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

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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. (including C auris), Rhizopus oryzae, Cryptococcus 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
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

<table>
<thead>
<tr>
<th>Type</th>
<th># of Patients</th>
<th>Prior Antifungal Treatment</th>
<th>Clinical effect with PC945 at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung transplants</strong>&lt;br&gt;(CF, α1-antitrypsin deficiency, IPF, hypersensitivity pneumonitis)</td>
<td>7</td>
<td>≥ 2.5 months to &gt;2 years (multiple azoles, caspofungin, neb amph B, terbinafine)</td>
<td>Favorable response in 6 patients, Stable disease in 1 patient (infection unconfirmed)</td>
</tr>
<tr>
<td><strong>Critical care</strong>&lt;br&gt;(lupus-related hemophagocytic syndrome)</td>
<td>1</td>
<td>1 month (IV isavuconazole, IV voriconazole, caspofungin, IV amph B, neb amph B)</td>
<td>Favorable response (treated for 6 weeks)</td>
</tr>
<tr>
<td><strong>ABPA</strong></td>
<td>1</td>
<td>&gt; 12 years (azole, caspofungin, neb amph B, IV amph B)</td>
<td>Favorable response</td>
</tr>
</tbody>
</table>

**Secondary prophylaxis**

<table>
<thead>
<tr>
<th>Type</th>
<th># of Patients</th>
<th>Prior Antifungal Treatment</th>
<th>Clinical effect with PC945 at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung transplant&lt;br&gt;(aspergilloma)</td>
<td>1</td>
<td>Surgical removal, multiple azoles, caspofungin, amph B contraindicated</td>
<td>Follow-up information pending</td>
</tr>
</tbody>
</table>
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
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
  - FEV₁ has increased by 450 mL (Pre 1.61 L, > 6 months 2.06 L)
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)
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

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Thank you

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