PULMOCIDE

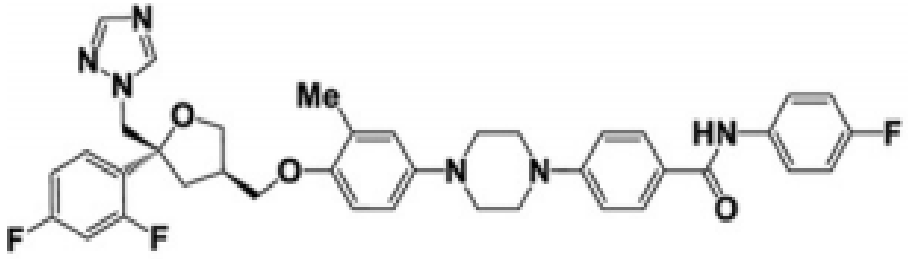
A Novel Inhaled Azole for Invasive Pulmonary Aspergillosis: Clinical and Regulatory Opportunities and Challenges

Lance Berman
Chief Medical Officer
Pulmocide, Ltd.

Pulmocide is developing PC945 for the management of pulmonary diseases caused by fungal infections

- Founded by former heads of GSK respiratory research with offices in the UK and the USA.
- PC945, is a novel inhaled compound specifically designed for use in the lung
  - Potential uses include treatment and prophylaxis in a range of patients at risk of, or suffering from, various forms of pulmonary aspergillosis.
  - Available clinical data demonstrate an apparent benefit in patients not responding to SOC with good tolerability, very low systemic exposure and no reported drug-drug interactions (DDIs) to date.

PC945 is a novel azole designed for inhaled delivery.



- ***Deep lung penetration***: Particle size distribution is typical of inhaled medicines (1-4 µm)
- ***Very low systemic exposure***: aqueous solubility is low and dissolution rate is slow resulting in minimal paracellular uptake into systemic circulation (ratio of lung:systemic concentrations is ~7000:1)
- ***Long residence time at the site of infection:*** drug accumulates and so has a long residence time in airway cells, such as alveolar macrophages and bronchial/alveolar epithelial cells. This could enhance the ability of host cells to clear the fungus - a potential advantage for treatment and prophylaxis.

- Antifungal effect has been demonstrated *in vitro, in vivo* and in humans
- Inhibits the growth of 96 fumigatus clinical isolates and is potent against other aspergillus species such as aspergillus flavus, niger, terreus, among the list.
- It also inhibits the growth of other fungi including various Candida sp. (includimg C auris), Rhizopus oryzae, Cryptococccus neoformans, Chaetomium globosum, Penicillium chrysogenum and Trichophyton rubrum.
- The drug product is a ready-to-use vial containing a single dose of room-temperature stable particulate solution
- Delivery is via an off-the-shelf nebulizer (PARI LC Sprint)
- 14.8 mg delivered dose is administered twice daily as 10-minute nebulizations

PULMOCIDE

PC945: clinical development programme

- Four clinical studies have been undertaken with PC945 to date
  - Phase 1:
    - Healthy volunteers and mild asthmatics
  - Phase 2:
    - Subjects with moderate to severe asthma or other chronic respiratory diseases (treatment)
    - Cystic Fibrosis subjects (treatment)
    - Lung transplant subjects (pre-emptive treatment of colonization)

- Special Needs program (UK):
  - In patients with IPA or ABPA who had failed other options (n=9)
  - In patients requiring secondary prophylaxis (n=1)

PC945: clinical development programme

- Current available data from the clinical development and Special Needs program support a favorable safety and tolerability profile:
  - No significant drug related AEs
  - No significant bronchial hyperreactivity, bronchospasm or changes in lung function
  - Patients tolerated nebulizations well; no unpleasant taste or smell
  - No reported DDIs in the Special Needs program (no immunosuppressant doses needed to be adjusted in Special Needs recipients when PC945 started and stopped)
  - Systemic concentrations are in the pg/mL range with a low risk for drug interactions

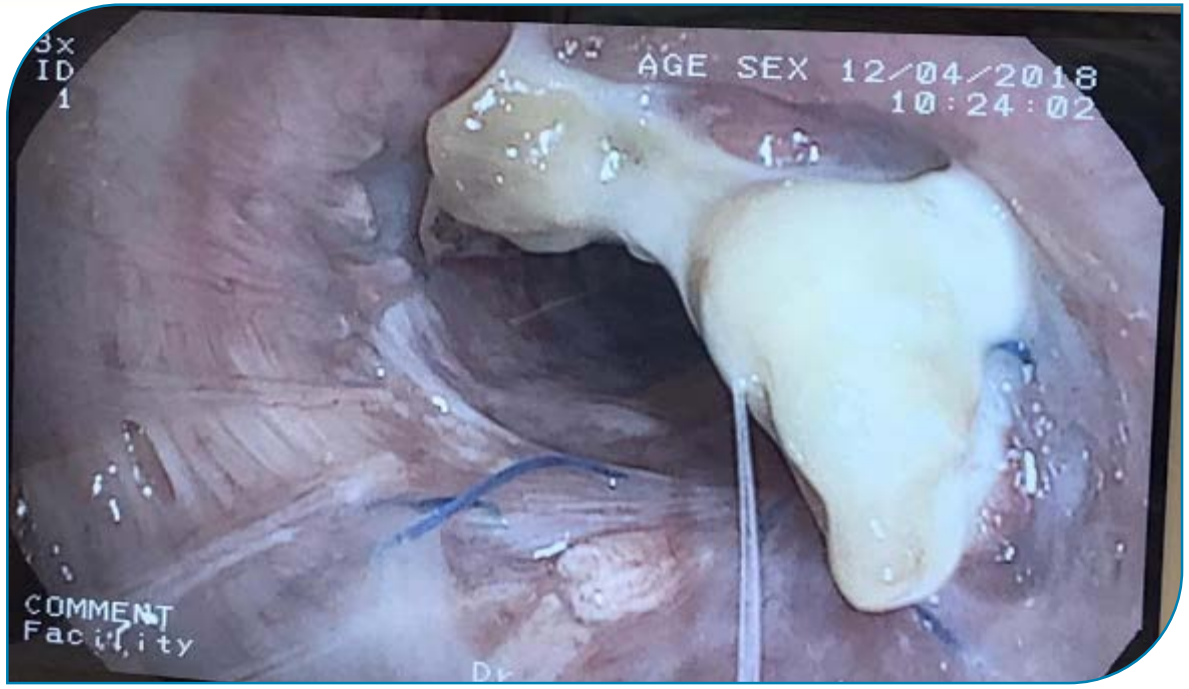
UK Special Needs program overview

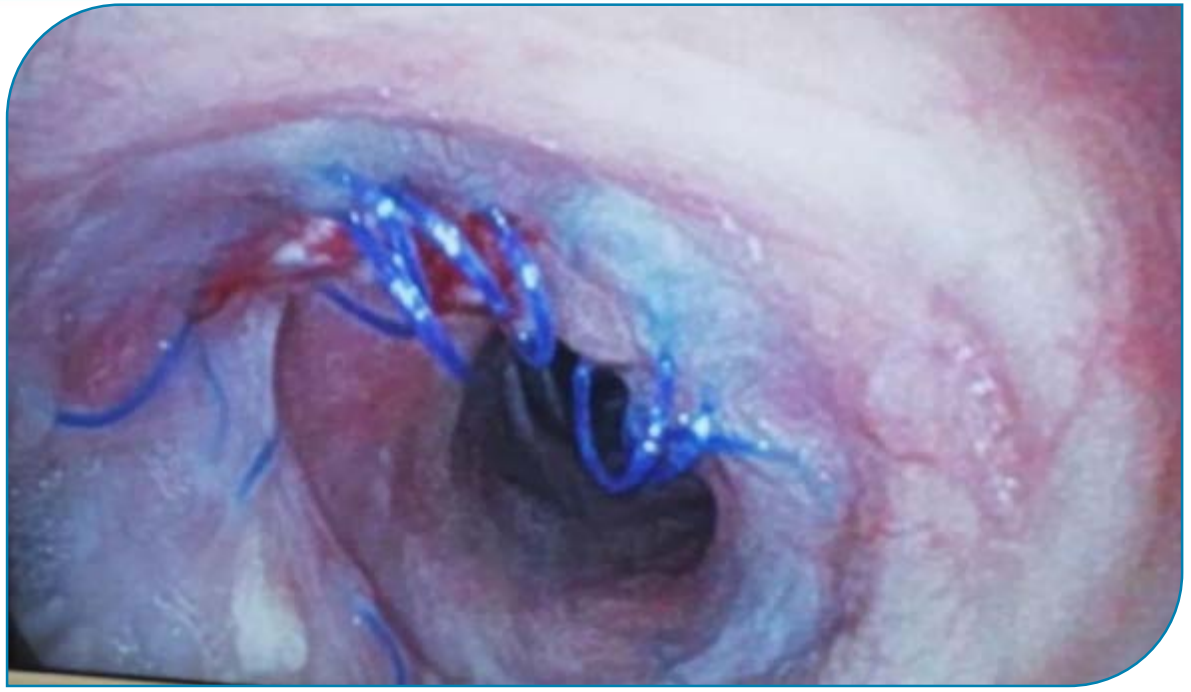
UK Special Needs program requests for PC945 for patients with no other treatment options

Type	# of Patients	Prior Antifungal Treatment	Clinical effect with PC945 at 3 months
Treatment			
Lung transplants (CF, α1-antitrypsin deficiency, IPF, hypersensitivity pneumonitis)	7	≥ 2.5 months to >2 years (multiple azoles, caspofungin, neb amph B, terbinafine)	Favorable response in 6 patients, Stable disease in 1 patient (infection unconfirmed)
Critical care (lupus-related hemophagocytic syndrome)	1	1 month (IV isavuconazole, IV voriconazole, caspofungin, IV amph B, neb amph B)	Favorable response (treated for 6 weeks)
ABPA	1	> 12 years (azole, caspofungin, neb amph B, IV amph B)	Favorable response
Secondary prophylaxis			
Lung transplant (aspergilloma)	1	Surgical removal, multiple azoles, caspofungin, amph B contraindicated	Follow-up information pending

PULMOCIDE

PC945 in a patient with invasive aspergillus tracheobronchitis





- 29 year old female with CF developed invasive *Aspergillus* 1-month post bilateral lung transplant
- Infection not responding to 2+ months on multiple antifungal treatments
  - Azoles, caspofungin, terbinafine & neb amphotericin B

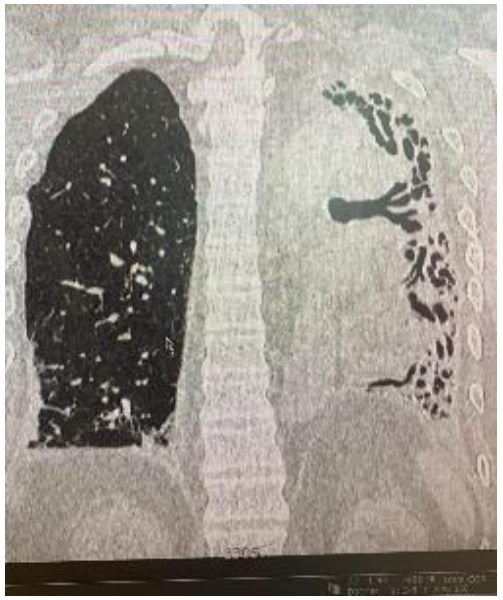
- After 2 weeks of PC945 inhalation the infection began to clear
- At 2 months no fungus was visible at site of infection and airway had healed (shown above)
- Treated with PC945 for 3 months
- Complete response

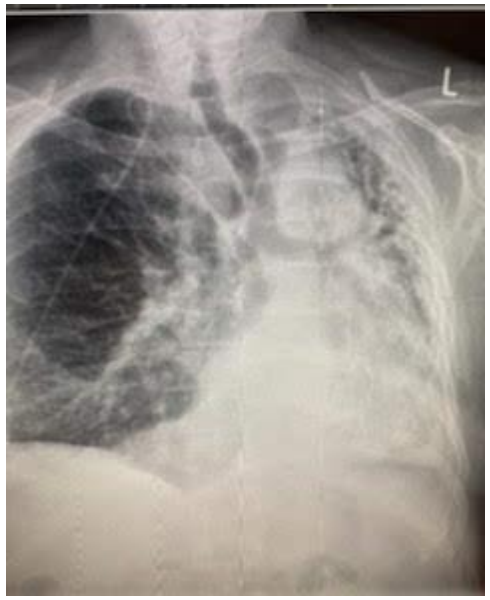
PULMOCIDE

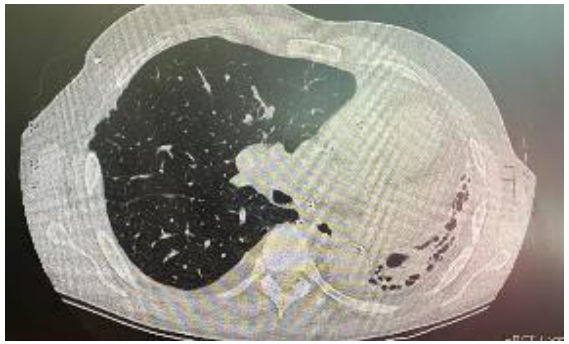
PC945 in a patient with chronic aspergillus lung Infection

- 63 yr old male, single lung transplant 15 yrs ago for idiopathic pulmonary fibrosis. Developed CLAD 5 yrs ago, 2nd single lung transplant.
- End stage, intractable parenchymal disease due to *A. fumigatus* in his single remaining lung:
  - Persisting despite IV, oral and nebulized antifungals
  - Requesting hospitalization every 2 weeks for IV caspofungin when his symptoms became intolerable and for recurrent exacerbations
- PC945 was added and voriconazole continued:
  - Excellent absorption from single lung: [plasma trough] = 4,860 pg/mL
- After 6 months of treatment:
  - Patient's life has been "transformed"
  - Intractable cough has gone; no longer waking at night coughing, now able to sleep
  - Since starting PC945, no exacerbations and no hospitalization for caspofungin to control symptoms
  - FEV_1 has increased by 450 mL (Pre 1.61 L, > 6 months 2.06 L)

Pre-PC945

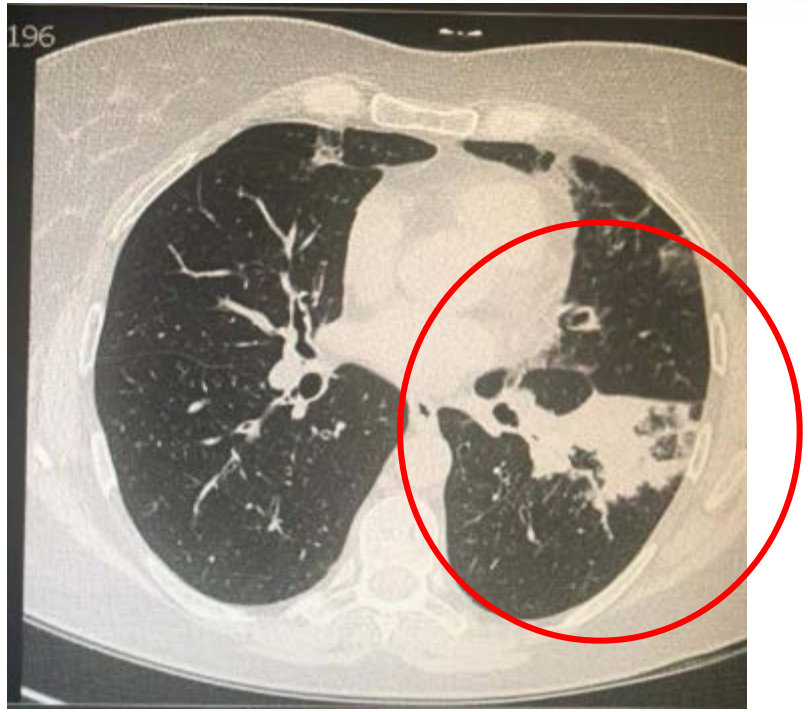




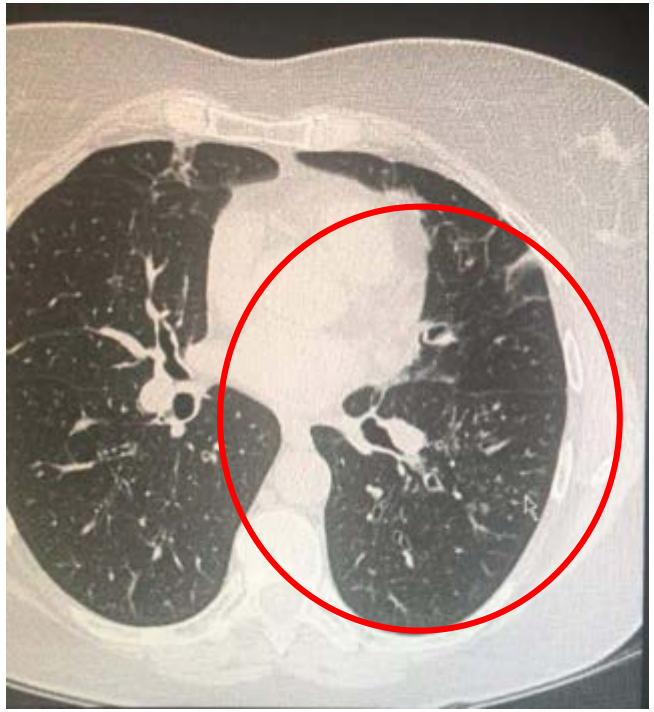


PULMOCIDE

PC945 in a patient with allergic broncho-pulmonary aspergillosis (ABPA)



- 54 year old female with severe asthma and ABPA managed with hospitalization for 1 week of IV hydrocortisone every 8 weeks
- ++ sputum production & mucus plugging
- Unresponsive to multiple courses of oral nebulized and IV antifungals for 12 years



- At 1 month after initiating PC945, CXR and CT (above) lesions resolved, cultures negative and no sputum production
- Total IgE ↓ and exercise tolerance improved ++
- No hospitalizations for IV steroids or antifungals since starting PC945 (> 1 year)

PULMOCIDE

Regulatory challenges and opportunities in the setting of IPA

- Heterogeneity of the study population and of clinical practice:
  - Enrolling subjects with different clinical backgrounds and risks of mortality
  - Defining standards of care for study qualification and for the management of background disease during the trial
  - Defining refractory patients
  - Differences in treatment effect sizes by background disease – are there issues in combining them?
  - Assessing the potential for additive, synergistic or antagonistic effects when adding an inhaled antifungal to standard of care.

Acknowledgements

- We would like to thank the patients whose clinical journey we presented for allowing us to include their experience on PC945, as well as the following physicians who were responsible for their care:

  - Dr Anna Reed - Respiratory and Transplant Medicine, Harefield Hospital, U.K.
  - Dr Darius Armstrong-James - Department of Infectious Diseases, Imperial College London, U.K.

PULMOCIDE

Thank you

Lance Berman
lance@pulmocide.com