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

NASDAQ: PULM

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

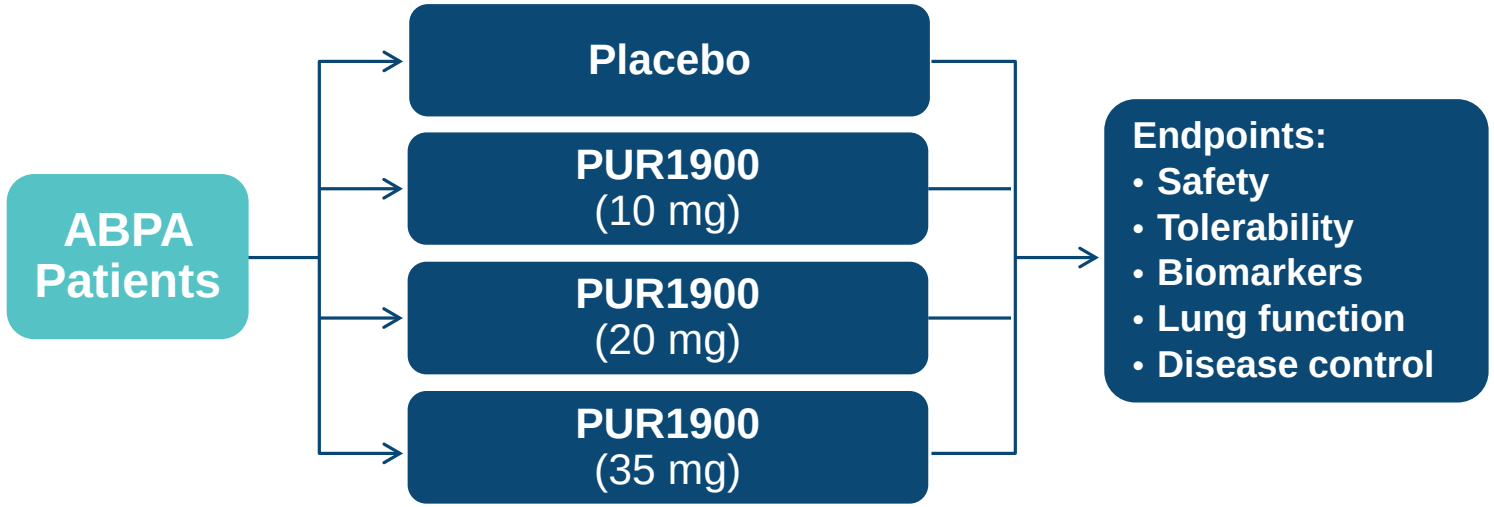
PUR 1900 (Pulmazole™)

- 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 (FEV_1)
- Serum IgE
- Disease control (ACQ-6)

- **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**

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Site Performance and Subject Recruitment

Site Identification

- 25+ sites in 5 countries with proven track record in clinical asthma studies
- Mix of freestanding clinical study sites and academic institutions

Inclusion/Exclusion Criteria

- Age 18-65; BMI >18 and <35
- Diagnosis of ABPA by ISHAM criteria
- Stage 2, 4, 5a, or 5b
- Total serum IgE $\geq$ 1000 IU/mL
- No Mab or azole therapy in last 6 months

Barriers to Recruitment

- Relatively small pool of potential subjects
- Subjects > 75 years of age; BMI >35
- Current IgE < 1500 IU/mL
- Omalizumab use

Learnings

- Site selection is key
- Academic sites perform better
- Inclusion criteria need to be wide
- Need to define a relevant and realistic lower threshold for IgE

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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_1
  - Standard endpoint for asthma studies
  - Variability enhanced in patients with ABPA
  - Few studies of ABPA demonstrate relatively small change in FEV_1
- Exacerbations
  - Definition – asthma or ABPA, or both?
  - What is an appropriate observation period?
- 6 minute walk
  - No data

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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

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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

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