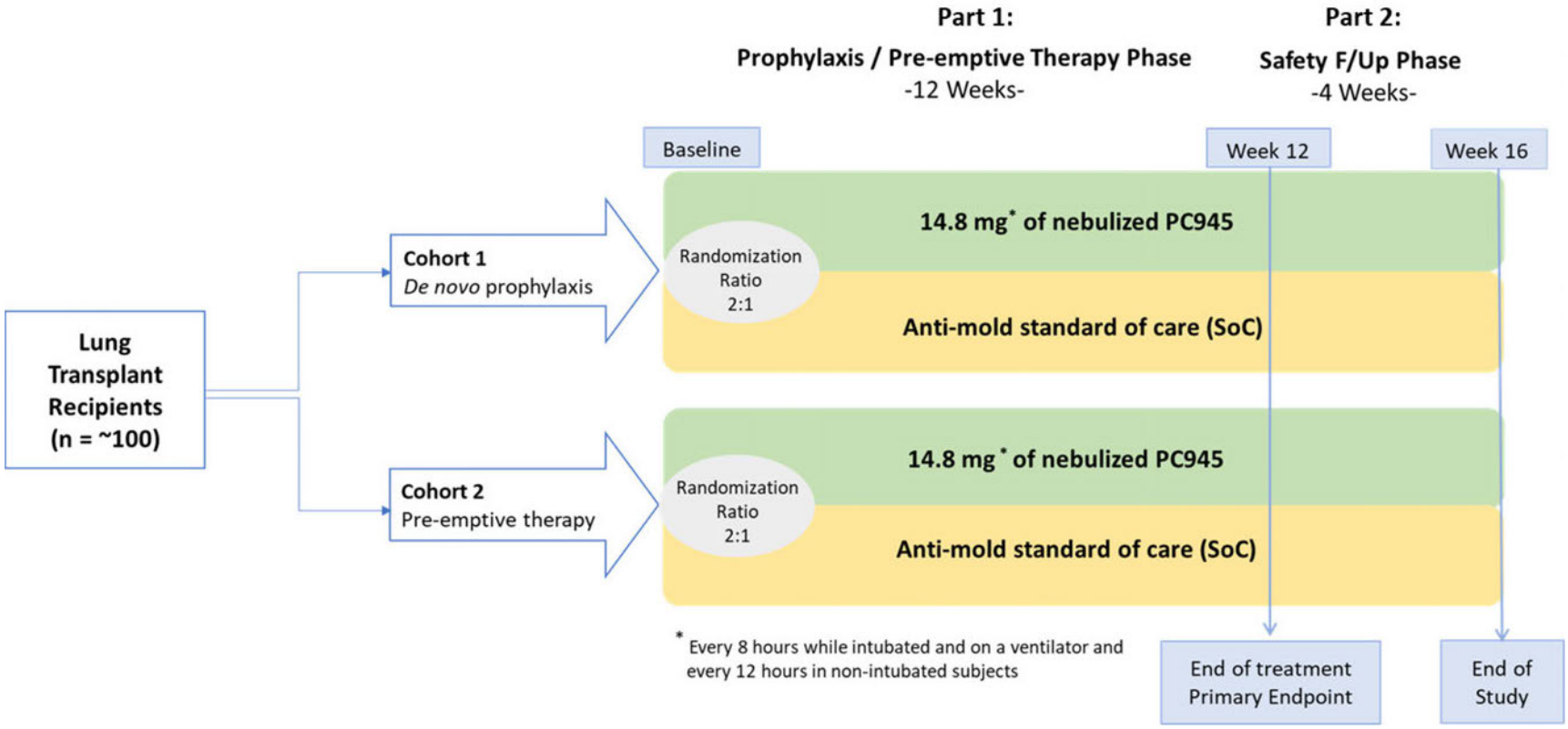
16.2. Appendix 2: Study Diagram

The study diagram is presented in Figure 5.

Figure 5 Study Diagram



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

Click on the following link for CTCAE version 5.0:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

16.4. Appendix 4: Listing of Safety and CCICCI Central Laboratory Assays

Serum chemistry panel	Hematology
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase (AST) Bicarbonate Bilirubin (total) Bilirubin (direct) Blood Urea Nitrogen (BUN) 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 **Urinalysis** Microscopic examination Specific gravity pH Protein Glucose Ketones Blood Urobilinogen Sodium Creatinine Leucocytes Nitrites Bilirubin

	Other
	CCI CCICCICCICCI CCI CCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCI CCICCICCI CCICCICCICCICCICCI CCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCI CCICCICCICCI CCICCICCICCICCICCICCICCICCICCI CCI CCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCI CCICCICCICCICCICCI CCICCICCI CCICCICCICCICCICCICCICCI

16.5. Appendix 5: Listing of Additional Exploratory Laboratory Analyses

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Serum chemistry panel	Hematology
N/A	N/A
	Urinalysis
	N/A
	Other
	CCI CCICCICCI CCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCI CCICCICCICCICCICCI

16.6. Appendix 6: Summary of changes made in previous Protocol Amendments (Amendments 1, 2 and 3)


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Protocol Amendment 2–Summary and Rationale for Changes


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Protocol Amendment 1–Summary and Rationale for Changes


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