Statistical Analysis Plan

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.

PC_ASP_007

Sponsored by:

Pulmocide Ltd

Protocol Version:

PC_ASP_007 Amendment 4

Date Protocol Approved:

17 April 2023

SAP Version: 2.4


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1 Study Description

PC945 is being studied to assess the safety and tolerability when administered as monotherapy prophylaxis or as pre-emptive therapy in lung transplant recipients.

1.1 Objectives

Study PC_ASP_007 contains primary, exploratory, and pharmacokinetic objectives. The primary objective is to,

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

1.2 Study Design


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Adjudication Committee

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, *et al* 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. The DRC will review subject data after the subject has completed the study. The DRC assessment will be the primary source of the information used to determine the study efficacy endpoints. The Data Review Committee Charter describes the processes to be followed by the Committee.

1.3 Method of Assigning Subjects to Treatment Groups

Approximately 100 subjects will be randomized into the study in a 2:1 ratio to either nebulized PC945 as monotherapy for pulmonary *Aspergillus* spp. prophylaxis/pre-emptive therapy or to anti-mold standard of care (SoC) prophylaxis/pre-emptive therapy. Randomization will be stratified by cohort and will be based upon permuted block randomization. There is no minimum or maximum number of subjects required for each cohort.

1.4 Blinding

The DRC adjudicating the presence of pulmonary fungal disease or fungal colonization will be blinded to treatment assignment. Access to unblinded study data is governed by the Study PC_ASP_007 Blinding Plan.

1.5 Sample Size

The total sample size is planned to be 100 subjects.

2 Statistical Methods

2.1 General Considerations

2.2 Populations Analyzed

Two analysis populations will be defined. These populations are:

- The intent-to-treat (ITT) population will consist of all randomized subjects. Analyses based upon the ITT population will be summarized by the randomized treatment.
- The safety population will consist of all randomized subjects who received at least one dose of study therapy. Safety analyses will be based upon the safety population. Operationally, if a subject has ever received PC945, they will be summarized under that treatment. Otherwise, they will be summarized as SoC.

2.3 Study Drug Dosing and Compliance

2.4 Colonization Subgroups

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2.5 Study Endpoints

Primary Endpoint

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

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Safety and Tolerability Endpoints

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Exploratory Efficacy Endpoints

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2.5.1 Primary Analysis

2.5.2 Analyses of Exploratory and Additional Endpoints

2.6 Study Day and Visit Windows

Following the protocol, study day is defined as:

Randomization Day = event date - randomization date +1 (on or after the day of randomization)

event date - randomization date (before the day of randomization)

Study Day = event date - dosing date +1 (on or after the day of dosing)

event date - dosing date (before the day of dosing)

For datasets where the resulting descriptive statistics will be displayed over time, the assessments will be assigned to visits based upon the date the assessment took place regardless of the CRF page completed. Assessments will be mapped to visits as outlined in Table 1. Should more than one assessment exist within a given visit window the value closest to the scheduled visit should be used (choose last if equally close).

Table 1 Visit Windows

Visit	Start of Window	End of Window
Screening/Baseline		1
Week 2	2	28
Week 6	29	63
Week 12	64	91
Week 16	92	

For subjects where the reference date is missing, the study day will also be missing.

2.7 Handling of Missing Data

[redacted]

2.8 Sensitivity Analyses, Subgroups and Covariates

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2.9 Pooling Strategy for Strata

Pooling of strata will not be required.

2.10 Safety Analyses

2.11 Interim Analysis

No interim analyses are planned.

3 Summary Tables Listings and Figures

3.1 General Conventions

3.2 Baseline Characteristics, Disposition, and Related Analyses

Unless specified elsewhere, baseline is defined as the last recorded value prior to the administration of study drug. For height and weight, the baseline record is on Day 1, if no record prior to treatment administration exists.

3.2.1 Subject Disposition and Treatment

The number of subjects randomized, treated, discontinued study drug early, terminated from the study early and in each of the analysis populations will be summarized. The reason for early termination of treatment or from the study will be summarized. The number of subjects who sign informed consent but are not randomized will be summarized. The number of subjects randomized but not included in an analysis population will be summarized.

A summary of subjects present at each visit will be presented for the ITT and Safety population by treatment arm, treatment status, and reason for loss to follow-up.

3.2.2 Violations of Inclusion/Exclusion Criteria

Subjects unintentionally enrolled in the trial without meeting the inclusion/exclusion criteria will be summarized for the ITT population and include information on treatment assigned, and the inclusion/exclusion criteria that were violated.

3.3 Study Treatment

The following information for the initial regimen will be presented by treatment arm, and overall:

- Duration of treatment (days)
- Medication taken as prescribed (% days) = (total number of days medication was taken as prescribed/total number of days with diary data available) x100%.

3.4 Demographics and Baseline Characteristics

Descriptive statistics will be provided for the safety population by treatment group and overall, for demographic variables, important laboratory parameters, and key medical history variables. Statistical testing between treatment groups will not be performed.

Demographic Variables

- Age (years)
- Age category (years)
  - 18-<65
  - 65-<75
  - ≥75
- Sex
- Race
- Ethnicity

Baseline Characteristics

- Weight (kg)
- Height (cm)
- Cohort
- Time of colonization

Lung Transplant history

- Primary reason for transplant
- Initial or re-transplant
- Double lung transplant
- Hospital length of stay (days)
- ICU length of stay (days)

Risk Factors for Invasive Pulmonary Aspergillosis:

- Single lung transplant
- History of either non-invasive pulmonary aspergillosis or completely cured invasive pulmonary aspergillosis
- Pre-transplant Aspergillus colonization within 1 year of screening
- Donor lungs found to have been colonized with *Aspergillus* prior to, or at the time of, transplant
- Early airway ischemia
- Rejection
- change in immunosuppression
- Induction therapy (alemtuzumab, anti-thymocyte globulin, IL-2 receptor inhibitor, others)
- Subject with cystic fibrosis
- Hypogammaglobulinemia
- Donor and recipient cytomegalovirus (CMV) status

3.4.1 Concomitant Medications

Concomitant Medications will be descriptively summarized based upon the coded values (WHO Drug) by treatment for the safety population. Data summaries will be sorted by the overall frequency within medication class. Medications with end dates prior to dosing will be listed but not summarized.

3.4.2 Medical History

Medical history, captured on the Medical History Form, will be descriptively summarized based upon the system organ class (SOC) and coded terms using the Medical Dictionary for Regulatory Activities (MedDRA) by treatment, and overall, for the safety population. Data summaries will be sorted by the overall frequency of reporting within SOC.

3.5 Analysis of Efficacy Endpoints

[redacted]

3.5.1 Primary Analysis

The analysis described in Section 2.5 will be presented overall, and by treatment group at the primary timepoint (Week 12). [redacted]

3.5.2 Exploratory Efficacy and Additional Analyses

[redacted]

3.5.3 Subgroup Analyses

[redacted]

3.6 Analysis of Safety Endpoints

All the tables described in the following are conducted using the Safety Population and will be summarized by treatment arm.

3.6.1 Adverse Events

[redacted]

Drug-Drug Interactions

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3.6.2 Clinical Laboratory Result Analysis

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3.6.3 Vital Signs

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3.6.4 Electrocardiogram Results

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3.6.5 Pregnancies

A listing of positive pregnancy tests will be produced.

Approval Sheet

Product:	PC945 Nebulizer Suspension
Protocol Number:	PC_ASP_007 Amendment 4
SAP Version:	2.4
Version Date:	3 January 2024

The individuals signing below have reviewed and approve this statistical analysis plan.