EFFICACY OF PUR1900, AN INHALED ANTIFUNGAL THERAPY, IN A GUINEA PIG MODEL OF INVASIVE PULMONARY ASPERGILLOSIS

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INTRODUCTION
Pulmonary fungal infections in asthma and cystic fibrosis patients, among others, are caused by allergic bronchopulmonary aspergillosis (ABPA) to invasive aspergillosis, underdiagnosed and can be a significant source of morbidity and mortality. Oral triazole treatment is commonly prescribed, but historically, oral bioavailability and achieved lung concentrations are variable and often subtherapeutic. In addition, triazoles like itraconazole have multiple drug-drug interactions (DDIs) that limit their utility as oral drugs. Pulmatrix has developed Pulmazole™ (PUR1900), an inhaled dry powder formulation of itraconazole that is formulated using our proprietary dry powder platform iSPERSE™, engineered to a mass median aerodynamic diameters (MMAD) of ~3μm and high fine particle dose (FPD; % of the nominal dose < 5μm), which results in more than 50% of the nominal dose reaching the lungs with reduced throat deposition. Notably, the aerosol target range of PUR1900 is similar to that of Aspergillus conidia, which, in theory, should result in PUR1900 delivery to lung sites where aspergillosis spores also deposit.

AIMS
- To assess efficacy of PUR1900 (Pulmazole™) in a model of invasive aspergillosis
- To compare efficacy against Sporanox®
- To assess systemic and lung exposure with both dose routes

METHODS
Both A. fumigatus challenge and PUR1900 dose were delivered using a directed flow inhalation system as shown in Fig 1.

Inhalation dosing
Eight animals per group were assigned to one of 4 dose groups as detailed in the table.

Delivered and Achieved Doses

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Target Dose (mg/kg/day)</th>
<th>Achieved Dose (mg/kg/day)</th>
<th>MMAD (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placebo</td>
<td>0</td>
<td>0</td>
<td>2.25</td>
</tr>
<tr>
<td>2</td>
<td>PUR1900</td>
<td>10</td>
<td>10.1</td>
<td>2.60</td>
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<tr>
<td>3</td>
<td>PUR1900</td>
<td>30</td>
<td>26.9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sporanox</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Pathogen Challenge
All manipulations using A. fumigatus conidia were performed at room temperature conducted using BSL-2/ABSL-2 containment facilities and practices. Potato dextrose agar (PDA) plates were inoculated with A. fumigatus and incubated at 37°C for 7 days. Conidia were harvested and processed, resulting in a dark green suspension that was stored on wet ice until use. All guinea pigs were immunosuppressed with cyclophosphamide and cortisone acetate on two occasions and challenged via nose-only inhalation for 45 minutes using a nebulizer suspension at a target concentration of approximately 5x10^8 conidia/mL.

RESULTS

Fig 2. Bioanalysis. On Day 1, immediately after dose, plasma itraconazole levels were generally low for both dose routes and very variable after oral Sporanox. Lung levels were high after inhalation dosing but not after oral dose. By 24 hours after dose, both plasma and lung levels had reduced significantly. By Day 14 (4 days after the last dose), significant lung levels remained in the inhalation dosed animals only, at levels that would be considered sufficient to provide efficacy, whereas only trace lung levels were seen in orally dosed animals. Plasma exposure in either inhaled or orally dosed animals was low for all groups on Day 14.

Fig 3. Body Weight and Temperature. Dosing period is shown as a red bar. Exposure to A. fumigatus resulted in weight loss between Days 4 and 9 in all groups. There was no significant effect of any treatment on body weight change. Similarly, exposure to A. fumigatus resulted in an increase in body temperature after Day 4. Treatment with either PUR1900 or Sporanox failed to significantly effect the magnitude of the temperature response but did delay the onset slightly. The reduction in temperature ion control animals is an artifact secondary to the death of infected animals.

CONCLUSIONS
- Inhaled PUR1900 provides higher lung exposure than oral Sporanox, relatively low systemic exposure and a high lung:plasma ratio.
- These data indicate that Pulmazole™ (PUR1900) shows potential as an inhaled therapy for pulmonary fungal infection.

REFERENCES