Orally Inhaled Antifungal Drug Development: Clinical Pharmacology Perspective

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Disclaimer

• This presentation reflects the views of the presenter and are not intended to represent official policy of the Food and Drug Administration
Aim & Objectives

• To discuss clinical pharmacology considerations relevant for developing an acceptable orally inhaled antifungal drug product (OIAD)
  – Device Considerations
  – Clinical Pharmacokinetics
  – Dose Finding
Rationale for Inhaled Drugs

- The lung is the target (assumption for this talk)
- Efficacy ➔ local delivery
- Systemic safety ➔ systemic drug exposure
  - Lung absorption
  - GI absorption
### Interface of Drug, Device, and Patient Characteristics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DEVICE</th>
<th>PATIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Solubility</td>
<td>• Particle size</td>
<td>• Disease &amp; disease severity</td>
</tr>
<tr>
<td>• Dissolution</td>
<td>• Velocity</td>
<td>• Mucus / aqueous layer</td>
</tr>
<tr>
<td>• Lipophilicity</td>
<td>• Efficiency</td>
<td>• Mucociliary clearance</td>
</tr>
</tbody>
</table>

**Impact**

- Site of deposition, absorption, and clearance
- Non-uniform lung exposure

PMID 25642831 | 1750017
Effect of Patient Factors on Lung Deposition

**Technique Challenges**

- Untrained Press-and-Breath MDI
- Trained Breath-actuated MDI
- Untrained Breath-actuated MDI

**Physiological Challenges**

- Lung distribution of OIAD dependent on coordination between device actuation and patient breathing
- Lung distribution of OIAD dependent on pathology and severity of disease

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**Effect of Inhalation Device on Efficacy**

<table>
<thead>
<tr>
<th>Dose (mcg)</th>
<th>Device 1</th>
<th>Device 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25</td>
<td>0.10</td>
<td>0.18</td>
</tr>
<tr>
<td>2.5</td>
<td>0.05</td>
<td>0.15</td>
</tr>
<tr>
<td>5</td>
<td>0.15</td>
<td>0.13</td>
</tr>
<tr>
<td>10</td>
<td>0.13</td>
<td>0.15</td>
</tr>
<tr>
<td>20</td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>

*Device 1 represents the test; Device 2 the comparator of the same drug.*

- Efficacy was deemed to be acceptable with 3-fold lower dose with Device 1
- Efficacy and safety depend on both drug formulation and device
- The **to-be-marketed** inhaled formulation & device are needed in clinical trials
OIAD Clinical PK Considerations

• Single and multiple dose PK in healthy subjects and/or targeted patient population
• Systemic PK, along with in vitro metabolism data, can be used to evaluate potential clinical drug-drug interactions
• Dose adjustment in renal or hepatic impairment are not possible because of local drug effect in lungs
• For antifungals with approved systemic formulations, systemic OIAD PK can be used to bridge systemic safety for the OIAD
• Efficacy for OIAD cannot be bridged using systemic PK to the approved systemically administered antifungals
Initial Dose Regimen Selection

• Nonclinical / animal models of fungal lung disease
  – Estimation of clinical starting dose / dose regimen
  – Lung PK-PD targets for initial dose regimen selection
    • Evaluation of ELF and alveolar macrophage drug concentrations provide information on drug penetration into the lungs & potential for clinical efficacy
    • Gap regarding nonclinical lung PK-PD targets to clinical efficacy

• In patients with invasive fungal lung infections
  • Interpretation of sputum, ELF, and/or alveolar macrophage antifungal drug concentrations are challenging due to:
    – High degree of variability, especially sputum
    – Not always reflective of lung target-site of action
Clinical Dose Regimen Selection

• Dose-Response and/or Dose-Finding should be an integral part of the Phase 2 drug development program
  – Phase 3 dose regimen should be informed by Phase 2 trials
  – Multiple ascending dose Phase 2 trial(s) need to include the anticipated Phase 3 inhaled clinical dose regimen and evaluate a range of dose regimens (low and high) & associated efficacy / safety
  – Important to enroll patients that will be reflective of Phase 3 target patient population
Conclusion

- Many influential factors - drug formulation, device, fungal lung disease severity, patient use - affect pulmonary PK of OIAD
- Nonclinical / animal models of fungal lung disease may be informative
- Phase 2 trial(s) needed to support the Phase 3 dose regimen
- To-be-marketed inhaled drug formulation & device need to be used in the Phase 2 / 3 development program
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