Perspectives on inhaled anti-fungal drug development
in ABPA

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Zambon

Zambon SpA is a family owned global pharma company founded in 1906 with HQ in Italy

Respiratory medicine portfolio focused on severe lung infection and inflammation

Marketed

- Fluimucil mucolytic (N-acetyl cysteine)
- Promixin (nebulized colistimethate sodium CMS) for *Pseudomonas Aeruginosa* (PA) infection in **Cystic Fibrosis** patients

Phase 3

- CMS I-neb for *PA* colonisation in **Non Cystic Fibrosis Bronchiectasis (NCFB)**
- Inhaled liposomal cyclosporin A (LCSA) for **Bronchiolitis Obliterans Syndrome (BOS)** in lung transplantation

Edry®. Proprietary dry powder formulation technology: Development programmes

Edry® inhaled voriconazole for ABPA

- **Completing Phase 1 evaluation**

Pre-clinical

- Edry® inhaled antibiotic for *Mycobacterium* infection
- Edry® inhaled anti-inflammatory for acute lung injury

ABPA unmet needs and objectives for new therapeutic agents

There is an unmet medical need for a therapeutic agent for ABPA that is shown to be safe and effective

Inhaled azole is a therapeutic approach that can potentially reduce or eliminate the burden of *Aspergillus fumigatus* in the lung while minimizing adverse events associated with systemic azole therapy

Principal objectives of a new treatment are:

- To reduce frequency of asthma exacerbations
- Reduce use of steroids
- Reduce use of systemic azole therapy
- Reduce healthcare utilization
- Improve patient function and quality of life

Development challenges: Patient identification

Number of ABPA patients in the pool is unclear

The prevalence of ABPA is unknown. The current best estimate of 2.5% was derived from retrospective studies conducted at referral centers that see mostly patients with severe asthma, so likely to be an overestimate for the general asthma population

Stage of ABPA to be treated

Acute ABPA exacerbation versus stable ABPA?

Diagnosis

There are no well-established criteria for diagnosis and classification of severity of ABPA

While some criteria have been published, these criteria do not necessarily reflect a consensus; nor lend themselves well to the application in clinical trials

Historical diagnosis for patients with stable ABPA and how may stable ABPA be defined?

ISHAM criteria: how best to apply to get a homogenous trial population without making recruitment unfeasible

Development challenges: Outcome measures

Registration trials for ABPA are new territory. Endpoints yet to be clearly defined
Endpoints used in asthma or cystic fibrosis trials may not be appropriate for ABPA

Surrogate markers vs clinical outcome measures:

What to use when? Early Phase vs Late Phase

Keep in mind the product label when selecting outcome measures

Surrogate endpoints

- Laboratory markers, eg IgE, galactomannan,
- Imaging, CXR and/or HRCT, pulmonary infiltrates, bronchiectasis
- Pulmonary function testing: FEV1, FVC etc

Clinical outcome measures

Pulmonary exacerbations

- How defined and how to capture duration of exacerbations?
- There are 3 main types of exacerbation. Should we separate, or combine asthma, ABPA and bronchiectasis exacerbations?
- Different types of exacerbations have different treatment regimens and therefore will have different duration
- Time to first exacerbation versus rate of exacerbations as a primary endpoint?

Other clinical outcome measures: primary or secondary?

- QoL
- Asthma questionnaires

Development challenges: Trial design and conduct

➢ **Selection of trial sites**

- There are no registries, and there is no mechanism to report cases at a regional or global level.
- There are no regional or global advocacy groups, and very few established “centers of excellence” for ABPA; making identification of trial sites difficult

➢ **Duration of treatment**

- Base on clinical practice for oral regimens for chronic ABPA treatment?
- Weeks, months, intermittent, continuous?

➢ **Minimising screen failures**

- Balancing the need for a coherent homogeneous trial population while not unnecessarily excluding patients who might benefit

➢ **Capture and management of exacerbations**

- Type and start and end of pulmonary exacerbations
- Tests supporting diagnosis of exacerbation type eg IgE and CXR
- Treatment of exacerbations: eg standardising steroid dosing regimens
- Need for hospital visit may cause under-reporting of exacerbations, unless patient very unwell and needs urgent care

➢ **Sample size estimation**

- Eg: If frequency of exacerbations is chosen as primary, there are little data on exacerbation frequency in this population
- Use examples from conditions such as NCFB as overlap in some patients?

Regulatory pathway considerations

- For existing azoles being developed for administration via the inhaled route there is already very substantial human safety data for the systemic routes of administration
- The objective of the inhaled route is to get high concentrations of azole direct to the fungus in the lung while reducing systemic exposure and the risk of systemic adverse effects ie to have a safer treatment for fungal lung disease
- The systemic toxicity is well characterized and the local lung toxicity will be characterised in the development programmes.
- From a clinical development standpoint, ABPA is like a rare disease, and therefore standard clinical development approaches may not be feasible

Given the points above can alternative regulatory pathways be considered to streamline development and bring the new treatments to patients more rapidly?

What could be an appropriate number and size of studies for an NDA?

Consider QIDP and Fast Track designations

Could LPAD be considered for ABPA?