Caspofungin Development Program

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Invasive Aspergillosis: Background

- Invasive aspergillosis is an increasing problem in the immunocompromised host
  - Often the leading cause of infection related mortality in transplant centers

- Mortality with documented disease may exceed 90%

- Amphotericin B has limited efficacy and is frequently associated with significant toxicity

- Despite the introduction of itraconazole and the lipid formulations of amphotericin B, morbidity and mortality remain unacceptably high
Potential Benefit of Caspofungin

- Member of a new class of antifungals, the echinocandins
  - Inhibitors of glucan synthesis in the fungal cell wall
  - Cell wall target absent from mammalian cells

- Spectrum of activity includes *Aspergillus* and *Candida* spp.

- Unique mechanism of action results in a lack of cross-resistance with azoles and polyenes
Caspofungin Development Program: Objective

- Demonstrate the safety, tolerability, and efficacy of caspofungin in well documented fungal infections due to *Aspergillus* and *Candida* spp.
  - Confirm caspofungin is at least as effective as amphotericin B and fluconazole in the treatment of patients with *Candida* infections
  - Favorable safety profile with few drug-related adverse experiences
    - Minimal, if any, nephrotoxicity
    - Few significant drug interactions
Objective of the Caspofungin Development Program for Invasive Aspergillosis

- Demonstrate efficacy in the treatment of patients with invasive aspergillosis who have limited therapeutic alternatives
  - Rigorous criteria for diagnosis and response to treatment
  - Documentation required
- Demonstrate a favorable safety profile with few drug-related adverse experiences
Caspofungin Overview

- Preclinical Microbiology
- Clinical Pharmacology
- Efficacy
- Safety Profile
Caspofungin Overview

- Preclinical Microbiology
  - Mechanism of action
  - Spectrum of activity
  - Activity against *Candida* spp.
  - Activity against *Aspergillus* spp.

- Clinical Pharmacology

- Clinical Efficacy

- Clinical Safety
Caspofungin Mechanism of Action

- Phospholipid bilayer of the fungal cell membrane
- β-(1,3)-glucan synthase
- β-(1,3)-glucan
- β-(1,6)-glucan
- Fungal cell wall
- Ergosterol
Caspofungin Mechanism of Action

Implications for Resistance

- Unique mechanism of action; cross-resistance with polyenes and azoles not expected
- Development of resistance to caspofungin is a rare event
Caspofungin Spectrum of Activity

- In vitro activity against *Aspergillus* and *Candida* spp.
- In vitro, no cross-resistance to *Candida* spp. with intrinsic or acquired resistance to fluconazole, amphotericin B or flucytosine
- No activity against *Cryptococcus neoformans*
- Activity against other fungi less well defined
Caspofungin In Vitro Activity Against *Candida* spp.

- Broth dilution endpoint for *Candida* is 100% inhibition of growth
- In vitro kill curves show fungicidal activity with 2 log reduction in colony forming units
Disseminated Candidiasis in Chronically Pancytopenic Mice: Survival

Days Post Infection

Percent Survival

Dosing

Sham

Fluconazole (80 mg/kg)

Fluconazole (20 mg/kg)

Caspofungin (1 mg/kg)

Amphotericin B (1 mg/kg)

Amphotericin B (0.25 mg/kg)

Caspofungin (0.25 mg/kg)

Day -3

Immunosuppression with Cytoxan™

Day 28
## Disseminated Candidiasis in Chronically Pancytopenic Mice: Tissue Burden

<table>
<thead>
<tr>
<th></th>
<th>Kidney Burden Reduction from Control at Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\log_{10}$ CFU Reduction</td>
</tr>
<tr>
<td>Caspofungin</td>
<td></td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>-4.84</td>
</tr>
<tr>
<td>0.25 mg/kg</td>
<td>-3.13</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td></td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>-3.52</td>
</tr>
<tr>
<td>0.25 mg/kg</td>
<td>-2.49</td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td>80 mg/kg</td>
<td>-0.92</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>+0.75</td>
</tr>
</tbody>
</table>
Characterization of Caspofungin In Vitro Activity Against *Aspergillus* spp.

Caspofungin exerts a clear in vitro effect against *Aspergillus* spp., but activity does not fit the classic definition of fungicidal or fungistatic

- Morphological alterations of hyphae seen after exposure to caspofungin
- Broth dilution testing shows substantial inhibition of growth
- Consistent reduction in colony forming units is not seen
Colony Forming Unit Quantitation

*Candida* spp. and Other Yeasts

- 10 Colony Forming Units
- 4 Colony Forming Units

*Aspergillus* spp.

- 1 Colony Forming Unit
Evaluation of Caspofungin Effect Against *Aspergillus* spp. In Vitro Using Vital Dyes

- Vital dyes differentiate viable from dead fungal cells after exposure to drug

<table>
<thead>
<tr>
<th>Status of Cell</th>
<th>Viable Stain (CFDA)</th>
<th>Non-Viable Stain (DiBAC₄(3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>Fluorescent</td>
<td>Non-fluorescent</td>
</tr>
<tr>
<td>Dead</td>
<td>Non-fluorescent</td>
<td>Fluorescent</td>
</tr>
</tbody>
</table>

- Demonstrates effect of caspofungin primarily at tips and branch points of hyphae, where most cell wall synthesis occurs.
Viable Stain - *Aspergillus fumigatus*

- Control
- Amphotericin B 0.15 µg/ml
- Caspofungin 0.30 µg/ml
- Itraconazole 2.5 µg/ml
Non-Viable Stain - *Aspergillus fumigatus*

- Control
- Amphotericin B 0.15 µg/ml
- Caspofungin 0.30 µg/ml
- Itraconazole 2.5 µg/ml
Disseminated Aspergillosis in Chronically Pancytopenic Mice - Survival

- Caspofungin 1 mg/kg
- Amphotericin B 1 mg/kg
- Caspofungin 0.25 mg/kg
- Amphotericin B 0.25 mg/kg
- Sham

Dosing: Day -3 to Day 28

Percent Survival

Days Post Infection

Immunosuppression with Cytoxan™

Day -3 → Day 28
Preclinical Microbiology Summary

- Spectrum of activity includes *Candida albicans*, non-*albicans* *Candida* spp., and *Aspergillus* spp.
- Caspofungin is fungicidal for *Candida* spp.
- Caspofungin demonstrates clear activity against *Aspergillus* spp.
  - In vitro
    - Kills cells with active cell wall synthesis
    - Effects are consistent with the mechanism of action
  - In vivo, there is a sustained activity in severely immunosuppressed mice with disseminated aspergillosis
Caspofungin Overview

- Preclinical Spectrum of Activity
- Clinical Pharmacology
  - Pharmacokinetics and metabolism
  - Pharmacokinetics in special populations
  - Evaluation of drug-drug interactions
- Efficacy
- Safety Profile
Pharmacokinetics and Metabolism

● Poor oral bioavailability in animals
● Distribution, metabolism, and elimination profile similar in animal safety species and man
● Plasma half life of 9 to 11 hours in man
● Plasma pharmacokinetics controlled primarily by distribution
  – Tissue uptake likely mediated through active transport
● Metabolic fate
  – Not oxidative metabolism. Metabolites are products of chemical degradation and hydrolysis
  – Not a substrate for nor an inhibitor of the cytochrome P-450 enzyme system
  – Low level of covalent binding to plasma proteins
Pharmacokinetics: Special Populations

- Caspofungin levels in patients are similar to, but more variable and range higher than, in healthy subjects.

- No clinically meaningful alteration in pharmacokinetics with age, gender, or race.

- No significant alteration of pharmacokinetics in patients with renal insufficiency.

- Increase in caspofungin AUC in subjects with moderate hepatic insufficiency; dose reduction recommended.
Evaluation of Drug-Drug Interactions

- No clinically significant pharmacokinetic interactions
  - Amphotericin B, itraconazole, or mycophenolate

- Tacrolimus administered with caspofungin
  - Tacrolimus AUC decreased 20%; no change in caspofungin pharmacokinetics
  - No change in tacrolimus dose when caspofungin initiated
  - Manage subsequent dosing through standard guidelines for monitoring tacrolimus levels
Drug Interaction Study with Cyclosporin A

- Cyclosporin A (1-2 doses) and caspofungin given to healthy subjects
- Pharmacokinetics
  - Cyclosporin A pharmacokinetics unchanged
  - Caspofungin plasma levels elevated
- Safety
  - Transient increase in ALT to 2- to 3-fold normal in 5 of 12 subjects
  - One *Aspergillus* patient received cyclosporin A and caspofungin for 9 days with no elevation in liver enzymes
  - Pending additional clinical data, use of cyclosporin A is not recommended
Population Pharmacokinetic Analyses

- Patients in caspofungin clinical trials received multiple concomitant medications
- Alterations in caspofungin concentrations due to drug interactions are uncommon
- Coadministration of inducers may result in reduced caspofungin concentrations
Summary of Caspofungin Pharmacology

- Half life of 9 to 11 hours supports once daily dosing
- Low levels of covalent binding to plasma proteins
- Dose adjustments not routinely necessary
- Dose reduction recommended for patients with moderate hepatic insufficiency
- Few clinically significant drug-drug interactions
  - Use of cyclosporin A not recommended until additional data are available
  - Caspofungin dose adjustment may be needed if coadministered with inducers
Caspofungin Overview

- Preclinical Spectrum of Activity
- Clinical Pharmacology
- Clinical Efficacy
  - Overview of clinical development program
  - Dose selection
  - Invasive aspergillosis
  - Esophageal and oropharyngeal candidiasis
- Clinical Safety
Caspofungin Clinical Development Program

Phase II Dose Ranging Studies
Esophageal/Oropharyngeal Candidiasis
35, 50, 70 mg/d Caspofungin

Dose Selection

Candida Esophagitis
Caspofungin vs. Fluconazole

Invasive Candidiasis
Caspofungin vs. Amphotericin B

Salvage Aspergillosis
Caspofungin
Additional Caspofungin Clinical Studies

- Empirical therapy in febrile neutropenia
- Pediatrics
- Compassionate use
Clinical Experience with Caspofungin

- >600 individuals received 1 to 162 days of caspofungin
  - 349 patients
    - 295 received ≥50 mg for at least 7 days
      - 108 received ≥50 mg for at least 14 days
      - 68 received 70 mg for at least 7 days
    - 274 healthy subjects
      - 126 received ≥50 mg for at least 7 days
  - 274 healthy subjects
    - 126 received ≥50 mg for at least 7 days

- An additional ~100 patients on caspofungin in ongoing blinded studies: data on serious adverse experiences
In vitro susceptibility data demonstrated the MIC$_{90}$ for *Aspergillus* and *Candida* spp. was $\leq 1\,\mu g/mL$

- Conservative target: maintain plasma concentration $\geq 1\,\mu g/mL$ throughout the dosing interval

Multiple doses of 50mg resulted in $C_{24hr} \geq 1\,\mu g/mL$ in 95% of patients

- 50 mg daily dose should meet target plasma concentration

Mean $C_{24hr}$ after 50 mg was $<1\,\mu g/mL$ early in therapy

- Addition of a 70 mg dose on day 1 produced levels above 1 $\mu g/mL$ throughout therapy
Caspofungin Dose Selection (Cont’d)

- Initial clinical evaluation in *Candida* esophagitis
  - Doses of 35, 50, and 70 mg once daily were effective and generally well tolerated
  - Response at 35 mg was numerically lower than 50 or 70 mg
  - Population pharmacokinetics showed lower $C_{24hr}$ more commonly associated with unfavorable outcome
Caspofungin Clinical Development Program

Phase II Dose Ranging Studies
Esophageal/Oropharyngeal Candidiasis
35, 50, 70 mg/d Caspofungin

Dose Selection

50mg/d

70mg X 1, then 50 mg/d

Candida Esophagitis
Caspofungin vs. Fluconazole

Invasive Candidiasis
Caspofungin vs. Amphotericin B

Salvage Aspergillosis
Caspofungin
Overview of Invasive Aspergillosis Studies

<table>
<thead>
<tr>
<th>Caspofungin Therapy</th>
<th>Standard Antifungal Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salvage Aspergillus</em> Study (Protocol 019)</td>
<td>Historical Control Study (Protocol 028/029)</td>
</tr>
<tr>
<td>58 patients</td>
<td>206 patients</td>
</tr>
<tr>
<td>11 additional patients</td>
<td></td>
</tr>
</tbody>
</table>

| Compassionate Use Study (Protocol 024/025) | |
| 3 patients | |
Caspofungin Salvage Aspergillus Study (Protocol 019) Design

- Multi-center, open-label, non-comparative study
  - Caspofungin 70 mg qd X 1, followed by 50 mg qd

- Diagnostic criteria
  - Documented invasive aspergillosis, AND
  - Meet criteria as refractory to or intolerant of standard therapy

- Definition of response
  - Favorable response: Complete or Partial Response
  - Unfavorable response: Failure, Stable disease

- Cases reviewed by independent Expert Panel
Efficacy analysis
  – Primary efficacy analysis: End of IV therapy
    • All patients who meet diagnostic criteria, receive at least one dose of caspofungin, and have any data on which to base outcome assessment are included

  – Secondary efficacy analyses
    • Patients meeting above criteria and treated for >7 days
    • Evaluation of relapse at 4 week follow-up visit in all patients with a favorable response at the end of caspofungin therapy
Challenges for Noncomparative *Aspergillus* Studies

- Diagnostic certainty
- Contribution of prior and/or concomitant antifungal therapy
- Documentation of response
- Consistent interpretation of definitions
Diagnostic Certainty in the Caspofungin Salvage *Aspergillus* Study

- Diagnosis of invasive aspergillosis modeled after Mycoses Study Group Criteria (NIAID)
  - **Definite diagnosis:** Histopathology or culture from an invasive procedure
    - Definite diagnosis required for all extrapulmonary cases
  - **Probable diagnosis:** Clinical and radiographic findings plus positive culture or galactomannan ELISA
    - Probable allowed only for pulmonary aspergillosis
Definitions of Refractory or Intolerant to standard therapy

- Refractory: Progression of disease or failure to improve after at least 7 days of therapy with an Amphotericin B formulation or itraconazole
- Intolerant: Doubling of serum creatinine or serum creatinine $\geq 2.5$ mg/dL or significant other drug-related toxicity

Documentation required for classification
Challenges for Noncomparative *Aspergillus* Studies

- Diagnostic certainty
- Contribution of prior and/or concomitant antifungal therapy
- Documentation of response
- Consistent interpretation of definitions
Contribution of Prior and Concomitant Antifungal Therapy to Outcome After Caspofungin

- Extent of disease documented at initial diagnosis and at study entry
  - In refractory patients, used to determine if there was progression of disease or if patient failed to improve
  - In intolerant patients, used to verify status of infection prior to study therapy

- Concomitant antifungal therapy prohibited

- Doses and duration of all antifungal therapy administered for treatment of this episode of invasive aspergillosis documented
Challenges for Noncomparative Aspergillus Studies

- Diagnostic certainty
- Contribution of prior and/or concomitant antifungal therapy
- Documentation of response
- Consistent interpretation of definitions
Documentation of Response in the Caspofungin Salvage *Aspergillus* Study

- Serial assessments of signs, symptoms, and radiographic abnormalities performed

- Favorable response defined as Complete or Partial Response
  - Stable disease considered unfavorable

- Collected reports and actual radiographs from all patients
  - Clear evidence of radiographic improvement required to be defined as a Partial Response
  - Complete Response required complete resolution of all attributable radiographic findings

- Changes in immunosuppression documented
Challenges for Noncomparative *Aspergillus* Studies

- Diagnostic certainty
- Contribution of prior and/or concomitant antifungal therapy
- Documentation of response
- Consistent interpretation of definitions
Consistent Interpretation in the Caspofungin Salvage Aspergillus Study

- Independent panel of 3 experts in invasive aspergillosis
  - Dr. Thomas Walsh, National Cancer Institute
  - Dr. David Denning, University of Manchester, UK
  - Dr. Thomas Patterson, University of Texas, San Antonio

- Each expert assessed diagnosis, response to standard therapy, and outcome after caspofungin therapy for every case

- Evaluation based on:
  - Case report form summaries
  - Official reports of radiographs, procedures, histopathology, and autopsies
  - Actual radiographs
# Caspofungin Salvage *Aspergillus* Study

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Interventions in Protocol 019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic certainty</td>
<td>Strict criteria applied; documentation required</td>
</tr>
<tr>
<td>Effect of other therapy</td>
<td>Extent of disease documented; concomitant antifungal prohibited</td>
</tr>
<tr>
<td>Documentation of response</td>
<td>Reports/radiographs collected; radiographic improvement required</td>
</tr>
<tr>
<td>Consistent interpretation</td>
<td>Expert Panel assessments primary</td>
</tr>
</tbody>
</table>
# Caspofungin Salvage Aspergillus Study
## Baseline Patient Characteristics (N=54)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>(61.1)</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>(38.9)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 40</td>
<td>16</td>
<td>(29.6)</td>
</tr>
<tr>
<td>41 to 65</td>
<td>31</td>
<td>(57.4)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>7</td>
<td>(13.0)</td>
</tr>
<tr>
<td><strong>Site of Infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>39</td>
<td>(72.2)</td>
</tr>
<tr>
<td>Disseminated</td>
<td>10</td>
<td>(18.5)</td>
</tr>
<tr>
<td>Single organ</td>
<td>5</td>
<td>( 9.3)</td>
</tr>
<tr>
<td><strong>Response to Prior Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>44</td>
<td>(81.5)</td>
</tr>
</tbody>
</table>
## Baseline Patient Characteristics (Cont’d)

<table>
<thead>
<tr>
<th>Certainty of Diagnosis</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>38</td>
<td>(70.4)</td>
</tr>
<tr>
<td>Probable</td>
<td>16</td>
<td>(29.6)</td>
</tr>
</tbody>
</table>

### Neutropenia (ANC <500)

<table>
<thead>
<tr>
<th>Neutropenia (ANC &lt;500)</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11</td>
<td>(20.4)</td>
</tr>
</tbody>
</table>

### Underlying Disease

<table>
<thead>
<tr>
<th>Underlying Disease</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancy</td>
<td>20</td>
<td>(37.0)</td>
</tr>
<tr>
<td>Allogeneic stem cell transplant</td>
<td>16</td>
<td>(29.6)</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>7</td>
<td>(13.0)</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>2</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>4</td>
<td>(7.4)</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>(9.3)</td>
</tr>
</tbody>
</table>
# Expert Panel Assessment of Outcome

## Efficacy Analysis

<table>
<thead>
<tr>
<th></th>
<th>Favorable Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary:</strong> All patients with diagnosis who receive at least 1 dose of caspofungin</td>
<td>22/54 (40.7)</td>
</tr>
<tr>
<td><strong>Secondary:</strong> Patients who received &gt;7 days of caspofungin</td>
<td>22/45 (48.9)</td>
</tr>
</tbody>
</table>
## Outcome by Patient Characteristics

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Favorable Response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>18/39</td>
<td>46.2%</td>
</tr>
<tr>
<td>Disseminated</td>
<td>2/10</td>
<td>20.0%</td>
</tr>
<tr>
<td>Other</td>
<td>2/5</td>
<td>40.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neutropenia</th>
<th>Favorable Response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenic (ANC &lt;500)</td>
<td>2/11</td>
<td>18.2%</td>
</tr>
<tr>
<td>Non-neutropenic</td>
<td>20/43</td>
<td>46.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Corticosteroid Use</th>
<th>Favorable Response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 mg prednisolone eq/d</td>
<td>15/32</td>
<td>46.9%</td>
</tr>
<tr>
<td>≥20 mg prednisolone eq/d</td>
<td>7/22</td>
<td>31.8%</td>
</tr>
</tbody>
</table>
## Reason for Study Entry by Response to Prior Therapy

<table>
<thead>
<tr>
<th>Reason for Study Entry</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory*</td>
<td>44 (81.5%)</td>
</tr>
<tr>
<td>Progression</td>
<td>34</td>
</tr>
<tr>
<td>Failure to respond</td>
<td>10</td>
</tr>
<tr>
<td>Intolerant</td>
<td>10 (18.5%)</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>9</td>
</tr>
<tr>
<td>Other toxicity</td>
<td>1</td>
</tr>
</tbody>
</table>

*Includes patients who are refractory and intolerant.
Outcome by Response to Prior Therapy

Refractory or Intolerant Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Favorable Response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory</td>
<td>15/44 (34.1)</td>
<td></td>
</tr>
<tr>
<td>Intolerant</td>
<td>7/10 (70.0)</td>
<td></td>
</tr>
</tbody>
</table>
Refractory Patients

Prior Antifungal Therapy

- Duration of prior therapy
  - >14 days in 31/44 (70%)
  - Of those treated 7 to 14 days:
    • 12/13 (92%) had progression of disease

- Prior therapy
  - 16/44 (36%) refractory to >1 antifungal
  - Patients refractory to itraconazole often also intolerant to amphotericin B
### Outcome by Prior Therapy

**Refractory Patients N=44**

<table>
<thead>
<tr>
<th>Prior Therapy</th>
<th>n/m</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>4/7</td>
<td>57.1</td>
</tr>
<tr>
<td>Lipid Amphotericin B</td>
<td>3/7</td>
<td>42.9</td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole alone</td>
<td>4/7</td>
<td>57.1</td>
</tr>
<tr>
<td>Itraconazole + Intolerant to AmB</td>
<td>1/6</td>
<td>16.7</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0/1</td>
<td>0.0</td>
</tr>
<tr>
<td>Refractory to multiple drugs</td>
<td>3/16</td>
<td>18.8</td>
</tr>
</tbody>
</table>
Intolerant Patients

Prior Antifungal Therapy

- Duration of prior therapy
  - 80% (8/10) received <14 days of prior therapy
  - Two patients received ≥14 days of prior therapy
    - Both intolerant to >1 antifungal

- Response to prior therapy
  - 8 had no improvement prior to entry
  - 2 who improved still had extensive disease
Outcome by Prior Therapy

Intolerant Patients  N=10

<table>
<thead>
<tr>
<th>Prior Therapy</th>
<th>n/m</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>4/4</td>
<td>100.0</td>
</tr>
<tr>
<td>Lipid Amphotericin B</td>
<td>1/3</td>
<td>33.3</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0/1</td>
<td>0.0</td>
</tr>
<tr>
<td>Multiple drugs</td>
<td>2/2</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Degree of Immunosuppression and Outcome

- Favorable responses seen in patients:
  - Receiving high dose corticosteroids
  - Receiving tacrolimus +/- mycophenolate
  - Who had progression of their underlying disease on therapy
  - Who received chemotherapy during the study
  - Who were neutropenic
    - Evidence of response prior to neutrophil recovery
Complete versus Partial Response

- **Definitions**
  - Complete Response: Complete resolution of all attributable signs, symptoms, and radiographic findings
  - Partial Response: Clinically significant improvement of all attributable signs, symptoms, and radiographic findings

- At the end of caspofungin therapy, a favorable response was seen in 22 patients
  - Complete Response: 3
  - Partial Response: 19
● 67 year old male with Acute Myelogenous Leukemia
  – Probable Pulmonary Aspergillosis (CT scan and sputum culture positive for *A. fumigatus* and *A. terreus*)
  – Initial antifungal therapy: Abelcet™ 350 mg/d X 10 days, then Abelcet™ 350 mg qod X 4 days

● Treated with caspofungin for 34 days
  – Experienced blast crisis and requested discontinuation of all therapy and discharge from the hospital
  – End of therapy evaluation: Partial Response
AN058

Pre-Study
Relapse Assessment at the 4 Week Follow-Up

- At the end of IV therapy, 22 patients had a favorable response
  - Seventeen of the 22 patients were evaluated at the 4 week follow-up
    - Two died from their underlying disease
    - Three were lost to follow-up

- Only 1 of the 17 patients evaluated at the 4 week follow-up had a relapse of invasive aspergillosis
Summary of Caspofungin Efficacy in the Salvage *Aspergillus* Study

- High prevalence of poor prognostic factors
  - 80% refractory to standard therapy
    - 70% received >14 days of treatment prior to entry
  - 67% hematologic malignancies or allogeneic stem cell transplants
  - 70% of cases were definite disease
    - All extrapulmonary cases had definite diagnoses
  - Most extrapulmonary cases were disseminated disease
Expert Panel determined that 41% of patients had a Complete or Partial Response at the end of caspofungin therapy.

Favorable outcomes seen in all high risk groups:
- Refractory patients, hematologic malignancies/bone marrow transplant, disseminated disease, corticosteroids, and neutropenia.

Documented relapse uncommon at 4 week follow-up.
Overview of Invasive Aspergillosis Studies

<table>
<thead>
<tr>
<th>Caspofungin Therapy</th>
<th>Standard Antifungal Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salvage Aspergillus Study</strong>&lt;br&gt;(Protocol 019)&lt;br&gt;- 58 patients&lt;br&gt;- 11 additional patients</td>
<td><strong>Historical Control Study</strong>&lt;br&gt;(Protocol 028/029)&lt;br&gt;- 206 patients</td>
</tr>
</tbody>
</table>

**Compassionate Use Study**<br>(Protocol 024/025)<br>- 3 patients
Expert Panel Assessment of 11 Additional Patients in the Caspofungin Salvage *Aspergillus* Study

- Patient characteristics similar to original 58
- Nine of 11 met diagnostic criteria
  - Six pulmonary; 3 disseminated disease
- All were refractory to an amphotericin B formulation
- Favorable responses seen in 4 of 9 (44.4%) patients
  - Three pulmonary; 1 disseminated disease
### Aspergillus Patients in the Compassionate Use Study

<table>
<thead>
<tr>
<th>Underlying Disease</th>
<th>Infection Site</th>
<th>Refractory/Intolerant</th>
<th>Expert Panel Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>Definite pulmonary</td>
<td>R: AmBisome™</td>
<td>Failure</td>
</tr>
<tr>
<td>No defined risk</td>
<td>Disseminated</td>
<td>R: AmBisome™</td>
<td>Complete Response</td>
</tr>
<tr>
<td>AIDS</td>
<td>Definite pulmonary</td>
<td>R: Itraconazole</td>
<td>Partial Response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I: Abelcet™</td>
<td></td>
</tr>
</tbody>
</table>
Efficacy of Caspofungin in Invasive Aspergillosis in Patients Refractory to or Intolerant of Other Therapy

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Favorable Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original 54 Patients</td>
<td>22/54</td>
</tr>
<tr>
<td>+ 9 Additional Patients</td>
<td>40.7%</td>
</tr>
<tr>
<td>+ 3 Patients in Compassionate Use</td>
<td>26/63</td>
</tr>
<tr>
<td></td>
<td>41.3%</td>
</tr>
<tr>
<td></td>
<td>28/66</td>
</tr>
<tr>
<td></td>
<td>42.4%</td>
</tr>
</tbody>
</table>
Overview of Invasive Aspergillosis Studies

Caspofungin Therapy
Salvage *Aspergillus* Study
(Protocol 019)
58 patients
11 additional patients

Compassionate Use Study
(Protocol 024/025)
3 patients

Standard Antifungal Therapy
Historical Control Study
(Protocol 028/029)
206 patients
Challenges for Historical Control Studies

- Identification of appropriate patients for comparison
  - Addressed in study design
  - Cannot duplicate a randomized controlled trial
- Differences in diagnosis and management over time
- Information available in a retrospective review
Historical Control Study (Protocol 028/029)

- **Design**: Retrospective medical chart review

- **Objectives**
  - Describe the efficacy of standard antifungal therapy in patients with invasive aspergillosis
  - Serve as comparison group for the caspofungin *Aspergillus* study
Historical Control Study (Protocol 028/029)

- Patient selection
  - Systematic identification of patients with invasive aspergillosis treated with standard antifungal therapy at ten centers
    - Review of medical records, microbiology, and pathology records backward in time from Dec98 to Jan95
    - Procedure intended to yield a consecutive series of cases at each site
    - Potential cases were screened for eligibility

- Evaluation of outcome
  - Investigator assessment using the same definitions of response as those used in the caspofungin *Aspergillus* study
Key Inclusion Criteria

Caspofungin Salvage Aspergillus Study

Definite Aspergillosis (any site)
Probable Pulmonary Aspergillosis
Age 18 to 80 years

Refractory
- Worsening or failure to improve after at least 7 days of therapy

Intolerant
- Nephrotoxicity
- Other severe toxicity

Receipt of at least 7 days of standard therapy

Historical Control Study
## Identification of Subpopulations in the Historical Control Study

### Historical Control Study Subpopulations Defined Based on Minimum Entry Criteria for Caspofungin *Aspergillus* Study

<table>
<thead>
<tr>
<th>Caspofungin <em>Aspergillus</em> Study</th>
<th>Historical Control Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Refractory</strong></td>
<td>Not improved at week 1</td>
</tr>
<tr>
<td>Progression of disease or failure to improve after ≥7 days of therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Intolerant</strong></td>
<td></td>
</tr>
<tr>
<td>Creatinine ≥2.5mg/dL; Doubling of creatinine; Other severe toxicity</td>
<td>Creatinine ≥2.5mg/dL and improved at week 1</td>
</tr>
<tr>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>
Identification of the Comparison Population in the Historical Control Study

Historical Cohort (N=229)

Refractory or Intolerant Population (R/I) (N=214)

Nonrefractory, Nonintolerant Population (NR/NI) (N=15)

Indeterminate at end of therapy (N=8)

Refractory or Intolerant (R/I) Population, Primary Comparison Population (N=206)
### Baseline Patient Characteristics in the Comparison Populations

<table>
<thead>
<tr>
<th>Predisposing Condition</th>
<th>Caspofungin (N=54)</th>
<th>Historical Control (N=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>Hematologic malignancy (stem cell transplant)</td>
<td>36</td>
<td>(66.7)</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>7</td>
<td>(13.0)</td>
</tr>
<tr>
<td>Other risk factors</td>
<td>9</td>
<td>(16.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neutropenic Status</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &lt;500</td>
<td>11</td>
<td>(20.4)</td>
</tr>
<tr>
<td>ANC ≥500</td>
<td>43</td>
<td>(79.6)</td>
</tr>
</tbody>
</table>
## Distribution of Diagnoses of *Aspergillus* Infection in the Comparison Populations

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Caspofungin N=54</th>
<th>Historical Control N=206</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>Definite Pulmonary</td>
<td>23</td>
<td>(42.6)</td>
</tr>
<tr>
<td>Probable Pulmonary</td>
<td>16</td>
<td>(29.6)</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>15</td>
<td>(27.8)</td>
</tr>
<tr>
<td>Disseminated</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sinus</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pulmonary/sinus</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of Outcomes: Caspofungin versus Standard Therapy in the Historical Control Study

<table>
<thead>
<tr>
<th>Population</th>
<th>Favorable Response</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caspofungin Protocol 019</td>
<td>Standard Therapy Historical Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n/m (%)</td>
<td>n/m (%)</td>
<td></td>
</tr>
<tr>
<td>Refractory or Intolerant</td>
<td>22/54 (40.7)</td>
<td>35/206 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>15/44 (34.1)</td>
<td>27/188 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Intolerant</td>
<td>7/10 (70.0)</td>
<td>3/5 (60.0)</td>
<td></td>
</tr>
</tbody>
</table>
## Outcome by Underlying Disease

<table>
<thead>
<tr>
<th>Underlying Disease</th>
<th>Favorable Response</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caspofungin</td>
<td></td>
<td>Historical Control</td>
</tr>
<tr>
<td></td>
<td>n/m</td>
<td>(%)</td>
<td>n/m</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>13/36</td>
<td>(36.1)</td>
<td>19/144</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>3/7</td>
<td>(42.9)</td>
<td>9/32</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>2/2</td>
<td>(100.0)</td>
<td>2/10</td>
</tr>
<tr>
<td>Other</td>
<td>4/9</td>
<td>(44.4)</td>
<td>5/20</td>
</tr>
</tbody>
</table>
# Outcome by Site of Infection

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Favorable Response</th>
<th></th>
<th>Favorable Response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caspofungin</td>
<td>Historical Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n/m (%)</td>
<td>n/m (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>18/39 (46.2)</td>
<td>32/154 (20.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated</td>
<td>2/10 (20.0)</td>
<td>0/41 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>1/1 (100.0)</td>
<td>1/2 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus</td>
<td>1/3 (33.3)</td>
<td>1/6 (16.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary/sinus</td>
<td>0/1 (0.0)</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>---</td>
<td>1/3 (33.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Outcome by Neutropenia and Corticosteroid Use

<table>
<thead>
<tr>
<th>Neutropenia</th>
<th>Favorable Response</th>
<th>Corticosteroids</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caspofungin</td>
<td>Historical Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n/m</td>
<td>n/m</td>
<td>(%)</td>
</tr>
<tr>
<td>Neutropenic (ANC &lt;500)</td>
<td>2/11 (18.2)</td>
<td>4/57 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Non-neutropenic</td>
<td>20/43 (46.5)</td>
<td>31/149 (20.8)</td>
<td></td>
</tr>
<tr>
<td>&lt;20 mg prednisolone eq. /day</td>
<td>15/32 (46.9)</td>
<td>27/132 (20.5)</td>
<td></td>
</tr>
<tr>
<td>≥20 mg prednisolone eq. /day</td>
<td>7/22 (31.8)</td>
<td>8/74 (10.8)</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of Favorable Outcome Adjusted for Multiple Baseline Characteristics

- Compares the likelihood of a favorable outcome with caspofungin in the Salvage Aspergillus Study and standard therapy in the Historical Control Study

- Adjusts for potential imbalance in important baseline characteristics between populations

- The protocol-specified analytic method adjusts for multiple baseline prognostic factors present in the same patient
Potential Predictors of Outcome

- Disseminated aspergillosis
- Neutropenia
- Bone marrow transplant
- High-dose corticosteroids
- Underlying disease
- Site of Infection
- Intolerance at baseline
- Gender
- Age
- Race
Caspofungin Salvage Aspergillus Study versus Historical Control R/I Population

Logistic Regression Analysis
Odds Ratio and 95% Confidence Interval

- Unadjusted
- Diss/Neut/BMT
- Diss/Neut/Cort
- Diss/Neut/BMT/Cort

Results favor standard therapy
Results favor Caspofungin
Caspofungin Salvage Aspergillus Study versus the Historical Control Study

Summary of Comparison

- Patient characteristics and important risk factors were well balanced between the 2 studies

- Caspofungin was more commonly associated with favorable outcomes than standard therapy in the Historical Control Study
  - Consistent effect across subgroups
  - Consistent effect in both adjusted and unadjusted analyses

- Results support the efficacy of caspofungin in the treatment of invasive aspergillosis
Caspofungin Clinical Development Program

Phase II Dose Ranging Studies
Esophageal/Oropharyngeal Candidiasis
35, 50, 70 mg/d Caspofungin

Dose Selection

Candida Esophagitis
Caspofungin vs. Fluconazole

Invasive Candidiasis
Caspofungin vs. Amphotericin B

Salvage Aspergillosis
Caspofungin
## Oropharyngeal/Eosophageal Candidiasis
### Phase II Studies

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Disease</th>
<th>Treatment Groups</th>
<th>Caspofungin</th>
<th>Amphotericin B</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>003</td>
<td>Esophagitis</td>
<td></td>
<td>X</td>
<td>X</td>
<td>14 days</td>
</tr>
<tr>
<td>004</td>
<td>Esophagitis</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagnostic Criteria:** Symptoms plus microbiological documentation

**Favorable Response:** Resolution of symptoms and significant reduction in endoscopic or oropharyngeal lesions
### Esophageal/Oropharyngeal Candidiasis Phase II Efficacy Data

Percentage of Patients with a Favorable Response at Test of Cure

<table>
<thead>
<tr>
<th>Caspofungin</th>
<th></th>
<th></th>
<th>Amphotericin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 mg</td>
<td>50 mg</td>
<td>70 mg</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>25/34 (73.5%)</td>
<td>70/80 (87.5%)</td>
<td>56/63 (88.9%)</td>
<td>61/89 (68.5%)</td>
</tr>
</tbody>
</table>
Caspofungin Overview

- Preclinical Spectrum of Activity
- Pharmacokinetics and Metabolism
- Efficacy
- Safety Profile
  - Preclinical Safety
  - Clinical Experience with Caspofungin
  - Safety in Controlled *Candida* Studies
  - Safety in the Salvage *Aspergillus* Study
  - Summary
Caspofungin Preclinical Safety

- The distribution, metabolism, and excretion of caspofungin in animal safety species is similar to that seen in humans.
- Caspofungin was evaluated at doses which produced exposures above that seen in patients.
- Across studies and species, caspofungin had a very favorable preclinical safety profile.
Caspofungin Preclinical Safety (Cont’d)

- Findings in 5- to 27-week studies:
  - Mild elevations in serum transaminases in the monkey
  - Histamine release in the rat
  - Irritation at the injection site in the rat and monkey

- With longer duration of dosing, there were no new findings and there was no progression of previously identified treatment-related effects

- No genotoxicity observed
623 individuals received caspofungin

546 received multiple doses
  - 197 healthy subjects
  - 277 patients with oropharyngeal/esophageal candidiasis
  - 72 patients with invasive aspergillosis

421 received ≥50 mg for ≥7 days
  - 126 subjects in Clinical Pharmacology studies
  - 295 patients with Candida or Aspergillus infections
    • 35 patients treated ≥28 days
Overview of Caspofungin Safety Data

- Final Case Report Form Data
  - Phase I Studies
  - Phase II/III *Candida* Studies (Protocols 003, 004, 020, 007)
  - Salvage *Aspergillus* Study (Protocol 019)

- Serious Adverse Experiences reported through Merck’s Worldwide Adverse Experience Experience System (WAES)
  - Invasive Candidiasis (Protocol 014)
  - Empirical Therapy (Protocol 026)
  - Compassionate Use (Protocol 024/025)
Caspofungin Safety Profile

- Generally well tolerated
- Patients with a wide spectrum of diseases and many concomitant medications included
- Favorable safety profile maintained with extended therapy (≥28 days)
- Few serious drug-related adverse experiences or discontinuations due to drug-related adverse experiences
- Elevations in serum transaminases similar to fluconazole and amphotericin B
Clinical Evaluation for Allergic Reactions

In the 623 individuals treated with caspofungin in clinical studies
  – Symptoms compatible with histamine release rarely noted
  – Fever, rash, and eosinophilia occurred
    • Uncommon and rarely occurred together
    • Underlying diseases commonly associated with these findings
    • Concomitant medications often known to be associated with these findings
    • Often isolated events or resolved during continued therapy
  – No pattern of findings were seen that were suggestive of allergic reactions
## Drug-Related Clinical Adverse Experiences

### Phase II/III Controlled *Candida* Studies

<table>
<thead>
<tr>
<th></th>
<th>Caspofungin 50 mg (N=164)</th>
<th>Caspofungin 70 mg (N=65)</th>
<th>Amphotericin B 0.5 mg/kg (N=89)</th>
<th>Fluconazole 200 mg (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>12.2%</td>
<td>26.2%</td>
<td>69.7%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>18.3%</td>
<td>15.4%</td>
<td>22.5%</td>
<td>17.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>8.5%</td>
<td>7.7%</td>
<td>19.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.4%</td>
<td>3.1%</td>
<td>11.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.3%</td>
<td>3.1%</td>
<td>21.3%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.2%</td>
<td>3.1%</td>
<td>13.5%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Chills</td>
<td>1.2%</td>
<td>1.5%</td>
<td>75.3%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
### Drug-Related Fever in the Caspofungin Controlled *Candida* Studies

#### Percentage of Patients with Drug-Related Fever

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Treatment Groups</th>
<th>Caspofungin</th>
<th>Amphotericin B</th>
<th>Fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35mg</td>
<td>50mg</td>
<td>70mg</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>003†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.3</td>
<td>39.3</td>
<td>68.5</td>
<td></td>
</tr>
<tr>
<td>004†</td>
<td>20.6</td>
<td>11.8</td>
<td>16.2</td>
<td>71.4</td>
</tr>
<tr>
<td>020‡</td>
<td></td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† N~30-50/group; ‡ N~85-90/group.
# Drug-Related Laboratory Adverse Experiences

## Phase II/III Controlled *Candida* Studies

<table>
<thead>
<tr>
<th></th>
<th>Caspofungin 50 mg (N=164)</th>
<th>Caspofungin 70 mg (N=65)</th>
<th>Amphotericin B 0.5 mg/kg (N=89)</th>
<th>Fluconazole 200 mg (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT ↑</td>
<td>10.5%</td>
<td>10.8%</td>
<td>22.7%</td>
<td>12.0%</td>
</tr>
<tr>
<td>AST ↑</td>
<td>13.0%</td>
<td>10.8%</td>
<td>22.7%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Alkaline phos ↑</td>
<td>10.4%</td>
<td>7.7%</td>
<td>19.3%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Hematocrit ↓</td>
<td>11.0%</td>
<td>1.5%</td>
<td>32.6%</td>
<td>5.4%</td>
</tr>
<tr>
<td>WBC count ↓</td>
<td>6.1%</td>
<td>4.6%</td>
<td>7.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Serum creatinine ↑</td>
<td>0.0%</td>
<td>1.5%</td>
<td>28.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Serum potassium ↓</td>
<td>3.7%</td>
<td>10.8%</td>
<td>31.5%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>
Summary of Caspofungin Safety in Controlled Candida Studies

- No dose-related toxicity noted
- Most common drug related clinical adverse experiences: fever, phlebitis/infused vein complications
  - Rarely limited therapy
- No serious drug-related adverse experiences
- Few drug-related adverse experiences lead to discontinuation
Overview of Safety

- Safety profile similar to that seen in controlled *Candida* studies
- Drug-related clinical and laboratory adverse experiences were uncommon
- Two serious adverse experiences considered by investigators to be drug-related
  - Pulmonary Infiltrates
  - Hypercalcemia
- Generally well tolerated in 27 patients treated for ≥ 28 days (up to 162 days)
- Safety profile in the 11 additional patients similar to that seen in the original 58
## Drug-Related Adverse Experiences

### Clinical Adverse Experiences

<table>
<thead>
<tr>
<th>Experience</th>
<th>n/m</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>2/58</td>
<td>(3.4)</td>
</tr>
<tr>
<td>Phlebitis/Infused vein complications</td>
<td>2/58</td>
<td>(3.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2/58</td>
<td>(3.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2/58</td>
<td>(3.4)</td>
</tr>
</tbody>
</table>

### Laboratory Adverse Experiences

<table>
<thead>
<tr>
<th>Experience</th>
<th>n/m</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased eosinophils</td>
<td>2/55</td>
<td>(3.6)</td>
</tr>
<tr>
<td>Increased urine protein</td>
<td>3/51</td>
<td>(5.9)</td>
</tr>
</tbody>
</table>
Caspofungin Safety Summary

- Favorable safety profile to date
- Few serious drug-related adverse experiences
- Few drug-related adverse experiences leading to discontinuation
- Incidence of drug-related elevations in liver enzymes is low
- Caspofungin is relatively free of clinically significant drug interactions
Clinical Presentation

Presentation by Dr. Carole Sable

– Background
– Preclinical Microbiology
– Clinical Pharmacology
– Clinical Efficacy
– Clinical Safety

Presentation by Dr. Jeff Chodakewitz
– Concluding remarks