Adequate and Well-Controlled Trials in Neonates: Lessons Learned from Neonatal Candidiasis Program

FDA Workshop
Studies in Neonatal and Young Infants
September 15, 2016

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Director, Global Development
Astellas Pharma Global Development, Inc.
Agenda

• Mycamine® (micafungin sodium)

• Design and conduct of a Phase 3 study of invasive candidiasis in neonates and young infants

• Lessons learned
Astellas Antifungal Agents and Pediatric Experience

• Three systemic antifungals
  • AmBisome® (amphotericin B liposomal formulation)
    • Approved for pediatric patients, aged 1 month to 16 years
  • Mycamine® (micafungin sodium)
    • Approved for pediatric patients, aged 4 months to 16 years
  • Cresemba® (Isavuconazonium sulfate)
    • Recently approved for adults, no pediatric studies to date
Mycamine® (micafungin sodium)

- Member of the echinocandin class of antifungals

- Approved in the U.S. for adults and pediatric patients > 4 months of age for:
  - Treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis, and abscesses;
  - Treatment of esophageal candidiasis;
  - Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplant
Neonatal and Young Infant Development Program

• Pediatric patients were included in the Mycamine development program prior to initial approval in 2005

• However, emerging data about invasive candidiasis in neonates necessitated further evaluation in this population
Key Question to Answer Before Proceeding with Pediatric Studies

• Is there something unique about the disease state or pathogenesis of the condition in neonates and young infants as compared to adult patients?

If the answer is yes, simply matching drug exposures to the efficacious and safe exposures in the adult population may not be adequate
Evolutions in the Field and Challenges to Face

• Pathogenesis of invasive candidiasis in neonates
  • CNS involvement is a prominent feature\textsuperscript{1,2,3}
  • Requires a unique strategy for appropriate dose finding

Higher Exposures Required to Penetrate and Treat CNS Infection

• Rabbit model of hematogenous *Candida* meningoencephalitis mimics pathogenesis of neonatal candidiasis¹

• The target Mycamine AUC to achieve efficacy in CNS infections is ≥ 170 mg·h/L

• The average exposure achieved by the recommended clinical dosage regimen used to treat invasive candidiasis in adults and older children is 100 mg·h/L

¹Hope et al, JID 2008; 197
Mycamine: Increased Weight-normalized Clearance in Infants < 4 Months of Age
Population PK Bridging Study Demonstrates Dose of 10 mg/kg is Most Appropriate

- Monte Carlo simulations demonstrated that a Mycamine dose of 10 mg/kg achieves the target exposure in >85% of the population with <10% of the population at risk of reaching the range where non-clinical toxicities were seen, notably liver enzyme changes.
Further Investigation in Neonates and Young Infants May Be Necessary

- Unique drug disposition compared to older children and adults
- Prominent CNS disease in this population
  - CNS involvement requires higher target exposures for treatment
- There was limited safety and efficacy of this dose and exposure
Designing a Phase 3 Study in Neonates and Young Infants

• Close collaboration with FDA
  • FDA Special Protocol Assessment and Type C meetings
  • Aligned on the protocol and the dosage regimen for the Phase 3 study

• Also worked closely with experts in ID with specific interest in neonatal infections

• Our goal was to create a study design that followed standard of care as closely as possible so that there is minimal impact and risk to the infant while still gathering an informative dataset for analysis
Phase 3 Study Overview

**Study Design:** Phase 3, randomized (2:1), multi-center, double-blind, non-inferiority study comparing micafungin to conventional amphotericin B

**Primary Endpoint:** Fungal free survival (FFS) at one week following the last dose of study drug

**Patient Population:** 225 Infants: > 48 hours of life up to day of life (DOL) 120 with culture proven candidiasis

**Randomization stratification:** Estimated gestational age and Region

**Independent Monitoring Committees:** Independent Data and Safety Monitoring Board (DSMB); Safety and Data Review Panel (DRP); Diagnosis and adjudicate outcome
## Phase 3 Study: Key Study Assessments

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Baseline</th>
<th>Every 48 Hours</th>
<th>7 Days After 1(^{st}) Dose of Study Drug</th>
<th>Every 4-7 Days</th>
<th>Day 1 - Last Dose of Study Drug</th>
<th>Post-Treatment Period (+/- 3 days)</th>
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<tbody>
<tr>
<td>Retinal Exam</td>
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<tr>
<td>Lumbar Puncture (LP)</td>
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<tr>
<td>Abdominal Ultrasound</td>
<td>X</td>
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<tr>
<td>Echocardiogram</td>
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<tr>
<td>Head Ultrasound, Computerized Tomography (CT), or\磁场共振成像 (MRI)</td>
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<td></td>
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<td>X</td>
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<tr>
<td>Urine &amp; Blood Fungal Culture</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Plasma Pharmacokinetic Sampling</td>
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<tr>
<td>CSF Pharmacokinetic Sampling</td>
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<td>X</td>
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Identified Optimal Plasma Sampling Times from Population PK Modeling

- Utilized D-optimal design to define the most informative sampling times
- Allowing for flexibility in plasma sample acquisition and minimizing the number of samples (3) required

Hope AAC, June 2010;54(6):2633–2637
Study Conduct: Getting Started

• Contacted pediatric clinical trial networks globally experienced with disease state, including:

• Established a Scientific Committee to advise on study
  – Daniel Benjamin, MD, PhD (Protocol Chair); Duke University Medical Center Durham, North Carolina, USA
  – William Hope, MD University of Liverpool Liverpool, UK
  – P. Brian Smith, MD Duke University Medical Center Durham, North Carolina, USA
  – David Kaufman, MD University of Virginia Charlottesville, Virginia, USA
  – Thomas J. Walsh, MD Weill Cornell Medical Center New York, New York, USA
  – Antonio Arrieta, MD Children’s Hospital of Orange County, Orange, California, USA
Site Selection Challenges

- Approached 597 sites / 70 countries
- Selected 93
- Initiated 71 sites / 23 countries
Reasons for Not Participating

- General lack of interest, 60%
- Insufficient patient population, 10%
- Insufficient staff and/or equipment, 6%
- Not enough experience with the target population, 5%
- Disagree with comparator, 3%
- EC and/or HA rejection of protocol, 7%
- Site not acceptable to Sponsor, 5%
Global Study

71 sites participating from 23 countries
Longer than Average Start-up Timelines

- Non-U.S. average HA/EC review time = 6.25 months (range 1-17.5 months)
- U.S. average IRB review time = 2.6 months (range 0.2-17.1 months)

Reasons for delays included:
- Multiple rounds of EC/HA Q&A’s to justify study design, including comparator and requested procedures
- Face-to-face meetings with HA
- Appeals after HA decisions
Low Yields from Monthly Screening

Only 51% (36 of 71) sites screened patients

Only 22% (16 of 71) sites enrolled patients
Enrollment and Screening by Site

14% screened were eligible for enrollment
Enrollment Challenges

216 screened

31 randomized

30 treated

2 years and 5 months
Main Reasons for Screen Failures

- Infected not confirmed, 41%
- Infant > 4 months old, 22%
- Received > 48 hours of systemic therapy, 15%
- Parent declined, 12%
- PI discretion, 5%
- Infant died before start, 2%
- Unknown, 2%
- Insufficient venous access, 1%
- Breakthrough infection while receiving prophylaxis with either MICA or CAB, 2%
Declining Incidence of IC in the NICU (1997-2010)
Paradigm Shifts in Treatment Practices

- Increased use of prophylactic treatment of high risk neonates

Fluconazole prophylaxis study in NEJM 2001

Study initiation

Prophylaxis per 1000 admissions

Year


< 750 g
750-999 g
1000-1499 g
>= 1500 g
Challenges During Study Conduct
## Compliance with Protocol Procedures is Challenging

<table>
<thead>
<tr>
<th>End Organ Assessment</th>
<th>Baseline</th>
<th>Treatment Period</th>
<th>Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Fungal Culture</td>
<td>100%</td>
<td>67%</td>
<td>n/a</td>
</tr>
<tr>
<td>CSF Culture</td>
<td>57%</td>
<td>10%</td>
<td>17%</td>
</tr>
<tr>
<td>Urine Fungal Culture</td>
<td>87%</td>
<td>27%</td>
<td>n/a</td>
</tr>
<tr>
<td>Retinal Exam</td>
<td>80%</td>
<td>37%</td>
<td>47%</td>
</tr>
<tr>
<td>Lumbar Puncture (LP) for CSF Analysis</td>
<td>83%</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td>Abdominal Ultrasound</td>
<td>100%</td>
<td>47%</td>
<td>60%</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>0</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>Head Ultrasound</td>
<td>97%</td>
<td>50%</td>
<td>60%</td>
</tr>
</tbody>
</table>
CSF Cultures Performed on Half of the Patients and None were Positive

- 57% (17) infants had a baseline CSF culture
  - 30% (9) infants had only a baseline CSF culture
  - 23.3% (7) infants had a baseline CSF culture plus at least one follow-up
    - Only 3 were done while on therapy

- All CSF cultures collected were negative
  - Consistent with the reported low yield of CSF cultures in this population.
  - Of the 3 cases with CNS involvement in the study, all 3 were diagnosed based on head ultrasounds.
Pharmacokinetic Sampling

- Plasma PK
  - 17 patients (57%)

- CSF PK
  - 2 patients (7%)
Lessons Learned
Lessons Learned

• Evolving epidemiology was not fully defined at the onset of the neonatal program
  • Finding eligible patients was difficult due to low incidence
• Well-established PK-PD models with data rich PK bridging studies provide valuable information to establish dosage regimens
• Regulatory acceptance of study design globally was a huge hurdle
  • Standard of care differs globally
• Neonatal population is vulnerable and parental consent is difficult to obtain
• Eligibility criteria increased the challenges in enrollment and sites ability to participate
• Data requirements and efficacy definitions require careful consideration and the expectations need to balance practical and logistical issues with the need for level of proof for regulatory assessment (e.g. 2 negative cultures to define eradication)
Future Direction

• A combination of well-established *in vivo* PK-PD models with data rich PK bridging studies, and an open-label clinical trial / registry leveraging comparisons to contemporaneous historical controls may be an appropriate development path