STATISTICAL ANALYSIS PLAN

A double-blind, randomized, placebo-controlled study to assess the safety and efficacy of nebulized PC945 when added to systemic antifungal therapy for the treatment of refractory invasive pulmonary aspergillosis (OPERA-T Study)

PC_ASP_006

Sponsored by:

Pulmocide Ltd

Protocol Version:

PC_ASP_006

Amendment 5

Date Amendment 5 Approved:

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SAP Version: 1.0

26 January 2026

PULMOCIDE
INHALED RESPIRATORY MEDICINE

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1 Study Description

This study is being conducted to assess the efficacy, safety, and tolerability of PC945 when administered in combination with systemic antifungal therapy for the treatment of refractory Invasive Pulmonary Aspergillus (IPA).

1.1 Objectives

Study PC_ASP_006 contains the following objectives:

- **Primary Objective:** To assess the efficacy of nebulized PC945 in combination with systemic antifungal therapy for the treatment of refractory IPA.
- **Safety Objective:** To assess the safety and tolerability of nebulized PC945 in combination with systemic antifungal therapy, for the treatment of refractory IPA.


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1.3 Data Review Committee (Adjudication Committee)

A blinded independent Data Review Committee (DRC) will adjudicate the following eligibility and efficacy measures (Protocol Section 6.9.8):

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

The DRC assessment will be the primary source of the information used to determine the study efficacy endpoints.

1.4 Method of Assigning Subjects to Treatment Groups

Approximately 123 subjects will be randomized with a permuted block plan into the study in a 2:1 ratio to either nebulized PC945 (82 subjects) or nebulized placebo (41 subjects). Randomization will be stratified by mortality risk (high vs low). [redacted]

1.5 Blinding

The Investigator, the Sponsor, its designees, and the subject will not know the allocation of study treatment. [redacted] To mitigate the risk of possible unblinding of the site personnel, the study medication will be packed [redacted]. In addition, whenever a study drug is administered in the clinic or hospital for inpatient subjects, study medication will be prepared and administered to the subject by a nurse, pharmacist, or other designated person who will not have any influence on the safety and efficacy assessments. Similarly, a nurse, pharmacist, or designated person will perform the drug accountability checks on dispensed [redacted]. These site personnel will be called the 'unblinded' site

personnel. Each site will develop a Site Blinding Plan which will outline the site's specific strategy for maintaining the study blind.

1.6 Sample Size

One hundred and twenty-three (123) subjects will be allocated to the active treatment group or placebo control group in a 2:1 ratio using permuted blocks. CCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI CCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCICCI

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1.7 Data Safety Monitoring Board

An unblinded independent DSMB will periodically review the accumulating study data to assess safety of the trial participants. The primary function of the DSMB will be to monitor safety. An additional function will be to make a recommendation to the Sponsor on whether to increase the sample size following a review of the results of the unblinded interim analysis as described in Section 1.6. The DSMB will not conduct a review of comparative efficacy for the purpose of closing the trial early for a finding of efficacy. CCICCICCICCICCICCICCICCI CCICCICCICCICCI

1.8 Termination of Study and Unblinding

When approximately 50% of the subjects had been randomized and had had sufficient time to complete the Day 84 visit, an interim analysis was conducted and reviewed by the DSMB for the purpose of sample size recalculation. The analysis showed a numerically lower favorable response rate and a numerically higher mortality rate in the PC945 arm compared to the control arm. As a result of this analysis, it was determined to terminate this study and prepare an abbreviated CSR. This SAP is written to support this abbreviated CSR and has been written after unblinding the statistical group.

2 Statistical Methods

2.2 Populations Analyzed

Four analysis populations will be defined. These populations are:

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

2.3 Subject Characteristics

Demographics. medical history, concomitant medications, prior and concomitant SoC antifungal medications, and study disposition will be summarized using descriptive statistics and listed.

2.4 Study Drug Dosing and Compliance

Study drug dosing and compliance will be summarized by providing descriptive statistics for the following:

- Duration of Treatment (days)

2.6 Study Endpoints

Unless otherwise indicated, treatment response endpoints will be derived from DRC provided information as of the interim analysis using the first 63 randomized subjects who also meet the criteria for the mITT population.

Primary Efficacy Endpoint

- Day 84 favorable overall response: being alive and having a complete or partial overall response at Day 84

Secondary Efficacy Endpoints

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

Safety and Tolerability Endpoints

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

2.6.1 Primary Analysis

[redacted]

2.6.2 Secondary Analyses

[redacted]

2.7 Study Day and Visit Windows

Study Day, Randomization Day, and Dosing Day will be defined using the following (Day 0 is not used as per protocol):

Study Day =	event date – first dose date +1
Randomization Day =	event date - randomization date +1 (on or after the day of randomization)
	event date - randomization date (before the day of randomization)
Dosing 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 CRF page completed.

2.10 Pooling Strategy for Strata

The pooling of strata will not be required.

2.11 Safety Analyses

[redacted]

2.12 Interim Analysis

Please refer to Section 1.6 for details on the unblinded interim analysis for the purpose of sample size re-calculation.

No formal interim analyses for efficacy are planned.

3 References

Lawrence J, Hung J (2003) Estimation and Confidence Intervals after Adjusting the Maximum Information. Biometrical J, 45; 2003; (2);143–152

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

4 Approval Sheet

Product:	PC945 Nebulizer Suspension
Protocol Number:	PC_ASP_006 Amendment 5
SAP Version:	1.0
Version Date:	26 January 2026

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