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# Caspofungin Development Program

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# Invasive Aspergillosis: Background

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- 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

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- 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

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- 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

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- 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

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- Preclinical Microbiology
- Clinical Pharmacology
- Efficacy
- Safety Profile

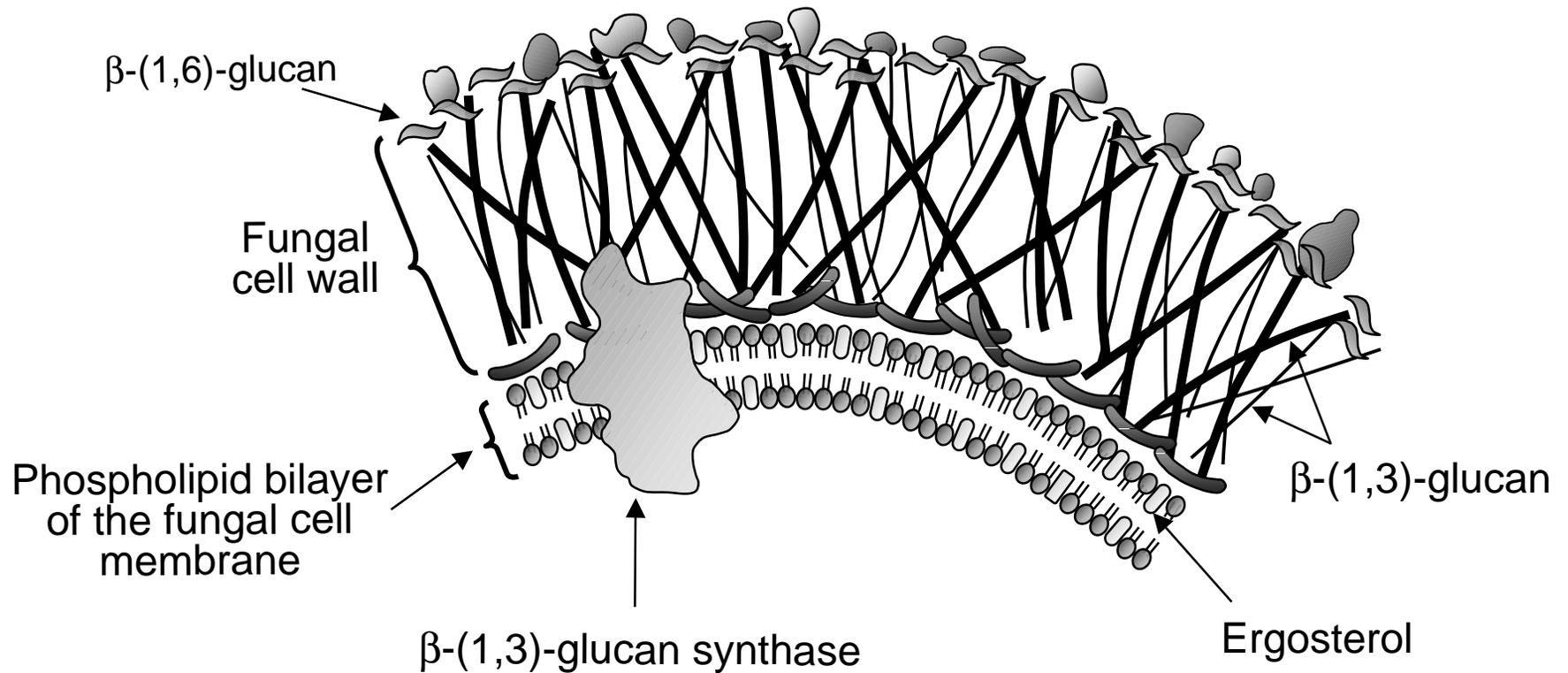
# Caspofungin Overview

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- 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

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# Caspofungin Mechanism of Action

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## 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

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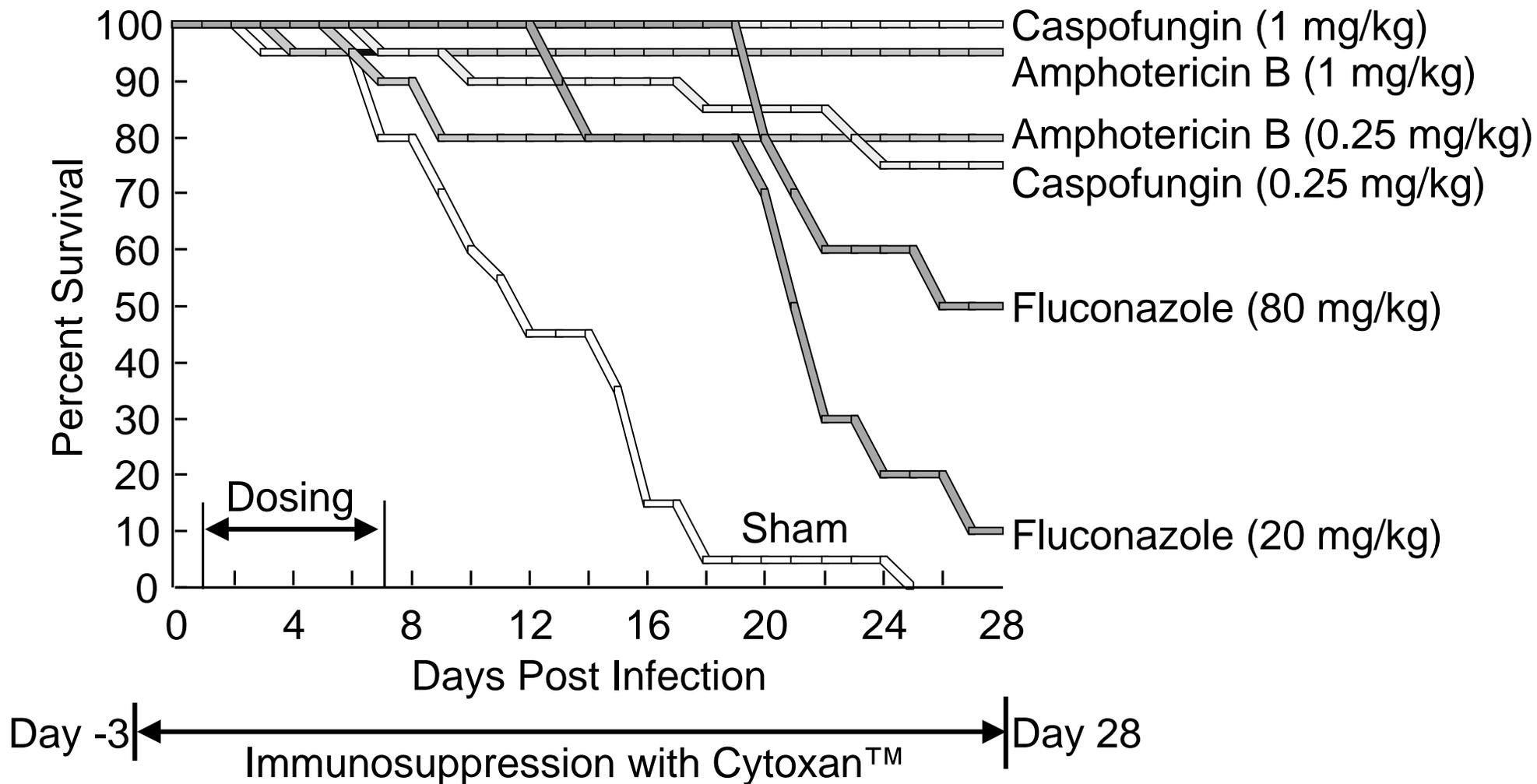
- In vitro activity against *Aspergillus* and *Candida* spp.
- In vitro, no cross-resistance to *Candida* spp. with intrinsic or acquired resistance to fluconazole, amphotericin B or flucytosine
- No activity against *Cryptococcus neoformans*
- Activity against other fungi less well defined

# Caspofungin In Vitro Activity Against *Candida* spp.

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- 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



# Disseminated Candidiasis in Chronically Pancytopenic Mice: Tissue Burden

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|                | Kidney Burden Reduction from Control at Day 28 |                  |
|----------------|--|------------------|
|                | <u>Log<sub>10</sub> CFU Reduction</u>          | <u>% Sterile</u> |
| Caspofungin    |  |                  |
| 1 mg/kg        | -4.84  | 100              |
| 0.25 mg/kg     | -3.13  | 40               |
| Amphotericin B |  |                  |
| 1 mg/kg        | -3.52  | 80               |
| 0.25 mg/kg     | -2.49  | 50               |
| Fluconazole    |  |                  |
| 80 mg/kg       | -0.92  | 20               |
| 20 mg/kg       | +0.75  | 0                |

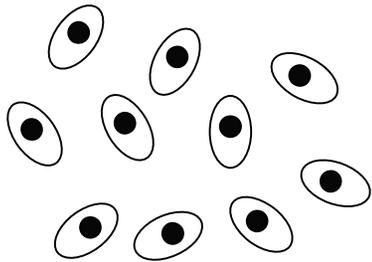
# Characterization of Caspofungin In Vitro Activity Against *Aspergillus* spp.

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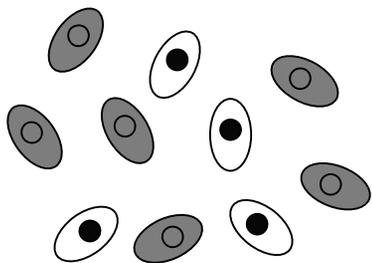
- Caspofungin exerts a clear in vitro effect against *Aspergillus* spp., but activity does not fit the classic definition of fungicidal or fungistatic
  - Morphological alterations of hyphae seen after exposure to caspofungin
  - Broth dilution testing shows substantial inhibition of growth
  - Consistent reduction in colony forming units is not seen

# Colony Forming Unit Quantitation

## Candida spp. and Other Yeasts

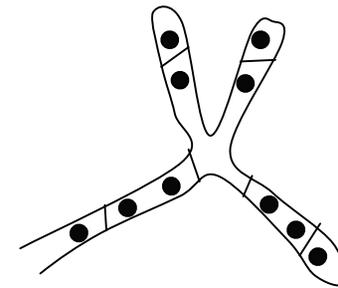


10 Colony Forming Units

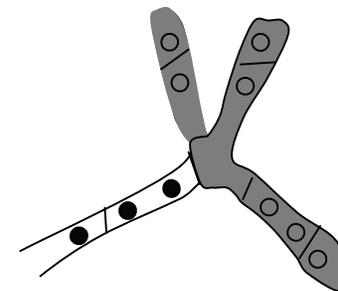


4 Colony Forming Units

## Aspergillus spp.



1 Colony Forming Unit



1 Colony Forming Unit

# Evaluation of Caspofungin Effect Against *Aspergillus* spp. In Vitro Using Vital Dyes

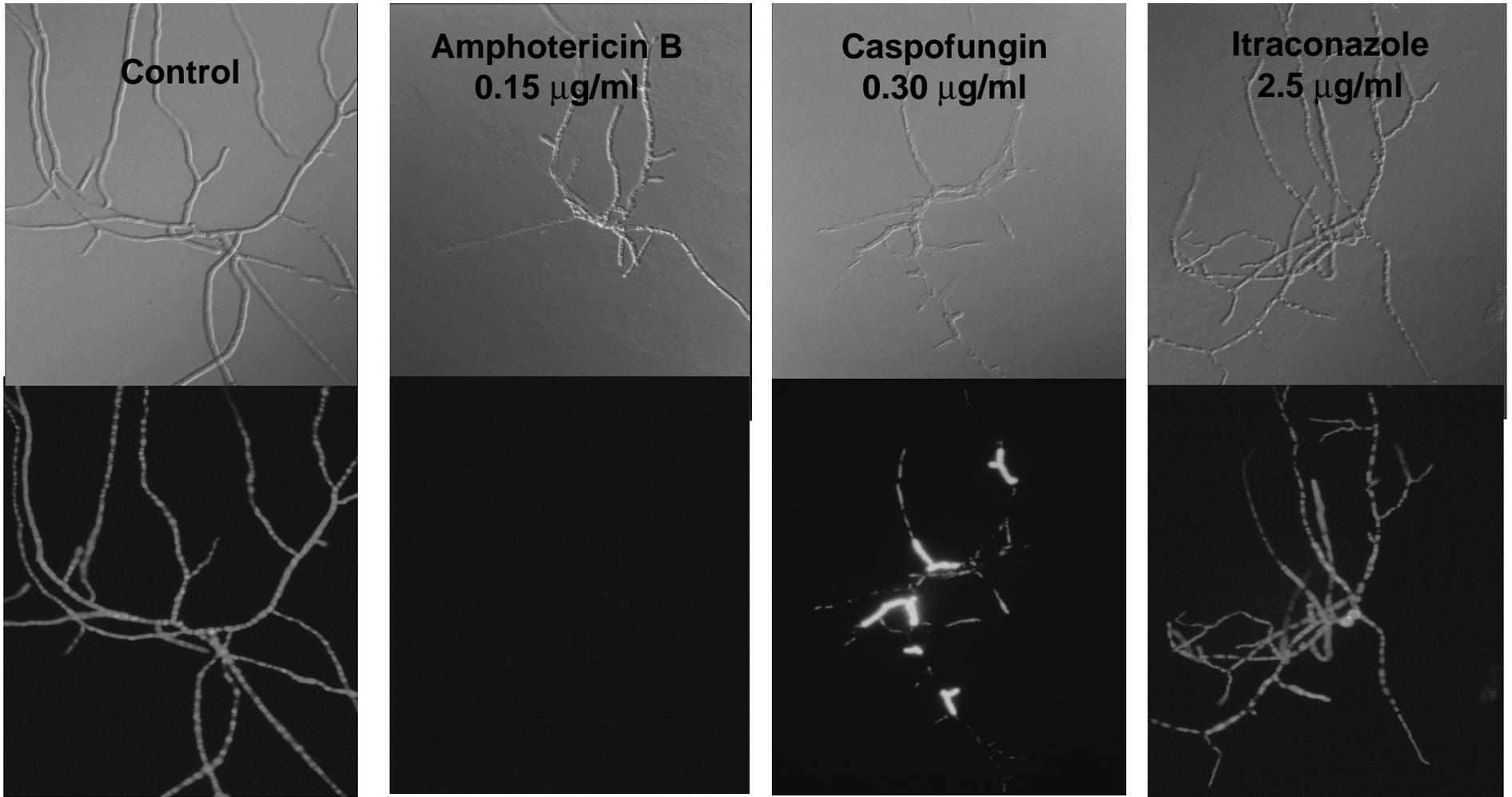
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- Vital dyes differentiate viable from dead fungal cells after exposure to drug

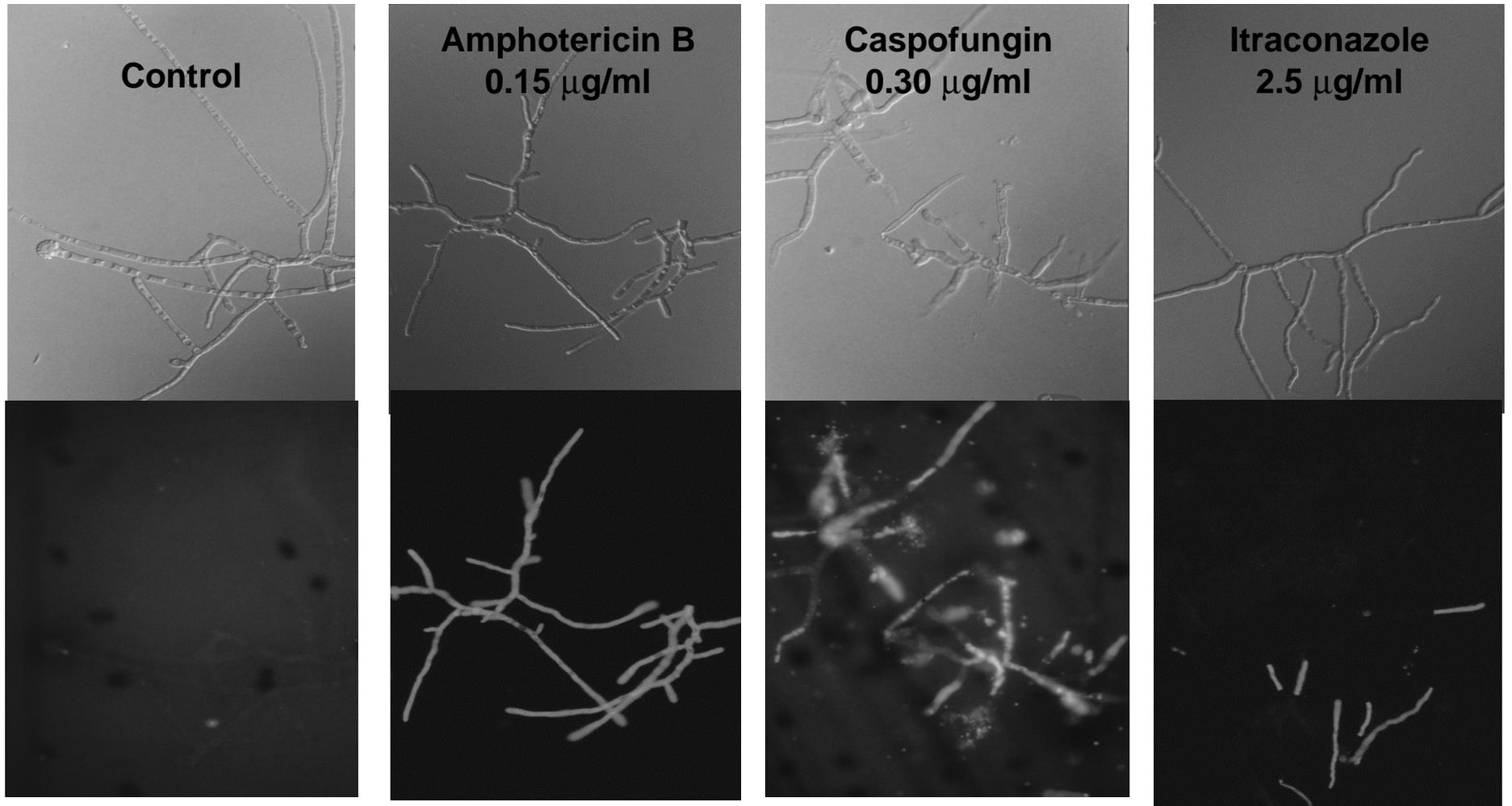
| <u>Status of Cell</u> | <u>Viable Stain<br/>(CFDA )</u> | <u>Non-Viable Stain<br/>(DiBAC<sub>4</sub>(3))</u> |
|-----------------------|---------------------------------|--|
| Alive                 | Fluorescent                     | Non-fluorescent                                    |
| Dead                  | Non-fluorescent                 | Fluorescent  |

- Demonstrates effect of caspofungin primarily at tips and branch points of hyphae, where most cell wall synthesis occurs

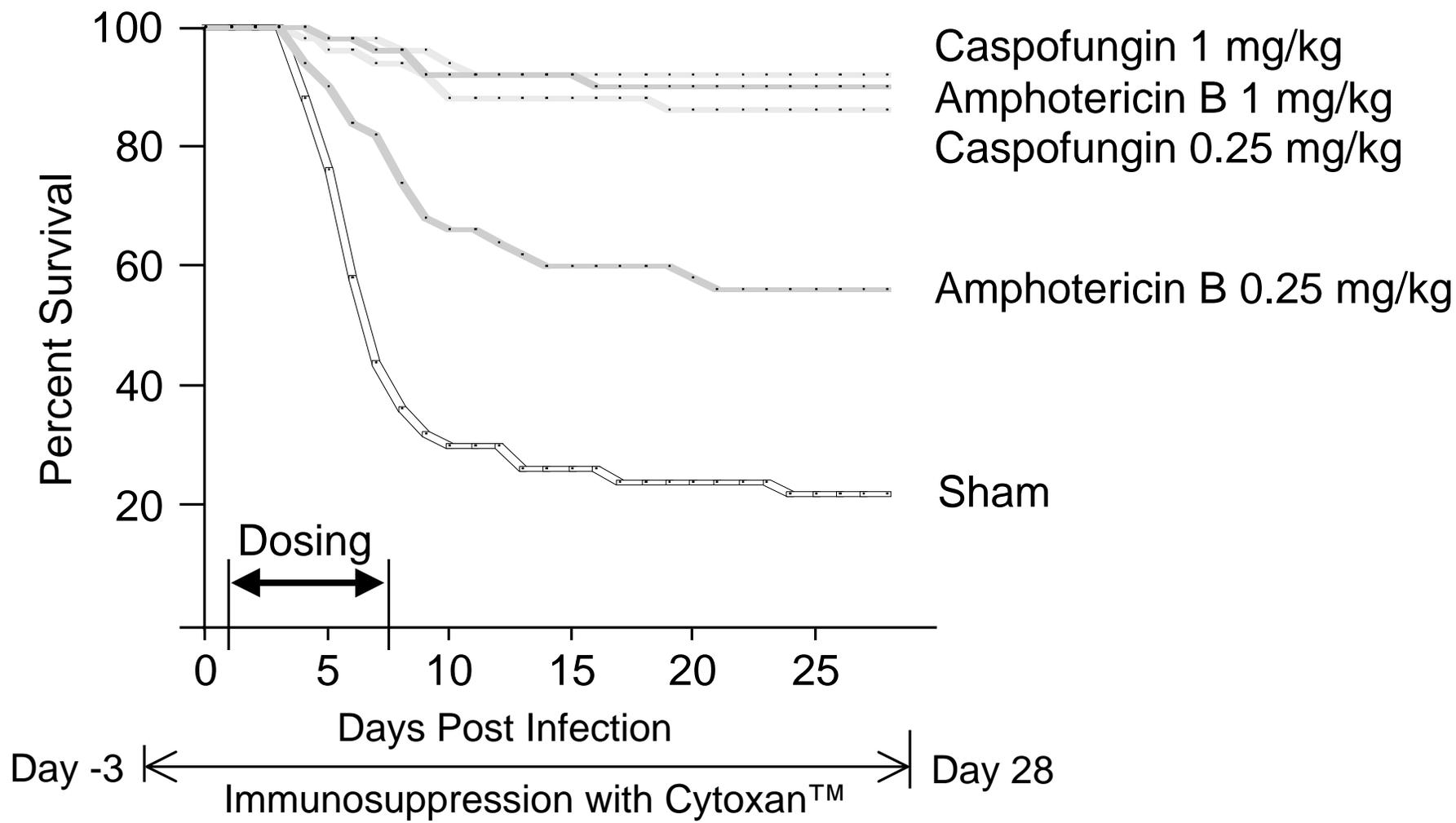
# Viable Stain - *Aspergillus fumigatus*



# Non-Viable Stain - *Aspergillus fumigatus*



# Disseminated Aspergillosis in Chronically Pancytopenic Mice - Survival



# Preclinical Microbiology Summary

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- 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

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

# Pharmacokinetics and Metabolism

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- 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

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- 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

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- 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

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- 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

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- 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

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- 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

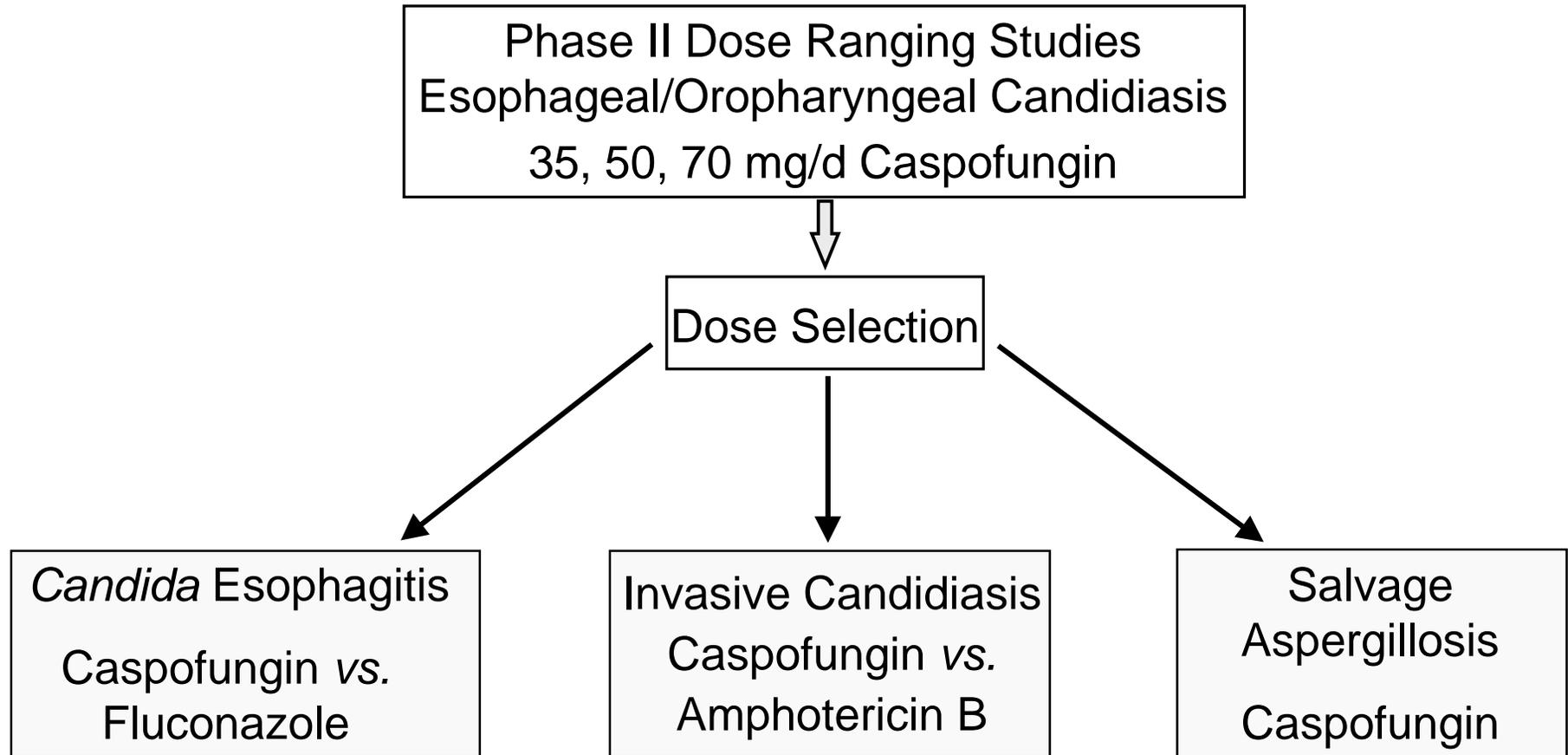
# Caspofungin Overview

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- 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

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# Additional Caspofungin Clinical Studies

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- Empirical therapy in febrile neutropenia
- Pediatrics
- Compassionate use

# Clinical Experience with Caspofungin

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- >600 individuals received 1 to 162 days of caspofungin
  - 349 patients
    - 295 received  $\geq 50$  mg for at least 7 days
      - 108 received  $\geq 50$  mg for at least 14 days
      - 68 received 70 mg for at least 7 days
    - 274 healthy subjects
      - 126 received  $\geq 50$  mg for at least 7 days
- An additional ~100 patients on caspofungin in ongoing blinded studies: data on serious adverse experiences

# Caspofungin Dose Selection

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- In vitro susceptibility data demonstrated the MIC<sub>90</sub> for *Aspergillus* and *Candida* spp. was  $\leq 1 \mu\text{g/mL}$ 
  - Conservative target: maintain plasma concentration  $\geq 1 \mu\text{g/mL}$  throughout the dosing interval
- Multiple doses of 50mg resulted in  $C_{24\text{hr}} \geq 1 \mu\text{g/mL}$  in 95% of patients
  - 50 mg daily dose should meet target plasma concentration
- Mean  $C_{24\text{hr}}$  after 50 mg was  $< 1 \mu\text{g/mL}$  early in therapy
  - Addition of a 70 mg dose on day 1 produced levels above  $1 \mu\text{g/mL}$  throughout therapy

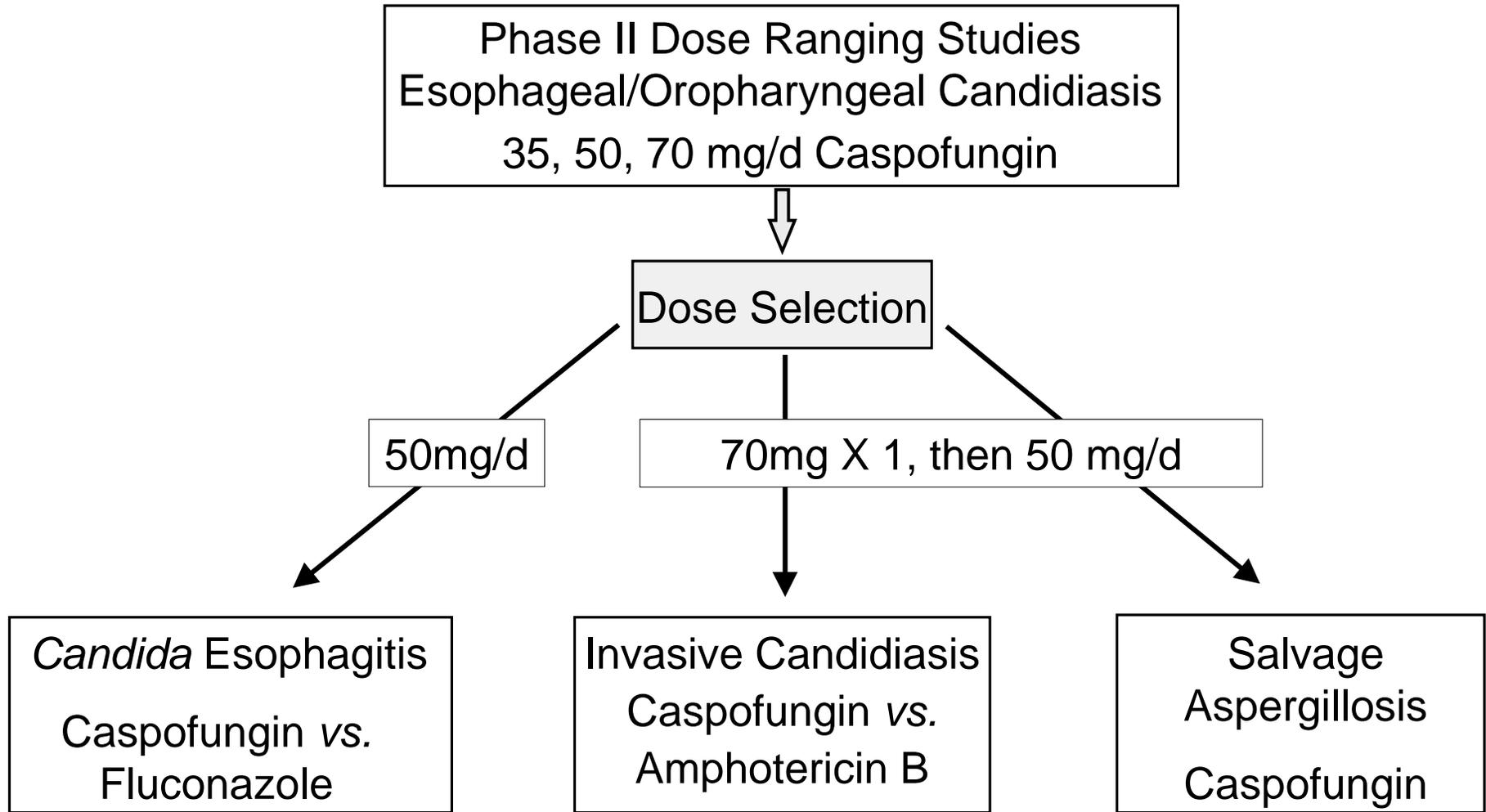
# Caspofungin Dose Selection (Cont'd)

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- 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

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# Overview of Invasive Aspergillosis Studies

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## 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

# Caspofungin Salvage *Aspergillus* Study (Protocol 019) Design

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- 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

# Caspofungin Salvage *Aspergillus* Study (Protocol 019) Design (Cont'd)

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- 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

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- 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

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- 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

# Diagnostic Certainty in the Caspofungin Salvage *Aspergillus* Study (Cont'd)

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- 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

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- 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

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- 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

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- 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

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- 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

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- 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

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- 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

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## Challenges

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Diagnostic certainty

Effect of other therapy

Documentation of response

Consistent interpretation

## Interventions in Protocol 019

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Strict criteria applied; documentation required

Extent of disease documented; concomitant antifungal prohibited

Reports/radiographs collected; radiographic improvement required

Expert Panel assessments primary

# Caspofungin Salvage *Aspergillus* Study

## Baseline Patient Characteristics (N=54)

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|                           |              | <u>N</u> | <u>(%)</u> |
|---------------------------|--------------|----------|------------|
| Gender                    | Male         | 33       | (61.1)     |
|                           | Female       | 21       | (38.9)     |
| Age (years)               | 18 to 40     | 16       | (29.6)     |
|                           | 41 to 65     | 31       | (57.4)     |
|                           | >65          | 7        | (13.0)     |
| Site of Infection         | Pulmonary    | 39       | (72.2)     |
|                           | Disseminated | 10       | (18.5)     |
|                           | Single organ | 5        | (9.3)      |
| Response to Prior Therapy | Refractory   | 44       | (81.5)     |

# Baseline Patient Characteristics (Cont'd)

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|                                 | <u>N</u> | <u>(%)</u> |
|---------------------------------|----------|------------|
| Certainty of Diagnosis          |          |            |
| Definite                        | 38       | (70.4)     |
| Probable                        | 16       | (29.6)     |
| Neutropenia (ANC <500)          | 11       | (20.4)     |
| Underlying Disease              |          |            |
| Hematologic malignancy          | 20       | (37.0)     |
| Allogeneic stem cell transplant | 16       | (29.6)     |
| Organ transplant                | 7        | (13.0)     |
| Solid tumor                     | 2        | (3.7)      |
| Corticosteroids                 | 4        | (7.4)      |
| Other                           | 5        | (9.3)      |

# Expert Panel Assessment of Outcome

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| <u>Efficacy Analysis</u>  | Favorable Response |            |
|---|--------------------|------------|
|   | <u>n/m</u>         | <u>(%)</u> |
| Primary: All patients with diagnosis who receive at least 1 dose of caspofungin | 22/54              | (40.7)     |
| Secondary: Patients who received >7 days of caspofungin                         | 22/45              | (48.9)     |

# Outcome by Patient Characteristics

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|                          | Favorable Response |          |
|--------------------------|--------------------|----------|
|                          | <u>n/m</u>         | <u>%</u> |
| Site of Infection        |                    |          |
| Pulmonary                | 18/39              | (46.2)   |
| Disseminated             | 2/10               | (20.0)   |
| Other                    | 2/5                | (40.0)   |
| Neutropenia              |                    |          |
| Neutropenic (ANC <500)   | 2/11               | (18.2)   |
| Non-neutropenic          | 20/43              | (46.5)   |
| Corticosteroid Use       |                    |          |
| <20 mg prednisolone eq/d | 15/32              | (46.9)   |
| ≥20 mg prednisolone eq/d | 7/22               | (31.8)   |

# Reason for Study Entry by Response to Prior Therapy

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|                    |            |
|--------------------|------------|
| Refractory*        | 44 (81.5%) |
| Progression        | 34         |
| Failure to respond | 10         |
| Intolerant         | 10 (18.5%) |
| Nephrotoxicity     | 9          |
| Other toxicity     | 1          |

\* Includes patients who are refractory and intolerant.

# Outcome by Response to Prior Therapy

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## Refractory or Intolerant Subgroups

|            | Favorable Response |            |
|------------|--------------------|------------|
|            | <u>n/m</u>         | <u>(%)</u> |
| Refractory | 15/44              | (34.1)     |
| Intolerant | 7/10               | (70.0)     |

# Refractory Patients

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## 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

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## Refractory Patients N=44

| Prior Therapy                    | Favorable Response |          |
|----------------------------------|--------------------|----------|
|                                  | <u>n/m</u>         | <u>%</u> |
| Amphotericin B                   | 4/7                | 57.1     |
| Lipid Amphotericin B             | 3/7                | 42.9     |
| Itraconazole                     |                    |          |
| Itraconazole alone               | 4/7                | 57.1     |
| Itraconazole + Intolerant to AmB | 1/6                | 16.7     |
| Voriconazole                     | 0/1                | 0.0      |
| Refractory to multiple drugs     | 3/16               | 18.8     |

# Intolerant Patients

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## Prior Antifungal Therapy

- Duration of prior therapy
  - 80% (8/10) received <14 days of prior therapy
  - Two patients received  $\geq 14$  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

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## Intolerant Patients N=10

| <u>Prior Therapy</u> | Favorable Response |          |
|----------------------|--------------------|----------|
|                      | <u>n/m</u>         | <u>%</u> |
| Amphotericin B       | 4/4                | 100.0    |
| Lipid Amphotericin B | 1/3                | 33.3     |
| Itraconazole         | 0/1                | 0.0      |
| Multiple drugs       | 2/2                | 100.0    |

# Degree of Immunosuppression and Outcome

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- 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

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- 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 |

# AN058

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- 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

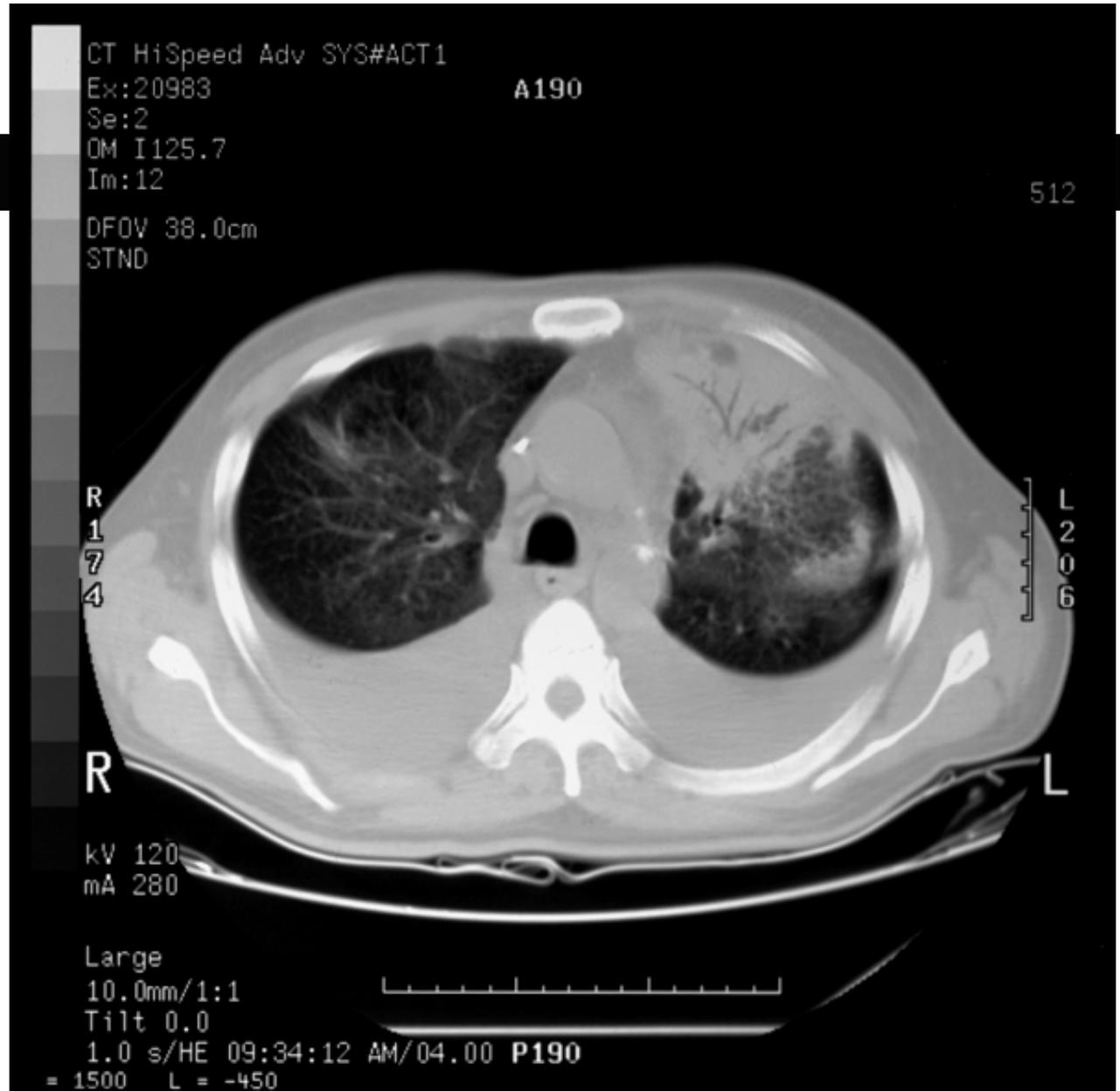
AN058

Pre-Study



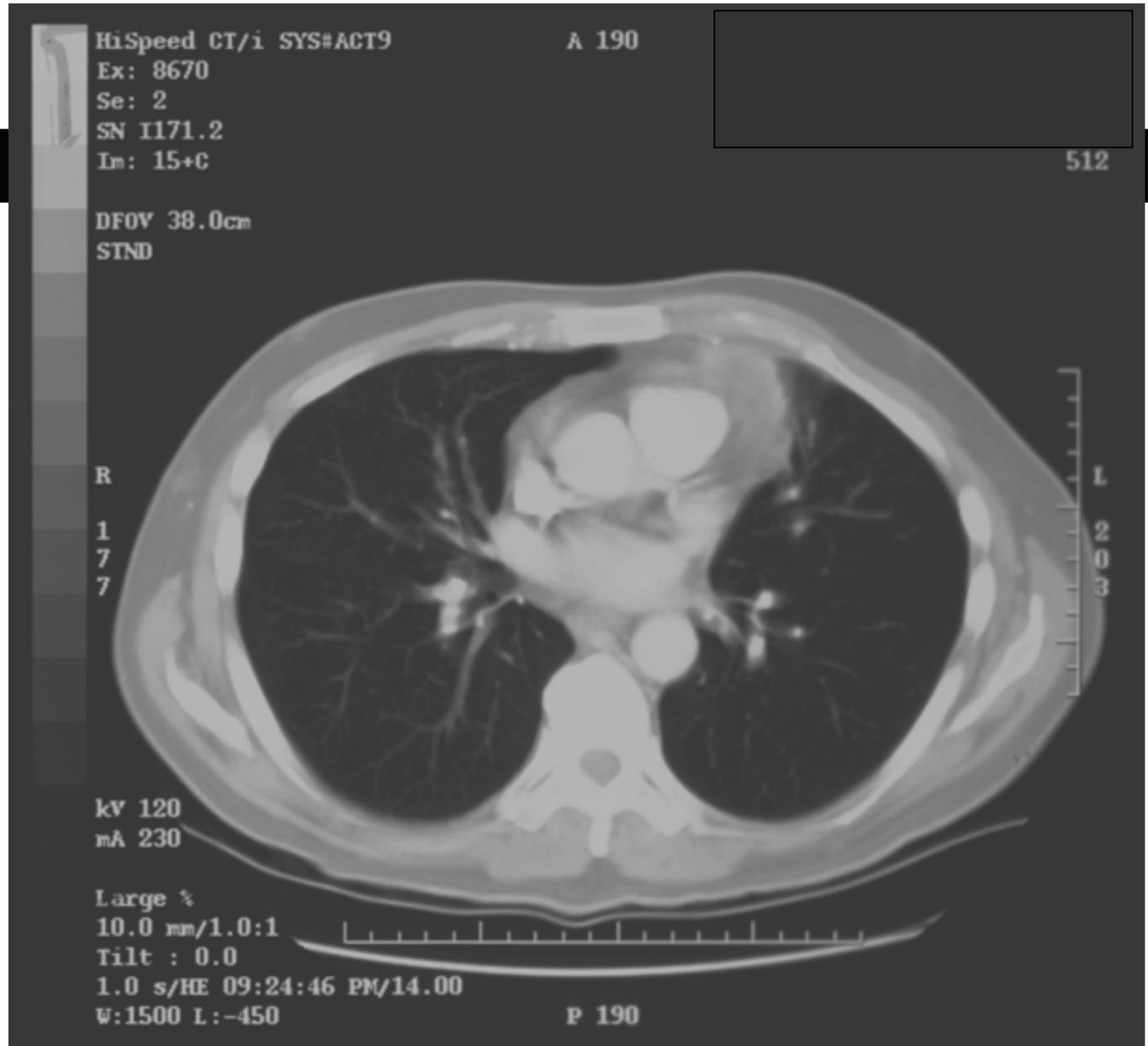
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Pre-Study



AN058

Day 31



AN058

Day 31



# Relapse Assessment at the 4 Week Follow-Up

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- 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

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- 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

# Summary of Caspofungin Efficacy in the Salvage *Aspergillus* Study (Cont'd)

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- 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

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## 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

# Expert Panel Assessment of 11 Additional Patients in the Caspofungin Salvage *Aspergillus* Study

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- 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

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| <u>Underlying Disease</u> | <u>Infection Site</u> | <u>Refractory/<br/>Intolerant</u> | <u>Expert Panel Outcome</u> |
|---------------------------|-----------------------|-----------------------------------|-----------------------------|
| Aplastic anemia           | Definite pulmonary    | R: AmBisome™<br>R: Itraconazole   | Failure                     |
| No defined risk           | Disseminated          | R: AmBisome™                      | Complete Response           |
| AIDS                      | Definite pulmonary    | R: Itraconazole<br>I: Abelcet™    | Partial Response            |

# Efficacy of Caspofungin in Invasive Aspergillosis in Patients Refractory to or Intolerant of Other Therapy

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| <u>Patient Population</u>            | Favorable Response |          |
|--------------------------------------|--------------------|----------|
|                                      | <u>n/m</u>         | <u>%</u> |
| Original 54 Patients                 | 22/54              | 40.7%    |
| + 9 Additional Patients              | 26/63              | 41.3%    |
| + 3 Patients in<br>Compassionate Use | 28/66              | 42.4%    |

# Overview of Invasive Aspergillosis Studies

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## 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

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- 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)

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- 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)

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- 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

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Caspofungin Salvage  
*Aspergillus* Study

Historical Control 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

# Identification of Subpopulations in the Historical Control Study

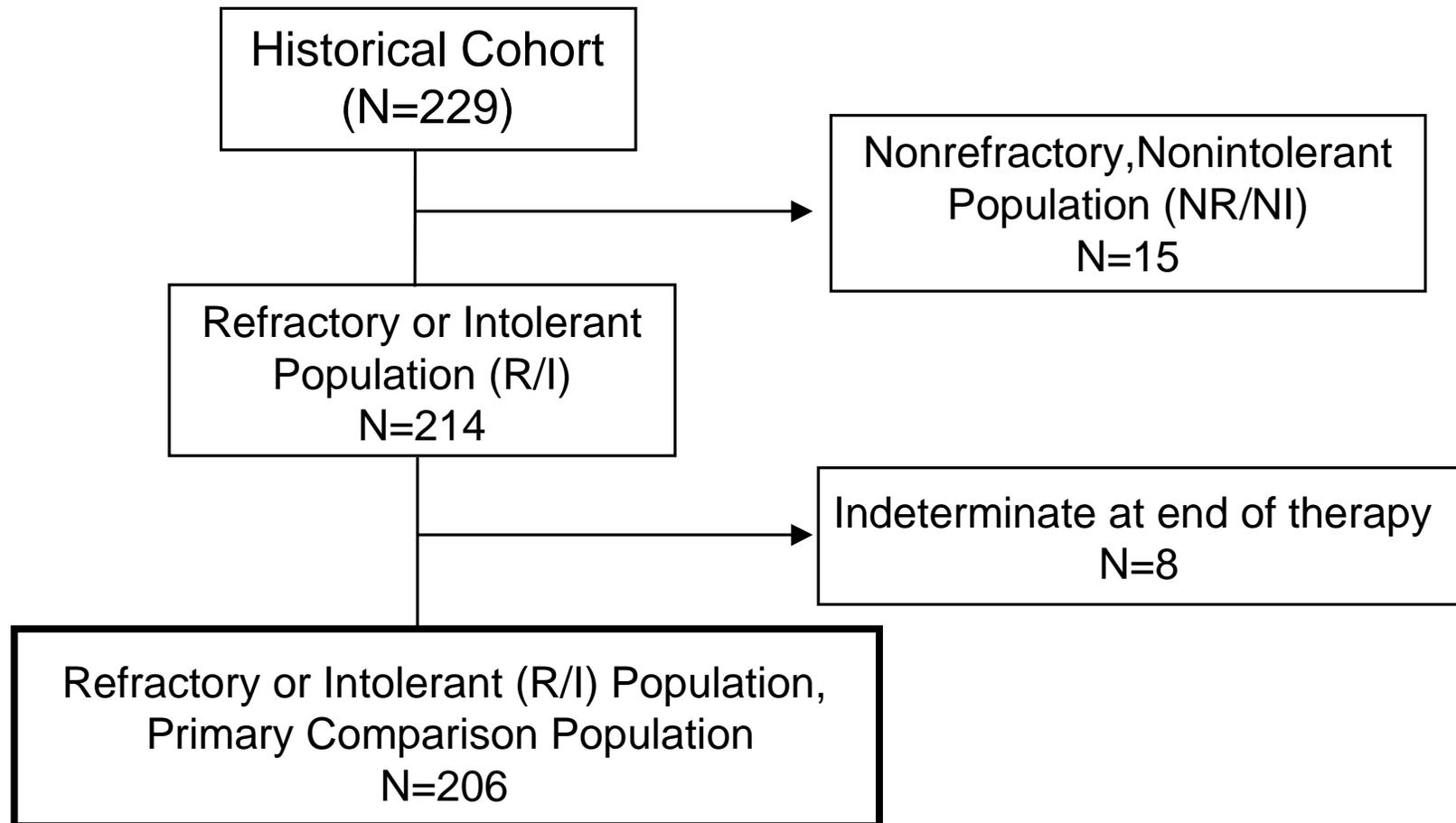
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Historical Control Study Subpopulations Defined Based on Minimum Entry Criteria for Caspofungin *Aspergillus* Study

|            | <u>Caspofungin <i>Aspergillus</i> Study</u>                                      | <u>Historical Control Study</u>                    |
|------------|--|--|
| Refractory | Progression of disease or failure to improve after $\geq 7$ days of therapy      | Not improved at week 1                             |
| Intolerant | Creatinine $\geq 2.5$ mg/dL;<br>Doubling of creatinine;<br>Other severe toxicity | Creatinine $\geq 2.5$ mg/dL and improved at week 1 |

# Identification of the Comparison Population in the Historical Control Study

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# Baseline Patient Characteristics in the Comparison Populations

|  | Caspofungin<br>(N=54) |            | Historical Control<br>(N=206) |            |
|--|-----------------------|------------|-------------------------------|------------|
|  | <u>n</u>              | <u>(%)</u> | <u>n</u>                      | <u>(%)</u> |
| <b>Predisposing Condition</b>                    |                       |            |                               |            |
| Hematologic malignancy<br>(stem cell transplant) | 36                    | (66.7)     | 144                           | (69.9)     |
| Organ transplant                                 | 7                     | (13.0)     | 32                            | (15.5)     |
| Solid tumor                                      | 2                     | (3.7)      | 10                            | (4.9)      |
| Other risk factors                               | 9                     | (16.7)     | 20                            | (9.7)      |
| <b>Neutropenic Status</b>                        |                       |            |                               |            |
| ANC <500   | 11                    | (20.4)     | 57                            | (27.7)     |
| ANC ≥500   | 43                    | (79.6)     | 149                           | (72.3)     |

# Distribution of Diagnoses of *Aspergillus* Infection in the Comparison Populations

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| <u>Site of Infection</u> | <u>Caspofungin<br/>N=54</u> |            | <u>Historical Control<br/>N=206</u> |            |
|--------------------------|-----------------------------|------------|-------------------------------------|------------|
|                          | <u>n</u>                    | <u>(%)</u> | <u>n</u>                            | <u>(%)</u> |
| Definite Pulmonary       | 23                          | (42.6)     | 79                                  | (38.3)     |
| Probable Pulmonary       | 16                          | (29.6)     | 75                                  | (36.4)     |
| Extrapulmonary           | 15                          | (27.8)     | 52                                  | (25.2)     |
| Disseminated             | 10                          |            | 41                                  |            |
| CNS                      | 1                           |            | 2                                   |            |
| Sinus                    | 3                           |            | 6                                   |            |
| Skin                     | 0                           |            | 3                                   |            |
| Pulmonary/sinus          | 1                           |            | 0                                   |            |

# Comparison of Outcomes: Caspofungin versus Standard Therapy in the Historical Control Study

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| <u>Population</u>        | <u>Favorable Response</u>           |            |  |            |
|--------------------------|-------------------------------------|------------|--|------------|
|                          | <u>Caspofungin<br/>Protocol 019</u> |            | <u>Standard Therapy<br/>Historical Control</u> |            |
|                          | <u>n/m</u>                          | <u>(%)</u> | <u>n/m</u>                                     | <u>(%)</u> |
| Refractory or Intolerant | 22/54                               | (40.7)     | 35/206   | (17.0)     |
| Refractory               | 15/44                               | (34.1)     | 27/188   | (14.4)     |
| Intolerant               | 7/10                                | (70.0)     | 3/5  | (60.0)     |

# Outcome by Underlying Disease

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| <b>Underlying Disease</b> | Favorable Response |            |                           |            |
|---------------------------|--------------------|------------|---------------------------|------------|
|                           | <u>Caspofungin</u> |            | <u>Historical Control</u> |            |
|                           | <u>n/m</u>         | <u>(%)</u> | <u>n/m</u>                | <u>(%)</u> |
| Hematologic malignancy    | 13/36              | (36.1)     | 19/144                    | (13.2)     |
| Organ transplant          | 3/7                | (42.9)     | 9/32                      | (28.1)     |
| Solid tumor               | 2/2                | (100.0)    | 2/10                      | (20.0)     |
| Other                     | 4/9                | (44.4)     | 5/20                      | (25.0)     |

# Outcome by Site of Infection

| Site of Infection | Favorable Response |            |                    |            |
|-------------------|--------------------|------------|--------------------|------------|
|                   | Caspofungin        |            | Historical Control |            |
|                   | <u>n/m</u>         | <u>(%)</u> | <u>n/m</u>         | <u>(%)</u> |
| Pulmonary         | 18/39              | (46.2)     | 32/154             | (20.8)     |
| Disseminated      | 2/10               | (20.0)     | 0/41               | (0.0)      |
| CNS               | 1/1                | (100.0)    | 1/2                | (50.0)     |
| Sinus             | 1/3                | (33.3)     | 1/6                | (16.7)     |
| Pulmonary/sinus   | 0/1                | (0.0)      |                    | ---        |
| Skin              |                    | ---        | 1/3                | (33.3)     |

# Outcome by Neutropenia and Corticosteroid Use

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|                              | Favorable Response |            |                           |            |
|------------------------------|--------------------|------------|---------------------------|------------|
|                              | <u>Caspofungin</u> |            | <u>Historical Control</u> |            |
|                              | <u>n/m</u>         | <u>(%)</u> | <u>n/m</u>                | <u>(%)</u> |
| <b>Neutropenia</b>           |                    |            |                           |            |
| Neutropenic (ANC <500)       | 2/11               | (18.2)     | 4/57                      | (7.0)      |
| Non-neutropenic              | 20/43              | (46.5)     | 31/149                    | (20.8)     |
| <b>Corticosteroids</b>       |                    |            |                           |            |
| <20 mg prednisolone eq. /day | 15/32              | (46.9)     | 27/132                    | (20.5)     |
| ≥20 mg prednisolone eq. /day | 7/22               | (31.8)     | 8/74                      | (10.8)     |

# Comparison of Favorable Outcome Adjusted for Multiple Baseline Characteristics

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- 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

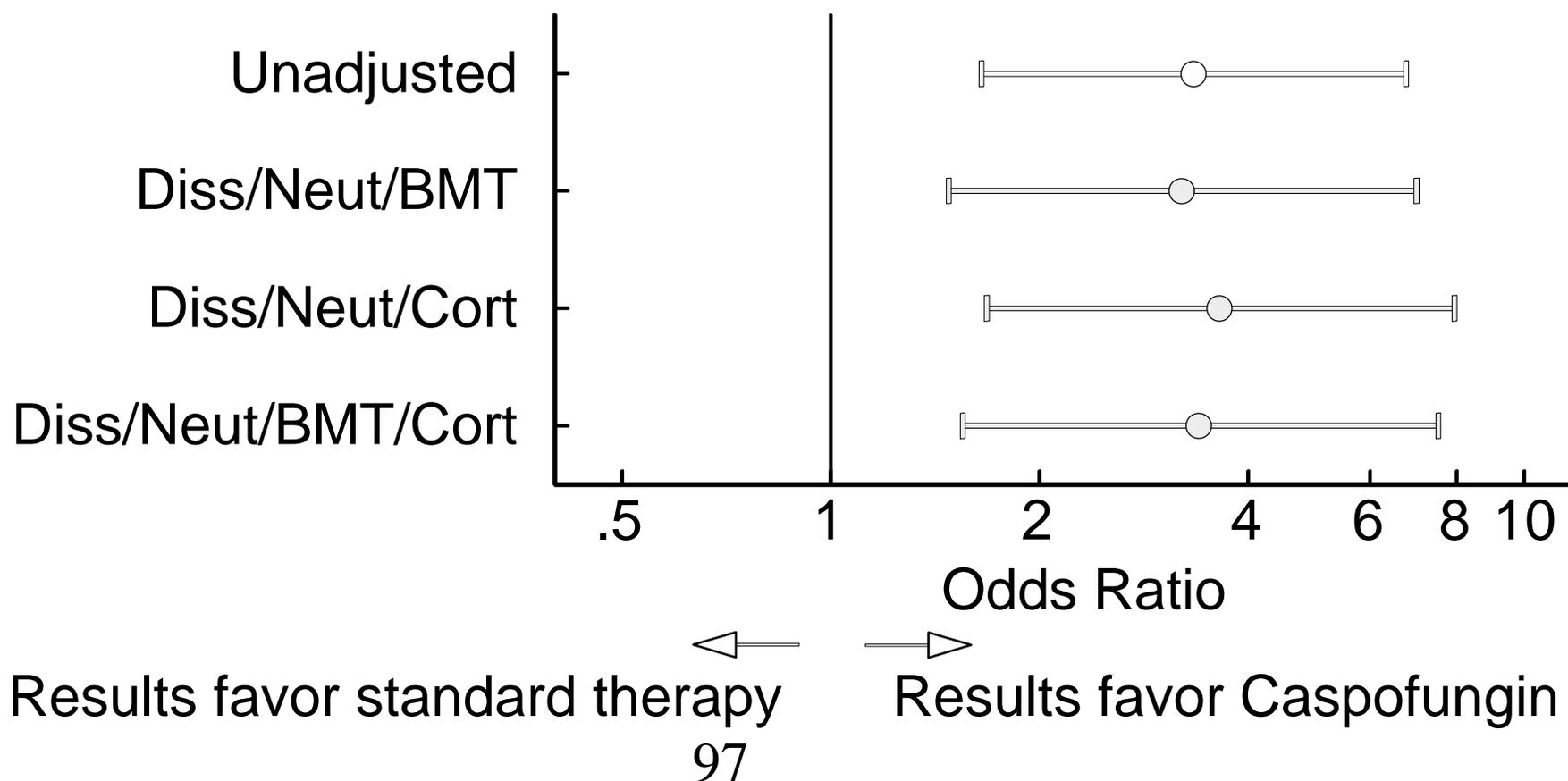
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Disseminated aspergillosis  
Neutropenia  
Bone marrow transplant  
High-dose corticosteroids

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



# Caspofungin Salvage *Aspergillus* Study versus the Historical Control Study

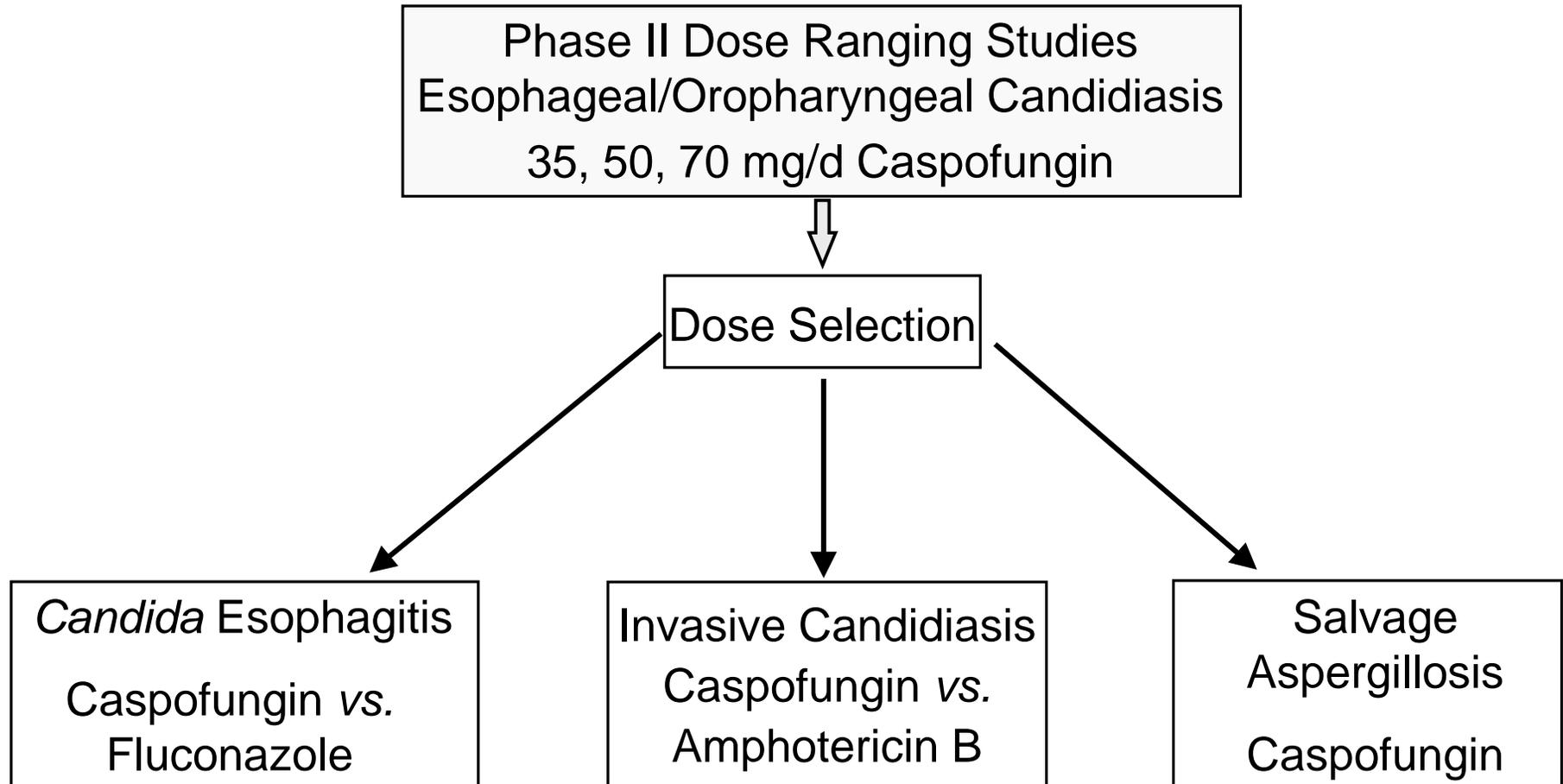
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## Summary of Comparison

- 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

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# Oropharyngeal/Esophageal Candidiasis Phase II Studies

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| Protocol | Disease                      | Treatment Groups |       |       |                             | Treatment Duration |
|----------|------------------------------|------------------|-------|-------|-----------------------------|--------------------|
|          |                              | Caspofungin      |       |       | Amphotericin B<br>0.5 mg/kg |                    |
|          |                              | 35 mg            | 50 mg | 70 mg |                             |                    |
| 003      | Esophagitis                  |                  | X     | X     | X                           | 14 days            |
| 004      | Esophagitis<br>Oropharyngeal | X                | X     | X     | X                           | 7 to 10 days       |

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

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Percentage of Patients  
with a Favorable Response at Test of Cure

| Caspofungin      |                  |                  | Amphotericin B   |
|------------------|------------------|------------------|------------------|
| <u>35 mg</u>     | <u>50 mg</u>     | <u>70 mg</u>     | <u>0.5 mg/kg</u> |
| 25/34<br>(73.5%) | 70/80<br>(87.5%) | 56/63<br>(88.9%) | 61/89<br>(68.5%) |

# Caspofungin Overview

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- 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

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- 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)

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- 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

# Caspofungin Clinical Exposure

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- 623 individuals received caspofungin
- 546 received multiple doses
  - 197 healthy subjects
  - 277 patients with oropharyngeal/esophageal candidiasis
  - 72 patients with invasive aspergillosis
- 421 received  $\geq 50$  mg for  $\geq 7$  days
  - 126 subjects in Clinical Pharmacology studies
  - 295 patients with *Candida* or *Aspergillus* infections
    - 35 patients treated  $\geq 28$  days

# Overview of Caspofungin Safety Data

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- 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 System (WAES)
  - Invasive Candidiasis (Protocol 014)
  - Empirical Therapy (Protocol 026)
  - Compassionate Use (Protocol 024/025)

# Caspofungin Safety Profile

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- Generally well tolerated
- Patients with a wide spectrum of diseases and many concomitant medications included
- Favorable safety profile maintained with extended therapy ( $\geq 28$  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

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- 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

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## Phase II/III Controlled *Candida* Studies

|           | Caspofungin      |                 | Amphotericin B<br>0.5 mg/kg<br>(N=89) | Fluconazole<br>200 mg<br>(N=93) |
|-----------|------------------|-----------------|---------------------------------------|---------------------------------|
|           | 50 mg<br>(N=164) | 70 mg<br>(N=65) |                                       |                                 |
| Fever     | 12.2%            | 26.2%           | 69.7%                                 | 1.1%                            |
| Phlebitis | 18.3%            | 15.4%           | 22.5%                                 | 17.2%                           |
| Headache  | 8.5%             | 7.7%            | 19.1%                                 | 1.1%                            |
| Diarrhea  | 2.4%             | 3.1%            | 11.2%                                 | 2.2%                            |
| Nausea    | 4.3%             | 3.1%            | 21.3%                                 | 6.5%                            |
| Vomiting  | 1.2%             | 3.1%            | 13.5%                                 | 3.2%                            |
| Chills    | 1.2%             | 1.5%            | 75.3%                                 | 0.0%                            |

# Drug-Related Fever in the Caspofungin Controlled *Candida* Studies

## Percentage of Patients with Drug-Related Fever

| Protocol         | Treatment Groups |      |      |                |             |
|------------------|------------------|------|------|----------------|-------------|
|                  | Caspofungin      |      |      | Amphotericin B | Fluconazole |
|                  | 35mg             | 50mg | 70mg | 0.5 mg/kg      | 200mg       |
| 003 <sup>†</sup> |                  | 28.3 | 39.3 | 68.5           |             |
| 004 <sup>†</sup> | 20.6             | 11.8 | 16.2 | 71.4           |             |
| 020 <sup>‡</sup> |                  | 3.6  |      |                | 1.1         |

<sup>†</sup> N~30-50/group; <sup>‡</sup> N~85-90/group.

# Drug-Related Laboratory Adverse Experiences

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## Phase II/III Controlled *Candida* Studies

|                    | Caspofungin      |                 | Amphotericin B      | Fluconazole      |
|--------------------|------------------|-----------------|---------------------|------------------|
|                    | 50 mg<br>(N=164) | 70 mg<br>(N=65) | 0.5 mg/kg<br>(N=89) | 200 mg<br>(N=93) |
| ALT ↑              | 10.5%            | 10.8%           | 22.7%               | 12.0%            |
| AST ↑              | 13.0%            | 10.8%           | 22.7%               | 13.0%            |
| Alkaline phos ↑    | 10.4%            | 7.7%            | 19.3%               | 12.0%            |
| Hematocrit ↓       | 11.0%            | 1.5%            | 32.6%               | 5.4%             |
| WBC count ↓        | 6.1%             | 4.6%            | 7.9%                | 8.7%             |
| Serum creatinine ↑ | 0.0%             | 1.5%            | 28.1%               | 2.2%             |
| Serum potassium ↓  | 3.7%             | 10.8%           | 31.5%               | 4.3%             |

# Summary of Caspofungin Safety in Controlled *Candida* Studies

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- 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

# Caspofungin Salvage *Aspergillus* Study (Protocol 019)

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## 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  $\geq 28$  days (up to 162 days)
- Safety profile in the 11 additional patients similar to that seen in the original 58

# Caspofungin Salvage *Aspergillus* Study (Protocol 019)

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## Drug-Related Adverse Experiences Occurring in >1 Patient

|                                      | Caspofungin 50 mg |            |
|--------------------------------------|-------------------|------------|
|                                      | <u>n/m</u>        | <u>(%)</u> |
| Clinical Adverse Experiences         |                   |            |
| Fever                                | 2/58              | (3.4)      |
| Phlebitis/Infused vein complications | 2/58              | (3.4)      |
| Nausea                               | 2/58              | (3.4)      |
| Vomiting                             | 2/58              | (3.4)      |
| Laboratory Adverse Experiences       |                   |            |
| Increased eosinophils                | 2/55              | (3.6)      |
| Increased urine protein              | 3/51              | (5.9)      |

# Caspofungin Safety Summary

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- 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

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Presentation by Dr. Carole Sable

- Background
- Preclinical Microbiology
- Clinical Pharmacology
- Clinical Efficacy
- Clinical Safety

Presentation by Dr. Jeff Chodakewitz

- Concluding remarks