LESSONS LEARNED FROM THE CRESEMBA™ DEVELOPMENT PROGRAM

August 4, 2020 – FDA Workshop

Development Considerations of Antifungal Drugs to Address Unmet Medical Need

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Astellas Pharma Global Development, Inc.
ORPHAN DRUG ACT (1983)

Definition: Any disease or condition which affects <200,000 persons in the US
  • Estimated 7,000 rare diseases

Financial incentives
  7 year market exclusivity
  50% tax credit for clinical testing
  Waiver of FDA user fees
  Orphan grants program

Non-financial incentives
  Does not provide a separate regulatory standard

Common Challenges for OD and AF Drug Development
  Small number of eligible patients
  Limited information on disease severity and rate of progression
  Lack of validated endpoints
  Standard of care may not be approved by regulatory authorities
  May not be ethical to use a placebo control
CRESEMBA® DEVELOPMENT PROGRAM
CRESEMBA* DEVELOPMENT PROGRAM LEADING TO APPROVAL

- Start of Isavuconazole Development
- 40 Phase 1 Clinical Studies (~$30M), In vitro database of 11,000 isolates, 14+ in vivo efficacy, PK-PD models covering fungal pathogens
- Phase 3 Trials Begin
- Astellas Licensed ISA Development
- NDA Submitted
  - 44 Studies
  - 2166 Subjects
  - Receiving ISA:
    - 1145 Healthy Subj
    - 144 in Phase 2
    - 403 in Phase 3
- QIDP & Orphan Status Granted
- FDA Approval granted
- Launch 1.5 mns post-approval


~13 year development program
~$100M for 2 Phase 3 (post-in-licensing)

*Cressemba or isavuconazonium sulfate is the produg of the triazole antifungal active moiety isavuconazole
Isavuconazonium sulfate is a water soluble prodrug

The active moiety is isavuconazole a broad-spectrum, triazole antifungal developed for the treatment of invasive fungal disease (IFD) in adults

Isavuconazole has potent activity against \textit{Aspergillus} spp., and Mucorales in vitro, and in animal models\textsuperscript{1,2}

\textsuperscript{1}Lepak et al 2013 Antimicrob Agents Chemother 57:6284–9
\textsuperscript{2}Luo et al 2014 Antimicrob Agents Chemother 58:2450–3
INVASIVE FUNGAL INFECTIONS: KEY POINTS

Typically occur in severely immunocompromised patients

- High comorbidities

Rare infections

- ~12,000 / year aspergillosis in US\textsuperscript{1,2}
- ~500 / year mucormycosis in US\textsuperscript{3}

Difficult to diagnose and treat

- High morbidity and mortality
- Limited therapeutic options

Survival Curves (mITT)

Patients Surviving (%)

Weeks

Voriconazole (N=144)

Amphotericin B (N=133)

P=0.02

Multimodal approach including\(^1\)

- Treatment of underlying condition
- Immediate antifungal therapy
  - Amphotericin B – Lipid formulation
  - Posaconazole as salvage therapy
- Surgical debridement
  - Often leads to blindness, facial disfiguration, or amputations

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Extremely rare condition

- No randomized controlled trials

**Amphotericin B deoxycholate**

- Only approved therapy
- Only available IV
- Toxicity limits use particularly in renally impaired patients
- Lipid formulations are the standard of care, but are not approved for mucormycosis
CRESEMBÄ® PHASE 3 PROGRAM

Study 0104 - SECURE
- Primary support for treatment of Invasive Aspergillosis
- Randomized, double-blind, non-inferiority study vs. voriconazole
- Treatment up to 84 days
- 516 patients enrolled in the primary analysis population (ITT)

Study 0103 - VITAL
- Primary support for treatment of Invasive Mucormycosis
- Open label study in adults; no concurrent control
- Included a range of rare moulds (including Mucorales), yeasts, and dimorphic fungal infections
- Treatment duration up to 180 days
- Primary therapy, refractory, intolerant
- 146 patients received Cresemba
INVASIVE MUCORMYCOSIS: MATCHED CASE-CONTROL METHODS

- Cresemba for primary therapy from the VITAL Study
- Amphotericin* for primary therapy from Fungiscope
- Matching criteria
  - Severe disease
  - Hematologic malignancy
  - Therapeutic debridement
- Matching conducted independently and blinded to outcomes
  - Up to 3 controls for each VITAL IM case
- Day 42 mortality rates analyzed

*Amphotericin B deoxycholate or lipid formulations

STUDY 0103/VITAL: MUCORMYCOSIS ANALYSIS POPULATIONS

Mucormycosis
N = 46

Mucormycosis Infection Only
N = 38

DRC Assessed
Proven / Probable (mITT)
N = 37

Primary
N = 21

Refractory
N = 11

Intolerant
N = 5

### Study 0103/VITAL: All-Cause Mortality Mucormycosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary N = 21</th>
<th>Refractory N = 11</th>
<th>Intolerant N = 5</th>
<th>Total N = 37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 42</td>
<td>33.3%</td>
<td>45.5%</td>
<td>40.0%</td>
<td>37.8%</td>
</tr>
<tr>
<td>Day 84</td>
<td>42.9%</td>
<td>45.5%</td>
<td>40.0%</td>
<td>43.2%</td>
</tr>
</tbody>
</table>

#### Literature – Amphotericin*

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Untreated</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roden</td>
<td></td>
<td></td>
<td>244/648</td>
</tr>
<tr>
<td>Skiada</td>
<td></td>
<td></td>
<td>59/152</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>233/241</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21/22</td>
</tr>
</tbody>
</table>

#### Fungoscope – Amphotericin*

<table>
<thead>
<tr>
<th>Day 42</th>
<th>Treated</th>
<th>Untreated</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>41/107</td>
<td></td>
<td></td>
<td>29/29</td>
</tr>
</tbody>
</table>

#### Meta-Analysis – Amphotericin*

<table>
<thead>
<tr>
<th>All**</th>
<th>Treated</th>
<th>Untreated</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>343/907</td>
<td></td>
<td></td>
<td>283/292</td>
</tr>
</tbody>
</table>

### Study 0103 – Cresemba

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mortality Rate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients – Day 42</td>
<td>14/37</td>
<td></td>
</tr>
<tr>
<td>Primary Therapy – Day 42</td>
<td>7/21</td>
<td></td>
</tr>
</tbody>
</table>

*Amphotericin B deoxycholate or lipid formulations

**Roden, Skiada, Fungoscope

Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).
CANDIDEMIA / INVASIVE CANDIDIASIS
LESSONS LEARNED
## ACTIVE: CRESEMBA VS CASPOFUNGIN IN INVASIVE CANDIDIASIS

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>Compare the efficacy of treatment with Cresemba vs caspofungin in patients with candidaemia or other invasive <em>Candida</em> infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multi-national, double-blind, randomised, non-inferiority study of intravenous (IV) Cresemba versus IV caspofungin; switch to oral treatment allowed from Day 11</td>
</tr>
<tr>
<td>Study population</td>
<td>450 adult patients with candidaemia or other invasive <em>Candida</em> infections to ensure at least 85% power to demonstrate non-inferiority of isavuconazole to caspofungin at a non-inferiority margin of 15%</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Overall response* at end of IV treatment (EOIVT) as determined by an independent, blinded Data-Review Committee (DRC) in the mITT population</td>
</tr>
<tr>
<td>Key secondary efficacy endpoints</td>
<td>DRC-assessed overall response at Follow-Up 1 (i.e., 2 weeks after end of treatment [EOT]) All-cause mortality by Day 14 and Day 56</td>
</tr>
</tbody>
</table>

*Successful overall response required successful clinical and mycological response plus no use of alternative systemic antifungal therapy (SAT) within 48 hours after the last dose of study drug.  
mITT, modified intent-to-treat population

ACTIVE INVASIVE CANDIDIASIS TRIAL ENROLLMENT CHALLENGES

Lengthy Enrollment – 5.75 years

Monthly enrollment never over 20 patients

- 30 countries of which 25 enrolled a patient
- 80% of enrollment in 8 countries
- 158 sites of which 111 enrolled at least 1 subj (70%); 43% enrolled 2 or less

- Focus on smaller set of countries?
  - Each new country adds $$$ to the operational costs – CHOSE CAREFULLY

Not a “more is better” situation!
MITIGATIONS

473 enrolled

23 withdrew before randomization

450 randomized

Analyzed
221 ITT population
199 mITT population
220 safety population

Analyzed
219 ITT population
201 mITT population
220 safety population

• Closed non-performing sites/countries mid-way through the trial.

• Re-examined the sample size assumptions:
  • actual vs projected (80%) evaluability rate
  • study power

Final evaluability rate was ~90%

• 526 to be randomized to get 420 in mITT at 90% power

• 420 to get 350 in mITT at 85% power


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TREMENDOUS EFFORT HOWEVER… TRIAL DIDN’T MEET PRIMARY ENDPOINT

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>Isavuconazole (n = 199)</th>
<th>Caspofungin (n = 201)</th>
<th>Adjusted difference (%) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful overall response at EOIV*</td>
<td>120 (60.3)</td>
<td>143 (71.1)</td>
<td>-19.9 - 10.8 -1.8</td>
</tr>
<tr>
<td>Successful overall response at EOT + 2 weeks</td>
<td>109 (54.8)</td>
<td>115 (57.2)</td>
<td>-12.6 -2.7 6.8</td>
</tr>
<tr>
<td>All-cause mortality Day 14</td>
<td>29 (14.6)</td>
<td>25 (12.4)</td>
<td>-8.9 -2.5 3.8</td>
</tr>
<tr>
<td>All-cause mortality Day 56</td>
<td>61 (30.7)</td>
<td>60 (29.9)</td>
<td>-10.0 -1.4 7.1</td>
</tr>
</tbody>
</table>

Adjusted difference (%; 95% CI) between isavuconazole versus caspofungin

*Stratified by geographical region and baseline neutropenia status

Taken from Kullberg et. al. ECCMID 2016 oral presentation
LIFE-CYCLE POST-APPROVAL

Post-approval commitments defined by the FDA

1. Registry - clinical efficacy-related outcome data on patients with IM or infection with non-
fumigatus Aspergillus species.

2. In vitro micro-surveillance - prospective study over a 5-year period

3. 2-year CARC rat & mouse

Pediatric Development

- Waived in US due to Orphan Drug Status
- Significant unmet need in pediatrics with IA and IM
- Astellas, in collaboration with our partner, Basilea, are committed to generating data to support the safe and effective use of Cresemba in pediatric patients and is working closely with the FDA to define and complete the pediatric development for Cresemba.

Costs ~$10mil

Not including costs of general product upkeep, including manufacturing, commercial activities, PV activities, MSL team, etc

Costs ~$15-20 mil
Typical Life Cycle

Product Life Cycle (dependent on market conditions)

Margin

Loss of exclusivity

Source for funding additional activities

ACTIVE Trial

Registry Trial

Pediatric Program

Other studies/programs

Additional LCM activities must either improve the life cycle value prior to LOE or grow future margin – improve blue curve or increase gap between curves, generating additional revenue potential to, at minimum, cover costs of investment.
TAKE HOME

• Cresemba development program is not likely to be replicated
  • Each Phase 3 study costs in excess of $125K per patient; global footprint is required and study durations are long
  • Alternative options to RCTs are available for orphan diseases per the regulations but generally accompany larger efficacy and safety trials in another invasive fungal disease
  • High cost of AF drug development from discovery to the initial marketing authorization, post-approval commitments, pediatric development topped with the cost of product upkeep, such as commercial manufacturing, product education are not a sustainable business scenario today and weigh heavy on the decisions to reinvest post-approval.
    – Emphasizing the need to continue to introduce new push and pull incentives to continue investment in new AF compounds to address the significant unmet needs of patients.
THANK YOU