Clinical trial results:
A double-blind, placebo-controlled study to assess the effects of inhaled PC945 in the treatment of culture-positive Aspergillus or Candida fungal bronchitis in subjects with moderate to severe asthma or other chronic respiratory diseases.

Summary

EudraCT number	2018-000244-26
Trial protocol	GB
Global end of trial date	01 June 2020

Results information

Result version number	v1 (current)
This version publication date	07 August 2021
First version publication date	07 August 2021

Trial information

Trial identification

Sponsor protocol code	PC-ASP-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03745196
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pulmocide Ltd
Sponsor organisation address	44 Southampton Buildings, London, United Kingdom, WC2A 1AP
Public contact	Dr Lance Berman, Pulmocide Ltd, +34 660 745 200 , Lance@pulmocide.com
Scientific contact	Dr Lance Berman, Pulmocide Ltd, +34 660 745 200 , Lance@pulmocide.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 January 2020
Global end of trial reached?	Yes
Global end of trial date	01 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the antifungal effect of PC945 on A. fumigatus complex/A. niger complex or Candida spp. in sputum.
Due to the early termination of the trial due to the COVID-19 pandemic only 13 patients were randomised. As a result, a robust statistical analysis for the primary endpoint could not be conducted.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. Known instances of non-conformance were documented and are not considered to have had an impact on the overall conclusions of the study.

Background therapy:

In addition to their study treatment subjects were treated according to their standard of care treatment

Evidence for comparator: -

Actual start date of recruitment	10 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 13
Worldwide total number of subjects	13
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	10

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Forty evaluable subjects were required to complete the study. Thirteen subjects participated in the study between 10 December 2018 and 15 January 2020. Eleven subjects completed the study; two subjects terminated the study early; four subjects ended treatment early but completed study visits.

Pre-assignment

Screening details:

A total of 38 subjects were screened for the study. Twenty-five subjects failed screening. Thirteen subjects met all of the eligibility criteria and were randomised to receive treatment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Due to a difference in appearance of the active and placebo treatments, the investigational product was prepared and dosed by independent staff team members who did not undertake any other study duties.

Arms

Are arms mutually exclusive?	Yes
Arm title	PC945

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PC945
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

PC945 5mg (emitted dose) administered once daily for 28 days

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Placebo, once daily inhalation via nebuliser for 28 days

Number of subjects in period 1	PC945	Placebo
Started	6	7
Completed	4	7
Not completed	2	0
termination of study	1	-
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	PC945
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	PC945	Placebo	Total
Number of subjects	6	7	13
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	2	3
From 65-84 years	5	5	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	67.3	67.0	
standard deviation	± 5.89	± 14.02	-
Gender categorical Units: Subjects			
Female	3	4	7
Male	3	3	6

End points

End points reporting groups

Reporting group title	PC945
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Proportion of subjects in the ITT population with A. fumigatus complex/A. niger complex negative or Candida spp. reduced by 50% at Visit 5

End point title	Proportion of subjects in the ITT population with A. fumigatus complex/A. niger complex negative or Candida spp. reduced by 50% at Visit 5[1]

End point description:

Analysis conducted on subjects with a positive Aspergillus value or a Candida spp. CFU count >200 at baseline and with an evaluable sputum sample at Visit 5.
Mean A. fumigatus complex/A. niger complex and Candida spp. CFUs declined similarly in both groups between baseline and the end of the study. However, the small sample size, imbalance at baseline between groups in fungal load, and the high variability of the fungal data throughout the study confounded the analyses.

End point type	Primary

End point timeframe:

Baseline to Visit 5 i.e. 4-7 days post end of 28 days treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the early termination of the trial due to the COVID-19 outbreak and limited subject numbers on both treatment arms to enable a robust analysis, no statistical analysis was performed on these data.

End point values	PC945	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[2]	7[3]		
Units: Percent	25	43		

Notes:

[2] - low subject numbers confounded analysis

[3] - low subject numbers confounded analysis

Statistical analyses

No statistical analyses for this end point

Secondary: PC945 Cmax Day 1

End point title	PC945 Cmax Day 1[4]

End point description:

Maximum PC945 plasma concentration observed from time 0 to 2 hours post dose; summary statistics provided.

End point type	Secondary

End point timeframe:

Day 1

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic results are reported for those patients on PC945 treatment; not applicable for the placebo arm.

End point values	PC945			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	0.177 (± 59.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: PC945 Cmax Day 14

End point title	PC945 Cmax Day 14[5]

End point description:

Maximum PC945 plasma concentration observed from time 0 to 2 hours post dose; summary statistics provided.

End point type	Secondary

End point timeframe:

Day 14

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic results are reported for those patients on PC945 treatment; not applicable for the placebo arm.

End point values	PC945			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	0.482 (± 108)			

Statistical analyses

No statistical analyses for this end point

Secondary: PC945 AUC 0-2h Day 1

End point title	PC945 AUC 0-2h Day 1[6]

End point description:

Area under the PC945 plasma concentration - time curve from 0 to 2 hour post dose; summary statistics provided.

End point type	Secondary

End point timeframe:

Day 1

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic results are reported for those patients on PC945 treatment; not applicable for the placebo arm.

End point values	PC945			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	0.197 (± 39.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: PC945 AUC 0-2h Day 14

End point title	PC945 AUC 0-2h Day 14[7]

End point description:

Area under the PC945 plasma concentration-time curve from 0 to 2 hour post dose; summary statistics provided.

End point type	Secondary

End point timeframe:

Day 14

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic results are reported for those patients on PC945 treatment; not applicable for the placebo arm.

End point values	PC945			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	0.849 (± 118)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs whether serious or non-serious, were reported from Visit 3 (baseline) until completion of the subject's last study-related procedure.

Adverse event reporting additional description:

PC945 was well tolerated in this study and no systemic or pulmonary safety signals were detected with no evidence of drug-induced bronchospasm or any of the AEs known to be associated with the triazole class of antifungal medications.
Two SAEs were reported and were assessed as unrelated by the Sponsor.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	PC945
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	PC945	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: Asthma exacerbation		
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	PC945	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	5 / 7 (71.43%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Swelling of eyelid			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Bronchiectasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Psoriasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Oral candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Onychomycosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Otitis externa			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Respiratory tract infection fungal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2018	Amendment 1, included: New phototoxicity data (removing the need for related study restrictions) and updated First In Human blinded safety data. It also included clarifications to the AE collection period and other minor changes and corrections.
11 December 2018	Amendment 2, included: Revisions to the eligibility criteria including the addition of subjects on GINA step 5 treatment plans and exclusion of patients with clinically significant bacterial chest infection which is not adequately treated at the screening visit. Addition of unblinded safety data from the First In Human study. Clarification on period within which oral antifungal therapy, a prohibited medication, can be used prior to study visit. Removal of the requirement for patients to fast prior to collection of samples for measurement of blood glucose levels. Minor changes and corrections were made throughout the document.
07 June 2019	Amendment 3 included: Revisions to the eligibility criteria including the addition of subjects with other chronic respiratory diseases as well as asthma. Revisions to the eligibility criteria including the addition of subjects with Candida infection up to a maximum of 10. Revisions to the eligibility criteria including the addition of subjects with Aspergillus niger infection as well as Aspergillus fumigatus. Addition of background information about Candida infection and other chronic respiratory lung conditions. Removal of unblinded safety data from the First In Human study as this data had been added to the IB. Updates to the study objectives and endpoints to reflect the changes to the study population which included changes to the primary endpoint. Change to dispensing procedures so that all study medication is dispensed at Day 1. Update to the statistical section to reflect changes to the endpoints and study population. The sample size calculation had been re-evaluated. Minor changes and corrections were made throughout the document (to ensure consistency with the new study population and objectives and endpoints).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 November 2019	The study had been placed on temporary hold due to a quality issue with the study drug (sweet odour/taste) that was attributed to the terminal sterilisation of the product via ionising radiation. There were no AEs owing to the quality issue. The quality issue had no impact on the active ingredient PC945 or product performance. The study was scheduled to be restarted using study drug manufactured via aseptic processing and approval from MHRA was received on 19 March 2020.	19 March 2020

01 June 2020	The PC_ASP_004 study was terminated early as a result of the COVID-19 outbreak as the study was being conducted in a vulnerable patient group that was at very high risk of severe illness from COVID-19 and recruitment was halted by the hospitals involved in the study. As it was not possible to predict when recruitment could recommence, and it was unlikely that the trials could be completed without significant changes to the protocols, the Sponsor stopped the study on 01 June 2020.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the early termination of the study due to the COVID-19 outbreak only a limited number of subjects were enrolled. As a result no formal analyses are presented for the primary endpoint and additional secondary endpoints.

Notes: