Clinical Development of Therapeutics for ABPA: Experiences from a clinical study and lessons learned

Addressing Challenges in Inhaled Antifungal Drug Development

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PULMATRiX develops inhaled medicines using the proprietary iSPERSE™ technology platform.

**iSPERSE Technology**
- Engineered dry powder delivery vehicle
- Potential use with broad range of therapeutic small molecules and biologics
- High dispersibility with low inspiratory flows
- Efficient delivery of high payloads
- Delivery device flexibility

**PUR 1900 (Pulmazole™)**
- Itraconazole for inhalation
- Developed for treatment of allergic bronchopulmonary aspergillosis (ABPA)
- Achieves MIC in sputum against *A fumigatus* for 24 hours after single 20 mg inhalation
- Single dose 20 mg inhaled plasma exposure ~85-fold lower than single dose 200 mg oral plasma exposure

Potential to eradicate *A fumigatus* from the lung, reduce corticosteroid exposure, and shorten disease course while minimizing the risks of systemic azole therapy.
Initial Phase 2 Study of PUR 1900 in Patients with ABPA

Objectives:
• Assess safety and tolerability of PUR 1900 in patients with asthma and ABPA
• Evaluate potential endpoints
• Identify optimal dose

Primary Endpoint
• Safety & Tolerability

Effect Measures
• Sputum eosinophils
• Pulmonary function (FEV₁)
• Serum IgE
• Disease control (ACQ-6)

Endpoints:
• Safety
• Tolerability
• Biomarkers
• Lung function
• Disease control

• M/F 18-75 years of age with asthma and stable ABPA
• Randomized, double-blind, placebo-controlled study (1:1:1:1 randomization; n = 16 per arm)
• QD dosing for 28 Days
## Site Performance and Subject Recruitment

<table>
<thead>
<tr>
<th>Site Identification</th>
<th>Inclusion/Exclusion Criteria</th>
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<tbody>
<tr>
<td>● 25+ sites in 5 countries with proven track record in clinical asthma studies</td>
<td>● Age 18-65; BMI &gt;18 and &lt;35</td>
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<td>● Mix of freestanding clinical study sites and academic institutions</td>
<td>● Diagnosis of ABPA by ISHAM criteria</td>
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<td>● Stage 2, 4, 5a, or 5b</td>
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<td></td>
<td>● Total serum IgE ≥ 1000 IU/mL</td>
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<td>● No Mab or azole therapy in last 6 months</td>
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<table>
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<tr>
<th>Barriers to Recruitment</th>
<th>Learnings</th>
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<tr>
<td>● Relatively small pool of potential subjects</td>
<td>● Site selection is key</td>
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<tr>
<td>● Subjects &gt; 75 years of age; BMI &gt;35</td>
<td>● Academic sites perform better</td>
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<td>● Current IgE &lt; 1500 IU/mL</td>
<td>● Inclusion criteria need to be wide</td>
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<td>● Omalizumab use</td>
<td>● Need to define a relevant and realistic lower threshold for IgE</td>
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Measures of Effect

- IgE
  - Used clinically as an indicator of improvement
- Sputum eosinophils
  - Technically challenging
- Specific IgE
  - Correlation to disease?
- Corticosteroid reduction
  - Clinically meaningful
- Radiographic evaluation
  - Requires standardized criteria
  - Correlation to disease?

- FEV\textsubscript{1}
  - Standard endpoint for asthma studies
  - Variability enhanced in patients with ABPA
  - Few studies of ABPA demonstrate relatively small change in FEV\textsubscript{1}

- Exacerbations
  - Definition – asthma or ABPA, or both?
  - What is an appropriate observation period?
- 6 minute walk
  - No data
Lessons Learned

- ABPA is an understudied entity
  - No large natural history studies, few interventional studies
- Prevalence of ABPA is likely lower than currently assumed
  - Conduct of clinical studies of ABPA mimic studies in rare disease populations
- Site selection is key, but site identification is challenging
  - ABPA not reported, no registries, no advocacy groups
- Inclusion criteria must be wide
  - Makes for a heterogeneous population
  - When is ABPA no longer ABPA?
- Endpoints and tools to assess effect poorly defined
  - Asthma versus ABPA endpoints
Implications

● Industry-sponsored intervention trials will likely enlarge the understanding of ABPA (“learn as you go”)
  ▪ Endpoint definition may need to evolve during development programs; acceptance of interim endpoints may be necessary

● Need to establish standard criteria defining ABPA, staging, and remission
  ▪ Is there a lower limit for IgE? other measures?

● Low prevalence of ABPA will not support standard clinical development approach for marketing authorization
  ▪ Multiple large studies not feasible; requires streamlined development program