Rezafungin for Injection Limited Use Indication for the Treatment of Candidemia and Invasive Candidiasis in Adult Patients

January 24, 2023

Cidara Therapeutics

Antimicrobial Drugs Advisory Committee

Introduction

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SVP, Regulatory Affairs & Quality Assurance

Cidara Therapeutics

Rezafungin is Part of Well-Established Echinocandin Class

- Derived from anidulafungin
  - Active pharmaceutical ingredient: rezafungin acetate
- Retains safety of echinocandins with
  - Improved chemical stability
  - Improved pharmacokinetics vs available antifungal agents[1]
  - Once-weekly dosing with high, front-load exposure
- IDSA 2016: Echinocandins are 1st line SoC for *Candida* infections

SoC = Standard of Care

1. James, 2017

FDA Guidance: Flexible Development Pathway for Antibacterial Therapies

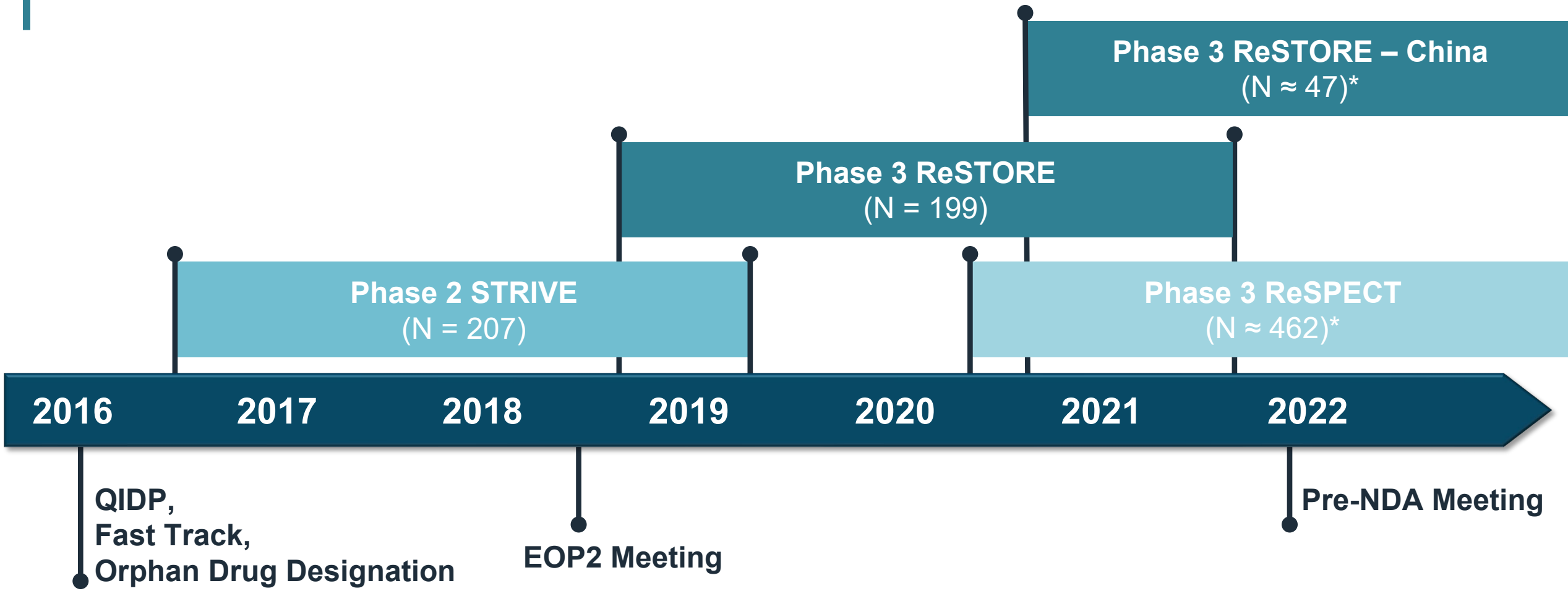
- Unmet medical need in treatment of serious bacterial diseases
  - Increasing threat and resistance of *Candida* species
- Safety database of ≥ 300 subjects exposed to proposed dose or higher
- Single pivotal trial
- Noninferiority trial design
  - Wider NI margin in setting of limited use indication
- Robust nonclinical program
  - *in vitro* and *in vivo* activity
  - PK / PD relationships
- Nonclinical safety studies

FDA Guidance for Industry, Antibacterial Therapies for Patients With an Unmet Medical Need for The Treatment of Serious Bacterial Diseases, 2017
Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers, 2022

Rezafungin Meets Unmet Need in a Serious Illness

- Comparable efficacy and safety to caspofungin
- Exposure levels achieve concentration-dependent killing and target attainment
- Activity against *Candida* isolates with reduced susceptibility
- No clinically meaningful DDIs
- Once weekly IV dosing allows for
  - Earlier removal of catheter
  - Outpatient treatment for those unable to maintain IV access and for whom oral therapy inappropriate

Regulatory History and Development Milestones



*Targeted enrollment
QIDP = Qualified Infectious Disease Product; EOP2 = End of Phase 2; Pre-NDA = Pre-New Drug Application

Rezafungin Clinical Development Program

- Enrolled > 300 subjects at proposed dose or higher across development program
- One Phase 3 trial with 20% NI margin to support limited-use indication for treatment
- Primary endpoint of All-Cause Mortality (ACM) at Day 30
  - Unique for echinocandin clinical development
- Secondary endpoint of Global Response at Day 14
- Phase 2 trial provides supportive data

Nonclinical Development Program Elevated Under Flexible Development Program Guidance

- Robust microbiology package
  - Antifungal spectrum and potency
  - Surveillance data since 2014
  - Mechanism of action
  - Resistance potential and mechanisms
  - Efficacy in animal models
- Comprehensive nonclinical safety package
  - Toxicology studies up to 6 months
  - Genotoxicity, reproductive / developmental toxicology, local tolerance, and phototoxicity

Overall Development Program Outcomes Support Positive Benefit / Risk of Rezafungin

- One pivotal Phase 3 and one supportive Phase 2 global randomized clinical trials in patients with candidemia and/or invasive candidiasis
- Clinical
  - Noninferiority (20% NI margin) achieved for ACM primary endpoint (Phase 3)
  - Comparable rates of global cure / overall success
  - Safety profile consistent with the class
- Microbiology and pharmacology
  - Broad *Candida* target attainment including less susceptible / resistant species (e.g., *C. glabrata* and *C. auris*)
  - Demonstrated tissue penetration, lack of DDIs, once weekly dosing
- Robust nonclinical data supports clinical safety and efficacy of rezafungin

Limited Use Indication

A limited use indication
for the treatment of candidemia and invasive candidiasis
in patients 18 years of age or older

Patients who could benefit from rezafungin include those who

- Need an echinocandin but unable to receive daily IV dosing
- Are unable to receive oral therapy
- Infected with non-susceptible *Candida* pathogen
- Have deep tissue infections
- Failed other antifungal therapies

Agenda

Unmet Need	**Jose Vazquez, MD, FACP, FIDSA** Chief of Infectious Disease and Professor of Medicine Medical College of Georgia at Augusta University
Pharmacology and Microbiology	**Shawn Flanagan, PhD** Vice President Clinical Pharmacology & Early Development Cidara Therapeutics
Clinical Efficacy	**Anita Das, PhD** Consultant Statistician
Clinical Safety	**Taylor Sandison, MD, MPH** Chief Medical Officer Cidara Therapeutics
Clinical Perspective	**Cornelius (Neil) J. Clancy, MD** Professor of Medicine, Associate Chief of Infectious Diseases University of Pittsburgh

Additional Responders

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Cofounder and CMO, Sfunga Therapeutics
Cofounder and CEO, Pearl Diagnostics

Michael Schlosser, PhD, DABT
Consulting Toxicologist

Unmet Need

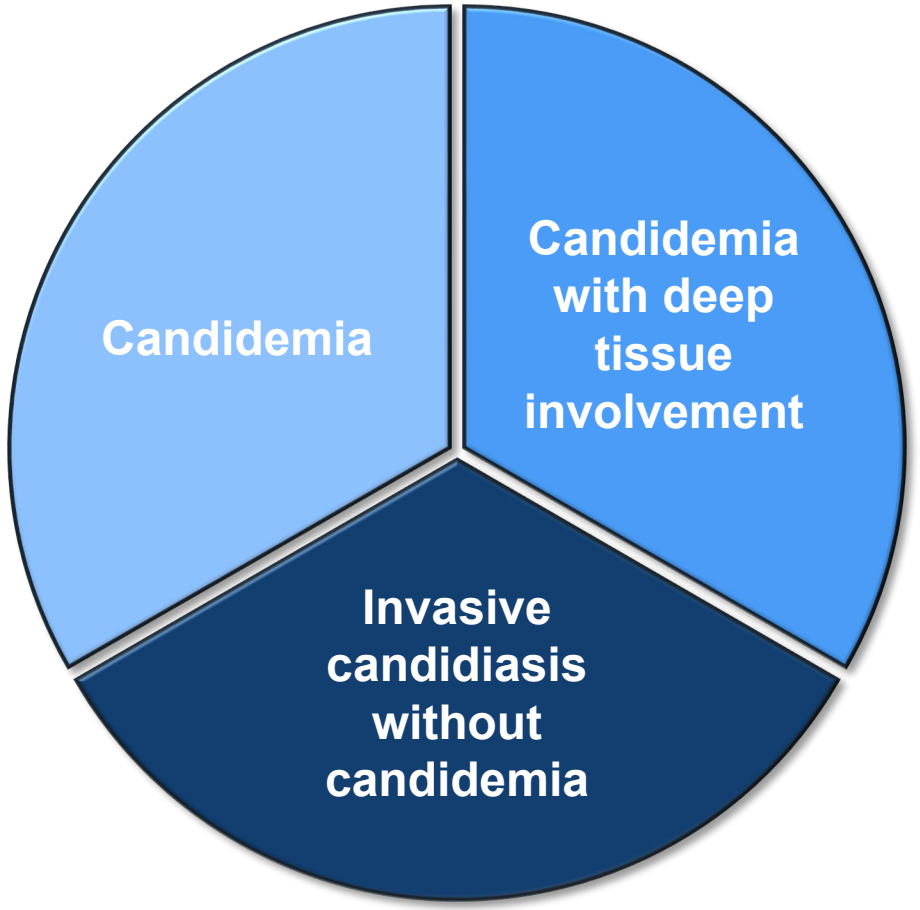
Jose Vazquez, MD, FACP, FIDSA

Chief of Infectious Disease and Professor of Medicine

Medical College of Georgia at Augusta University

Spectrum of Candidemia and Invasive Candidiasis

Affects bloodstream and/or deep / visceral tissues



Risk Factors and Characteristics Predisposing Patients to *Candida* Infection

Risk factors

- Central venous catheters
- Broad spectrum antibiotics
- Recent major surgery, especially abdominal
- Hemodialysis
- Corticosteroids

Patient characteristics

- Critically ill, particularly those on mechanical ventilation
- Solid organ transplant
- Solid organ tumors
- Hematologic malignancy
- Diabetes mellitus

Beck-Sague JID, 1993; Paphitou N. Med Mycol, 2005; Kullberg BJ NEJM, 2015

Candidemia and Invasive Candidiasis: Serious, Life-Threatening Fungal Infections

- Among most serious fungal infections in US[1]
  - Incidence of 9 / 100,000 people
  - ~ 25,000 cases / year
- *Candida* species second leading pathogen among bloodstream infections in acute care hospitals[2]
  - Increasing frequency of non-*C. albicans* spp. (38%)[3]
  - Past decade, *C. glabrata* and *C. auris* increasing in US[4,5,6]
- Invasive candidiasis on CDC threat list[4]

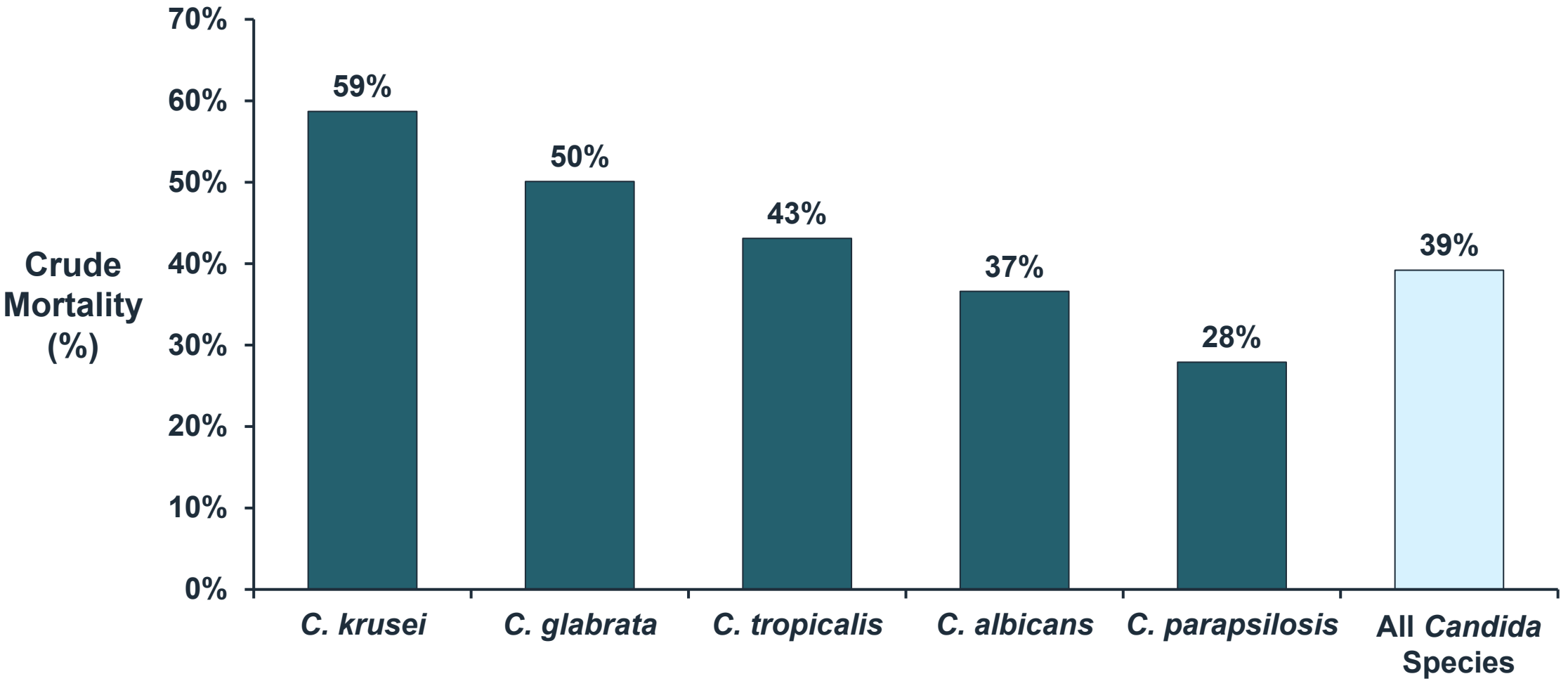
1. Tsay, 2018; 2. Magill, 2018; 3. Horn DL et al., 2007; 4. CDC, 2019; 5. Pappas, 2018; 6. WHO Fungal Priority Guide 2022

Candidemia and Invasive Candidiasis Associated with High Morbidity and Mortality

- Symptoms vary from fever to septic shock
- Lead to long hospital stays
  - Additional 3 to 13 days of hospitalization with each infection[1]
- Crude mortality rates for treated patients remains > 40%[2]

1. CDC, 2021; 2. Mazi, 2022

Candidemia and Invasive Candidiasis Associated with High Mortality



Wisplinghoff, 2004

Early Appropriate Therapy and Source Control Key for Successful Outcomes

- Need to treat early with appropriate therapy[1, 2]
- Need to control source of infection[1, 2]
  - Catheter removal
  - Removal of any hardware from bloodstream or body
  - Draining abscesses, surgical washout

1. Pappas, 2016; 2. Kullberg BJ NEJM, 2015

IDSA Guidelines: Echinocandins are First-Line Therapy for Candidemia and Invasive Candidiasis[1]

Echinocandins – Standard of Care

- Anidulafungin, caspofungin, and micafungin
- Well-established efficacy and safety profile
- Strong fungicidal activity
- Improved outcomes including survival in randomized controlled trials[2]

Azoles – Second Line Treatment

- Might be considered for step down therapy for patients ready to leave hospital

1. Pappas, 2016; 2. Reboli, 2007

Rising Threat of Resistance Challenges Current Treatment Options

- Increasing rates of azole resistance
  - *C. glabrata:* fluconazole (FLU)[1]
  - *C. parapsilosis:* FLU[2]
  - *C. tropicalis:* FLU[3]
  - *C. auris:* FLU 90%[4], amphotericin B 30%[4]; echinocandin < 8%[3]
  - *C. krusei:* intrinsic FLU resistance[5]; some azole/polyenes MDR[1]
- Growing resistance to current echinocandins (*C. glabrata* and *C. auris*) underscores need for additional therapies for these critically ill patients

1. Pappas, 2018; 2. Escribano, 2022: 3. WHO Fungal Priority Guide 2022; 4. Biagi, 2019; 5. Khalifa, 2022

Limitations of Approved Echinocandins

- Low therapeutic exposures in specific populations / situations resulting in poor outcomes and increased risk of resistance
  - Critically ill[1]
  - *Candida* isolates with elevated echinocandin MIC values
  - Invasive candidiasis, especially intra-abdominal and peritoneal candidiasis[1]
- Daily IV therapy required
  - Conflicts with need to remove catheter as source of infection for candidemia patients
  - Outpatient dosing results in PICC line placement and daily healthcare touchpoints in an already vulnerable population

1. Grau, 2015

Urgent Need for New Antifungal Treatment

- Candidemia and invasive candidiasis are serious, life-threatening infections
- Gaps in current treatment continue to exist
- New antifungal needed with
  - Deep tissue penetration
  - Well-studied dosing
  - Rapid efficacy without DDIs
  - Ability to overcome resistant strains
  - Dosing to support both in-hospital and outpatient setting

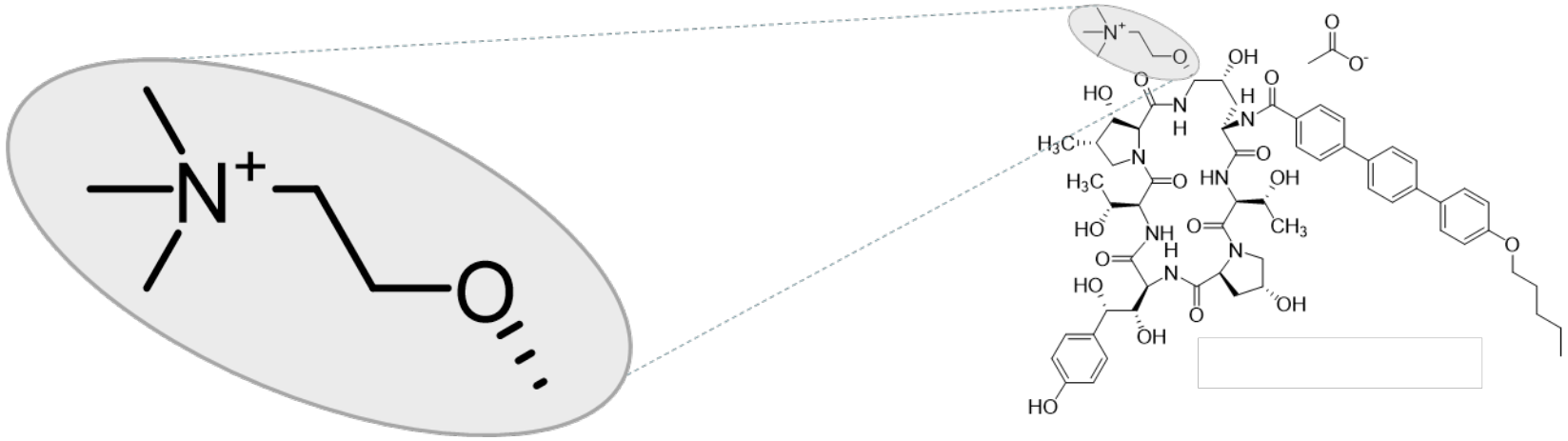
Pharmacology / Microbiology

Shawn Flanagan, PhD

Vice President Clinical Pharmacology & Early Development

Cidara Therapeutics

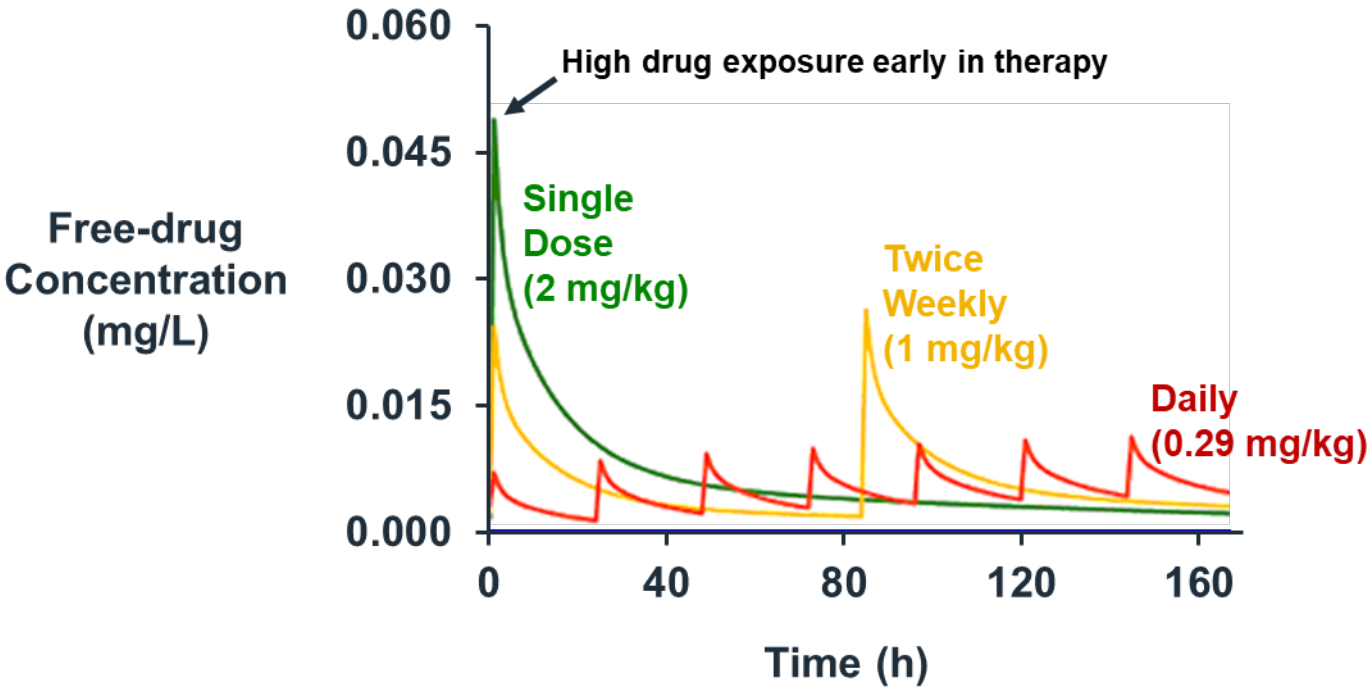
Rezafungin: Structural Modifications Improves Stability

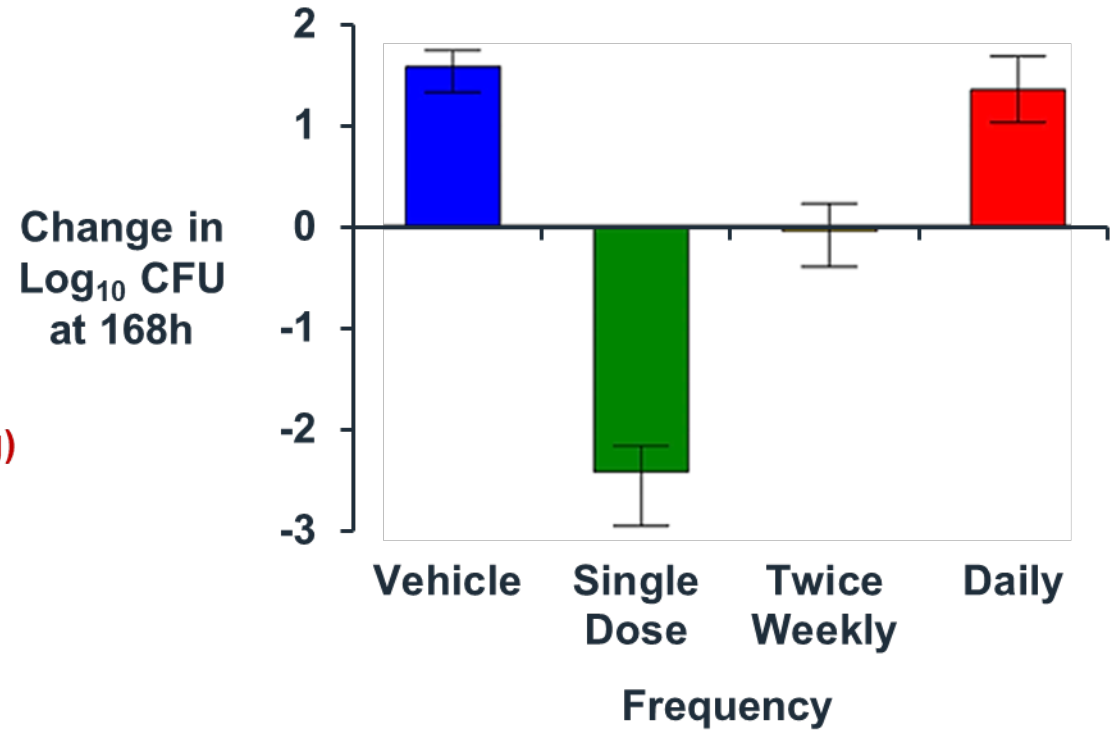


Stability is key to

- Eliminating toxic degradation products – – – – Avoidance of dose limiting liver effects of class
- Long half-life / prolonging PK – – – – – – – – – Once-weekly dosing in clinical studies
- Allowing high exposures – – – – – – – – – – – – Improved cidality and tissue distribution

High Drug Exposure Following Once-Weekly Dosing Resulted in Greater Fungal Killing than Divided Doses (Same Weekly Exposure)

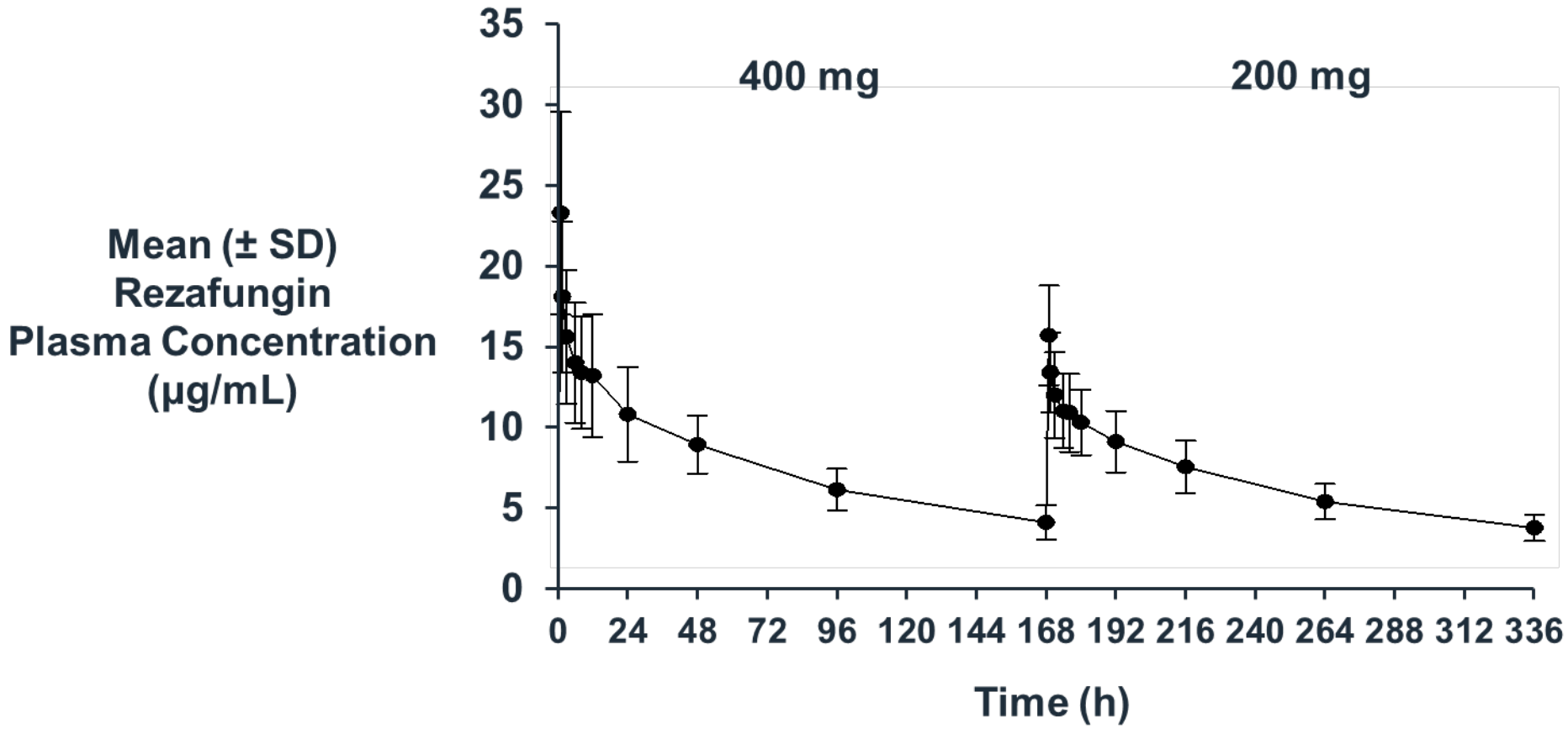




Lakota, 2017

CFU = Colony-Forming Units

Stability and Long-Half Life Allows for Once-Weekly Dosing



Key Rezafungin Clinical Pharmacology Results

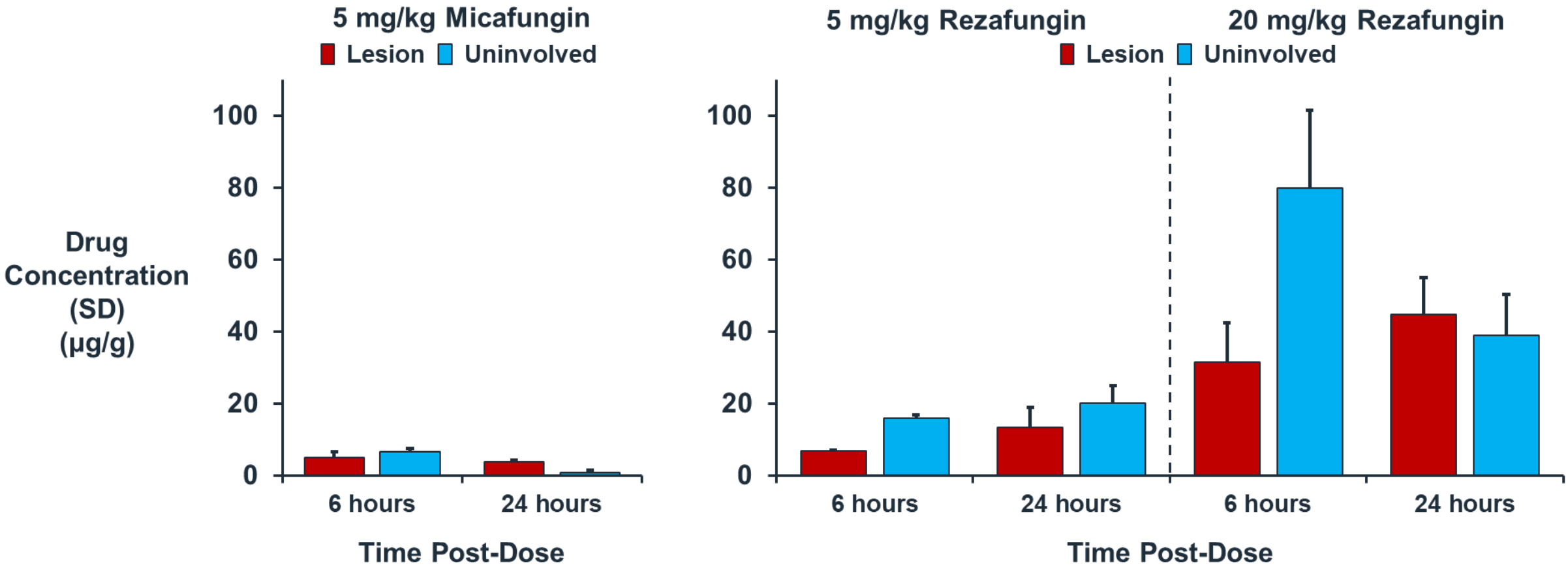
- No potential for clinically meaningful drug-drug interactions with rezafungin
- Rezafungin should not require any dose adjustments
- At doses up to 1,400 mg (3.5-times proposed 400 mg dose), rezafungin does not affect QTc interval

Rezafungin Distribution

- Protein binding is high (97.4%), similar to other echinocandins
- Overall volume of distribution relatively small (~40 L), similar to anidulafungin and ~2x that of other echinocandins
- Distribution to tissues rapid, similar to other echinocandins
  - Greatest in highly perfused tissues, except in brain
- Distribution data requires careful interpretation
  - Concentrations in bulk tissue may not reflect drug at site of action within tissue
  - Concentrations at site of action may not reflect intact or active drug

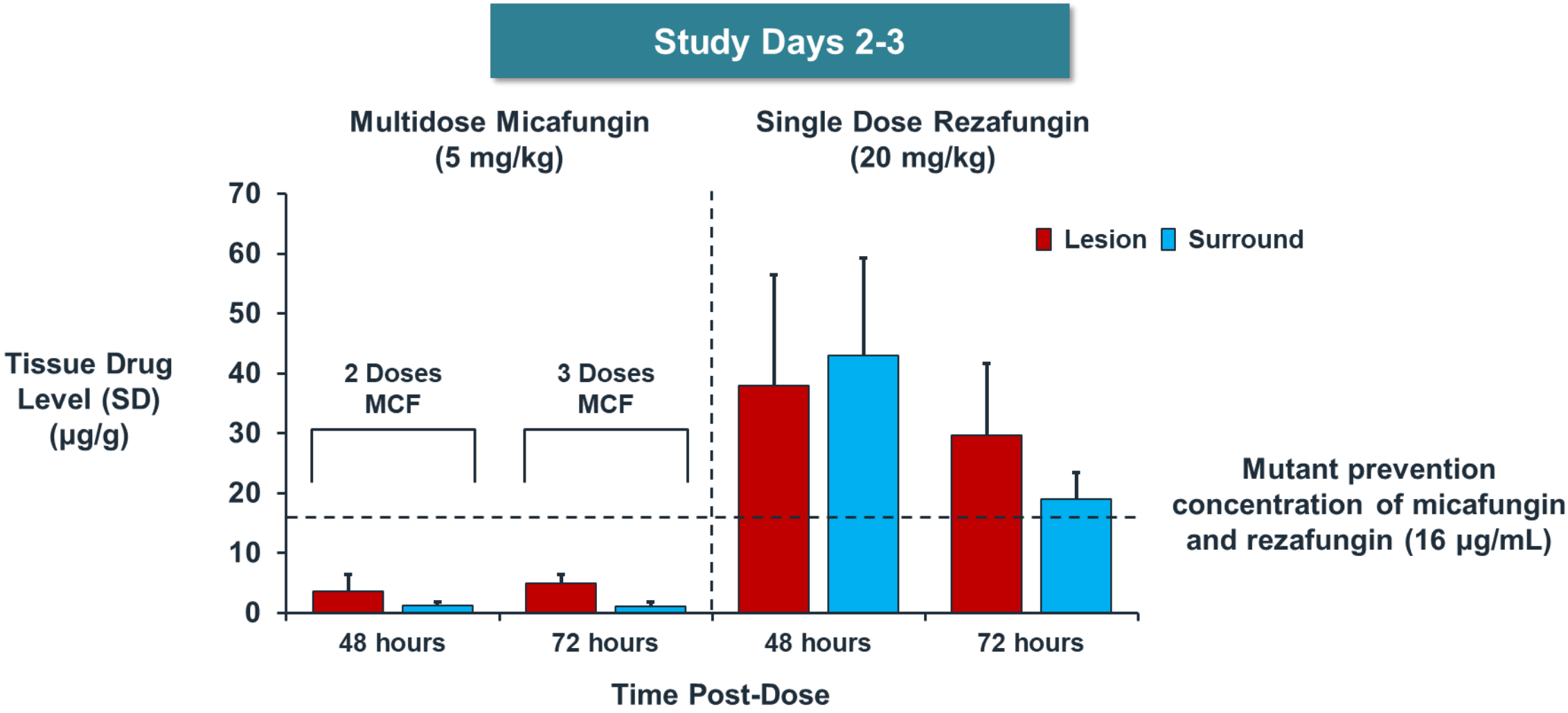
Rezafungin Reaches Site of Infection Better than Micafungin (Intra-Abdominal Infection Model)

Study Day 1



Adapted from Zhao, 2017

Rezafungin Reaches Site of Infection Better than Micafungin (Intra-Abdominal Infection Model)



Adapted from Zhao, 2017; Adapted from Zhao, 2016

Rezafungin *In Vitro* Activity is Consistent with Other Echinocandins

	MIC_{90} (µg/mL)			
Candida species (n)	Rezafungin	Anidulafungin	Caspofungin	Micafungin
C. albicans (2,370)	0.06	0.06	0.03	0.03
C. glabrata (1,054)	0.12	0.12	0.06	0.03
C. parapsilosis (897)	2	4	0.5	1
C. tropicalis (557)	0.06	0.06	0.06	0.06
C. krusei (172)	0.06	0.12	0.25	0.12
C. dubliniensis (179)	0.12	0.12	0.06	0.03
fks mutant subset only (43)*	2	4	≥ 8	2

CLSI methodology employed for MIC (M27) determination

*43 isolates include *C. glabrata* (n=38), *C. albicans* (n=3), and *C. tropicalis* (n=2) with characterized *fks* hot spot alterations

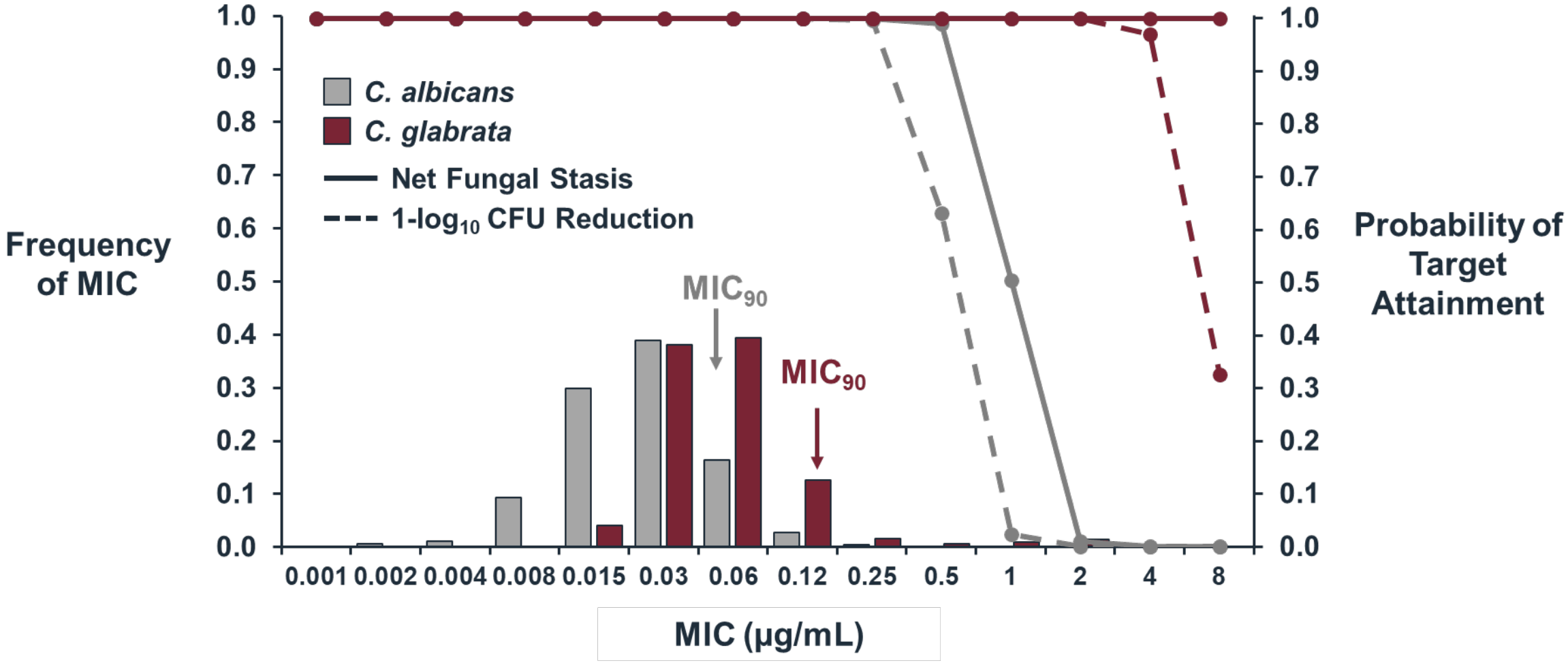
Isolates collected in the JMI international SENTRY Antifungal Surveillance Program (2014–2021)

Pfaller, AAC 2017; Pfaller, IJAA 2017; Pfaller, AAC 2020; Carvalhaes, JCM 2022; Carvalhaes, IDWeek 2022

PK / PD Target Attainment

- Highly predictive for anti-infectives
- Neutropenic mouse disseminated candidiasis PK / PD model
  - Conducted for echinocandins at University of Wisconsin (Dr. Andes)
  - Same researchers independently studied rezafungin for several *Candida* species
    - Selected strains across a range of rezafungin MICs
- PK / PD modeling used for rezafungin throughout clinical development
- Results contribute to overall breakpoint determination

High Probability of Target Attainment for Typical *Candida* Species



Summary of Pharmacology and Microbiology

- Structural modification yields improved chemical and biological properties
- *In vitro* activity similar to other echinocandins
- Long half life allowing for front-loaded exposure
- Extensive tissue distribution and excellent lesion penetration
- Reduced potential for resistance development
- High probability of target attainment for *Candida* species
  - Potential to treat *Candida* infections with higher MICs

Clinical Efficacy

Anita Das, PhD

Consultant Statistician

STRIVE

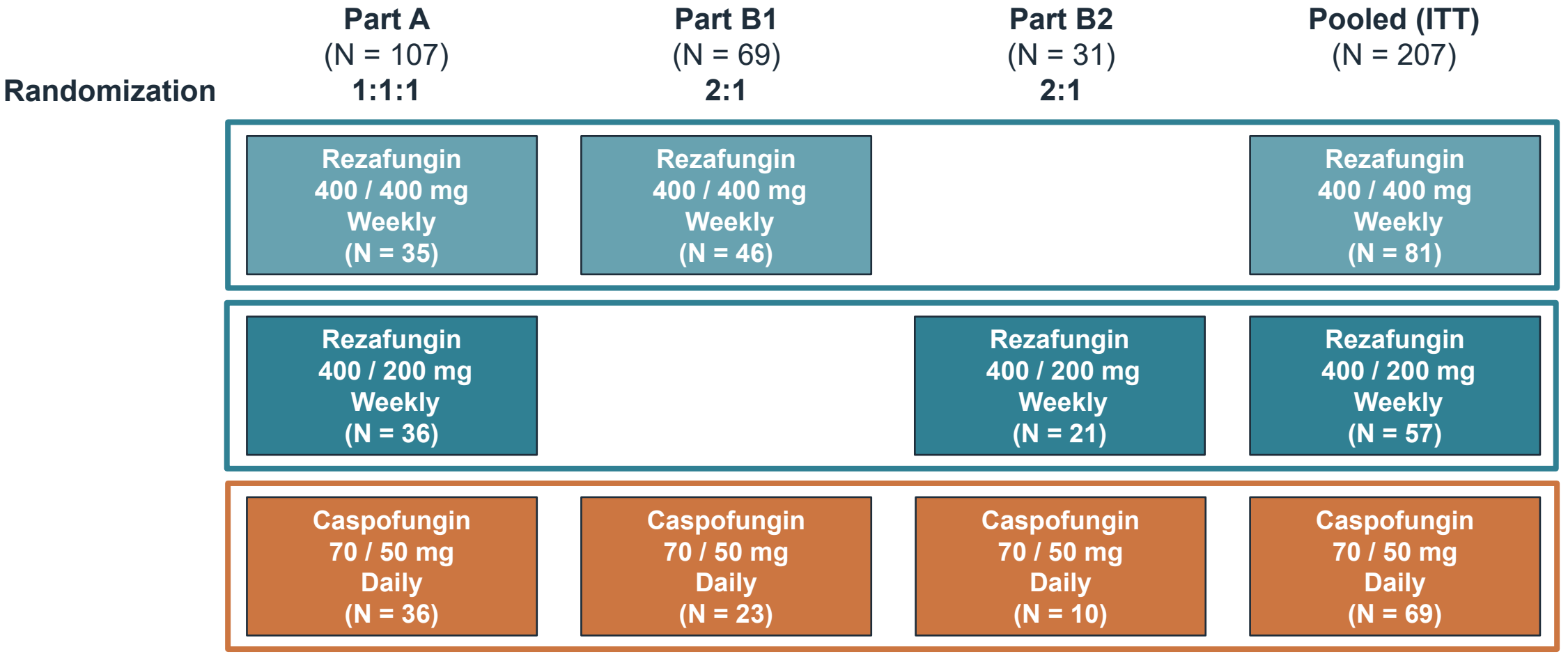
Supportive Phase 2

Randomized, double-blind study

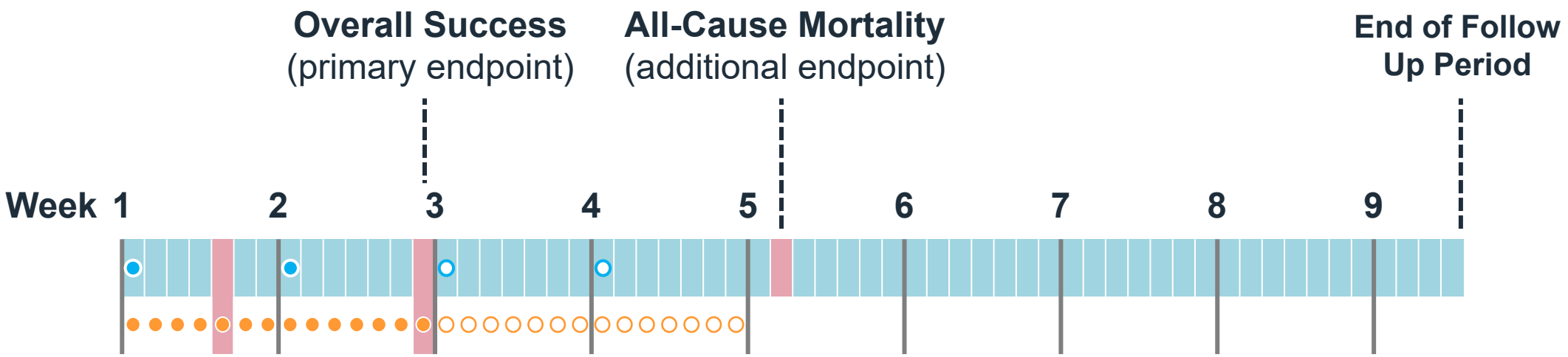
STRIVE: Enrollment Criteria

- Key inclusion
  - ≥ 18 years of age
  - Established mycological diagnosis of candidemia and/or invasive candidiasis
  - ≥ 1 systemic sign: fever, hypothermia, hypotension, tachycardia, tachypnea, or local signs of inflammation
- Key exclusion
  - Septic arthritis in prosthetic joint, osteomyelitis, endocarditis, myocarditis, meningitis, endophthalmitis, CNS infection, neutropenia, elevated liver enzymes (> 10 × ULN), or severe hepatic impairment

STRIVE: Randomization Schedule



STRIVE: Study Design



- Rezafungin dosed weekly IV on Days 1 and 8 with optional IV doses on Days 15 and 22
- Caspofungin dosed daily IV

●/○ Rezafungin dose / optional dose ●/○ Caspofungin dose / optional dose

STRIVE: Efficacy Endpoints

- Primary endpoint
  - Overall response at Day 14 in mITT population
    - Mycological success (eradication / presumed eradication)

    AND
    - Resolution of attributable systemic signs attributable to candidemia and/or invasive candidiasis present at baseline
- Secondary endpoints
  - Mycological response
  - Clinical response evaluated at study visits
- Additional endpoint
  - All-cause mortality assessed at Day 30

STRIVE: Demographics

Characteristic	Rezafungin 400 / 400 mg (N = 76)	Rezafungin 400 / 200 mg (N = 46)	Caspofungin 70 / 50 mg (N = 61)
Age, mean years (min, max)	**60** (24, 88)	**60** (26, 91)	**59** (24, 93)
Sex, Male	**55%**	**61%**	**56%**
Race			
White	**87%**	**78%**	**84%**
Black	**8%**	**13%**	**7%**
Other	**5%**	**9%**	**10%**
Geographic Region			
North / South America	**30%**	**37%**	**36%**
Europe / Israel / Turkey	**70%**	**63%**	**64%**

mITT Population

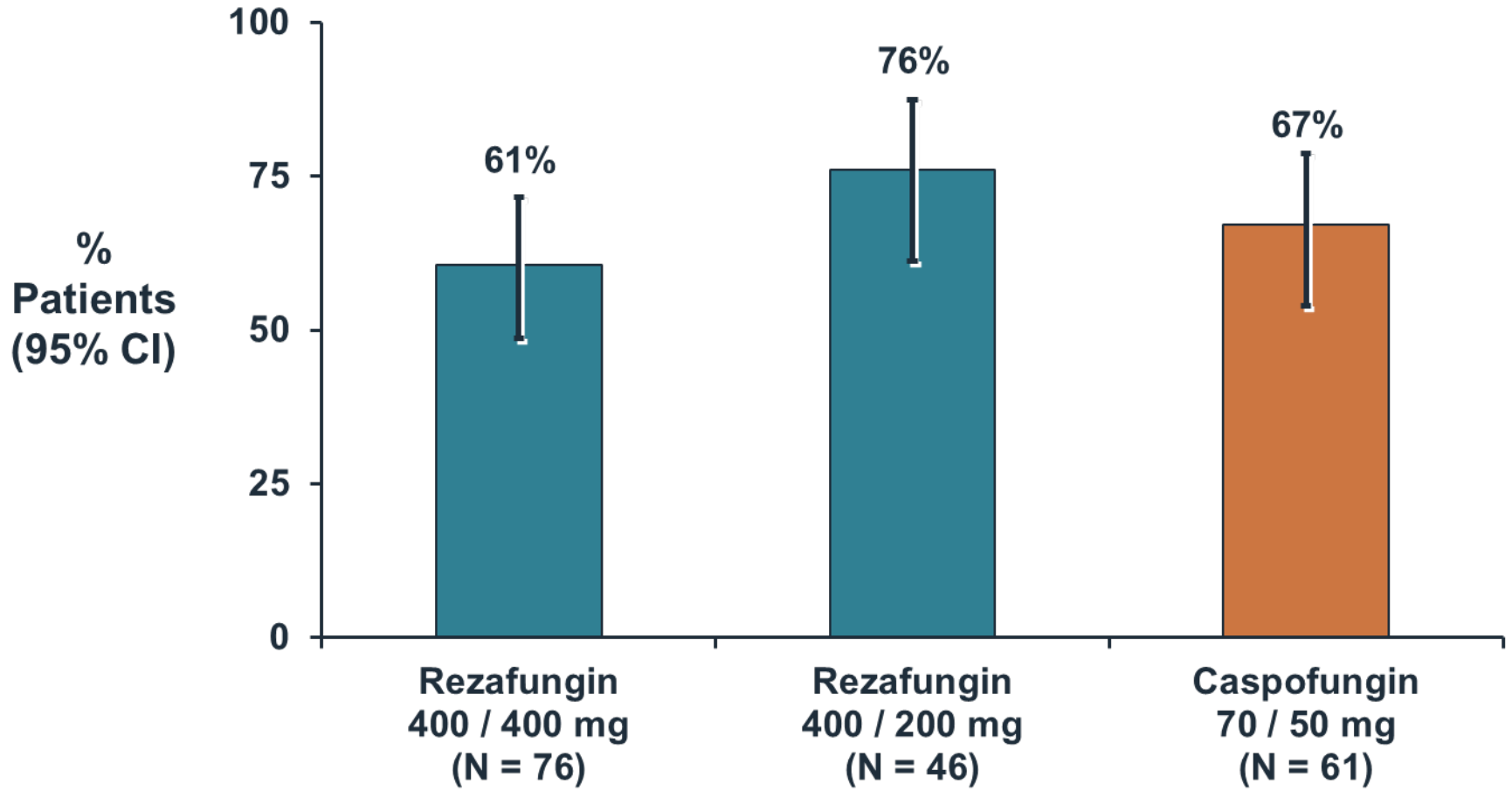
STRIVE: Baseline Characteristics

Characteristic	Rezafungin 400 / 400 mg (N = 76)	Rezafungin 400 / 200 mg (N = 46)	Caspofungin 70 / 50 mg (N = 61)
Diagnosis			
Candidemia only	**75%**	**78%**	**79%**
Invasive candidiasis	**25%**	**22%**	**21%**
Modified APACHE II score			
Median (min, max)	**12.0** (2, 31)	**13.0** (2, 27)	**13.0** (1, 35)
≥ 20	**21%**	**20%**	**15%**
< 20	**76%**	**78%**	**80%**
Missing	**3%**	**2%**	**5%**
ICU at time of dosing	**42%**	**37%**	**49%**
Moderate / Severe renal impairment (< 60 mL/min CrCL)	**22%**	**39%**	**38%**

mITT Population

STRIVE: Primary Endpoint Results
Overall Success at Day 14

Overall success rates high in all treatment groups



mITT Population

STRIVE: 30-Day All-Cause Mortality

Rates of all-cause mortality provided positive efficacy data for rezafungin

Characteristic	Rezafungin 400 / 400 mg (N = 76)		Rezafungin 400 / 200 mg (N = 46)		Caspofungin 70 / 50 mg (N = 61)	
	n	%	n	%	n	%
Deceased / Unknown survival	18	23.7%	4	8.7%	10	16.4%
Known deceased	12	15.8%	2	4.3%	8	13.1%
Unknown survival status	6	7.9%	2	4.3%	2	3.3%

mITT Population

ReSTORE

Pivotal Phase 3

Multicenter, randomized, double-blind study

ReSTORE: Enrollment Criteria

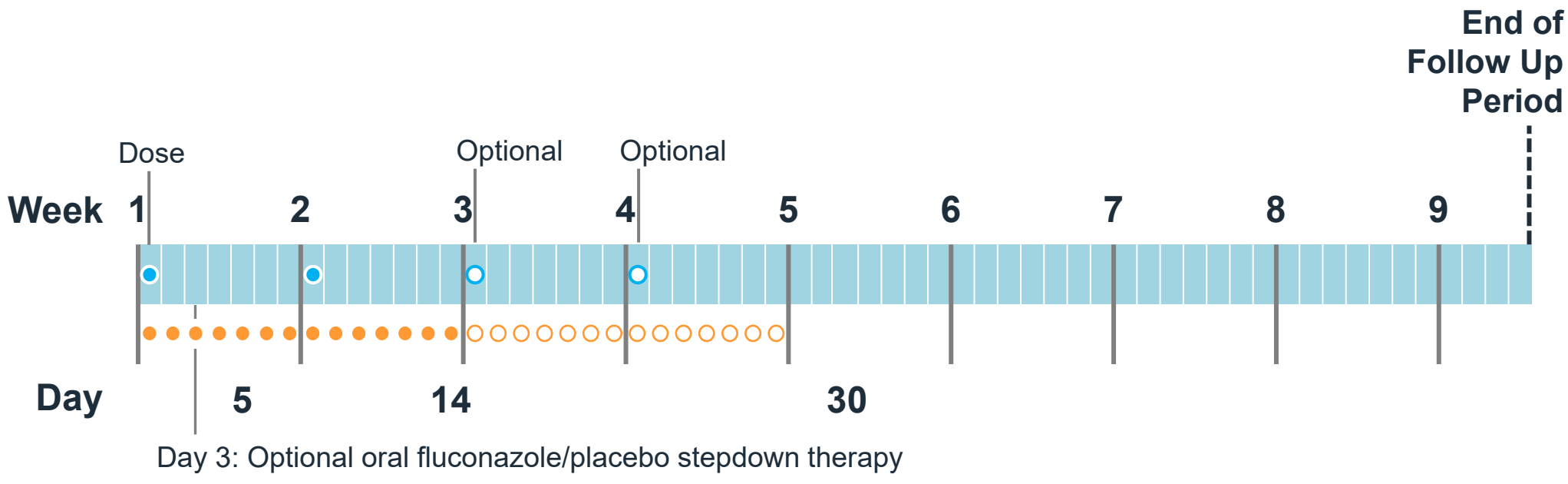
- Key inclusion
  - ≥ 18 years of age
  - Established mycological diagnosis of candidemia and/or invasive candidiasis
  - ≥ 1 systemic sign: fever, hypothermia, hypotension, tachycardia, tachypnea, or local signs of inflammation
- Key exclusion
  - Septic arthritis in prosthetic joint, osteomyelitis, endocarditis, myocarditis, meningitis, endophthalmitis, CNS infection, elevated liver enzymes (> 10 × ULN), or severe hepatic impairment

ReSTORE: Study Design

Rezafungin (N = 100)
400 / 200 mg Weekly

Randomization 1:1

Caspofungin (N = 99)
70 / 50 mg Daily



●/○ Rezafungin dose / optional dose

●/○ Caspofungin dose / optional dose

ReSTORE: Analysis Population and Primary Efficacy Endpoint

- Analysis Population
  - Modified intent-to-treat (mITT)
    - Received at least one dose of study drug
    - Documented *Candida* infection from blood culture or other normally sterile site within 96 hours of randomization
- Primary endpoint
  - All-cause mortality at Day 30 in mITT
  - Discontinuations from study prior to Day 30 were followed for survival status

ReSTORE: Secondary Efficacy Endpoints

- Key secondary endpoint
  - Global Cure at Day 14 (Data Review Committee assessed)
    - Composite of clinical cure and mycological eradication and radiologic cure (for invasive candidiasis patients)
- Other secondary endpoints
  - Mycological eradication at Days 5 and 14
    - Clearance of baseline positive blood or sterile site culture
    - No change in antifungal therapy for treatment of candidemia and/or invasive candidiasis
  - Global cure and mycological eradication assessed at other visits

ReSTORE: Statistical Analysis Plan NI Margin and Sample Size

- Sample size of N = 184 in mITT population based on
  - 90% power
  - 20% all-cause mortality rate
  - 1-sided alpha = 0.025
  - 20% NI margin
    - Acceptable to support a limited use indication

ReSTORE: Demographics

Characteristic	Rezafungin 400 / 200 mg (N = 93)	Caspofungin 70 / 50 mg (N = 94)
Age, mean years (min, max)	**60** (19, 89)	**62** (20, 91)
Sex, Male	**67%**	**60%**
Race		
White	**63%**	**59%**
Asian	**25%**	**33%**
Black	**5%**	**4%**
Other / Not reported	**7%**	**4%**
Geographic Region		
North / South America	**28%**	**26%**
Europe / Israel / Turkey	**41%**	**39%**
Asia-Pacific	**31%**	**35%**

mITT Population

ReSTORE: Baseline Characteristics

Characteristic	Rezafungin 400 / 200 mg (N = 93)	Caspofungin 70 / 50 mg (N = 94)
Diagnosis		
Candidemia only	**69%**	**71%**
Invasive candidiasis	**31%**	**29%**
Moderate / Severe renal impairment (< 60 mL/min)	**39%**	**38%**
ICU at time of dosing	**31%**	**39%**
Mechanical ventilation	**17%**	**30%**
Modified APACHE II score, median (min, max)	**12.0** (0, 40)	**11.5** (0, 37)
≥ 20	**13%**	**18%**
< 20	**86%**	**82%**

mITT Population

ReSTORE: Baseline Pathogens Represented in Both Groups

Candida Species	Rezafungin 400 / 200 mg (N = 93)		Caspofungin 70 / 50 mg (N = 94)	
	n	%	n	%
C. albicans	39	42%	40	43%
C. glabrata	24	26%	25	27%
C. tropicalis	20	22%	17	18%
C. parapsilosis	8	9%	17	18%
C. dubliniensis	3	3%	1	1%
C. krusei	2	2%	2	2%
Other	4	4%	2	2%

- 99.5% of pathogens susceptible to rezafungin and caspofungin (CLSI M27M44S Ed3 2022)

mITT Population
Patients may have multiple pathogens

ReSTORE: Primary Endpoint Result 30-Day All-Cause Mortality

Rezafungin met primary efficacy endpoint of non-inferiority to caspofungin

Characteristic	Rezafungin 400 / 200 mg (N = 93)		Caspofungin 70 / 50 mg (N = 94)	
	n	%	n	%
Deceased / Unknown survival	22	23.7%	20	21.3%
Difference in death rate vs caspofungin (95% CI)	2.4 (-9.7, 14.4)			
Known deceased	19	20.4%	17	18.1%
Unknown survival status	3	3.2%	3	3.2%

mITT Population

ReSTORE: Key Secondary Endpoint Result Global Response at Day 14

Global cure rates similar between treatment groups

Data Review Committee Global Response	Rezafungin 400 / 200 mg (N = 93)		Caspofungin 70 / 50 mg (N = 94)	
	n	%	n	%
Cure	55	**59.1%**	57	**60.6%**
Difference vs caspofungin (95% CI)	**-1.5** (-15.4, 12.5)			
Failure	28	**30.1%**	29	**30.9%**
Indeterminate	10	**10.8%**	8	**8.5%**

mITT Population

ReSTORE: Secondary Endpoint Result Mycological Response at Day 5 and Day 14

Rates of mycological eradication high and similar between treatment groups

Response	Rezafungin 400 / 200 mg (N = 93)		Caspofungin 70 / 50 mg (N = 94)	
	n	%	n	%
Day 5				
Eradication	64	68.8%	58	61.7%
Difference vs caspofungin (95% CI)	7.1 (-6.6, 20.6)			
Failure / Indeterminate	29	31.2%	36	38.3%
Day 14				
Eradication	63	67.7%	62	66.0%
Difference vs caspofungin (95% CI)	1.8 (-11.7, 15.2)			
Failure / Indeterminate	30	32.3%	32	34.0%

mITT Population

ReSTORE: Day 14 Global Cure and Mycological Eradication by *Candida* Species

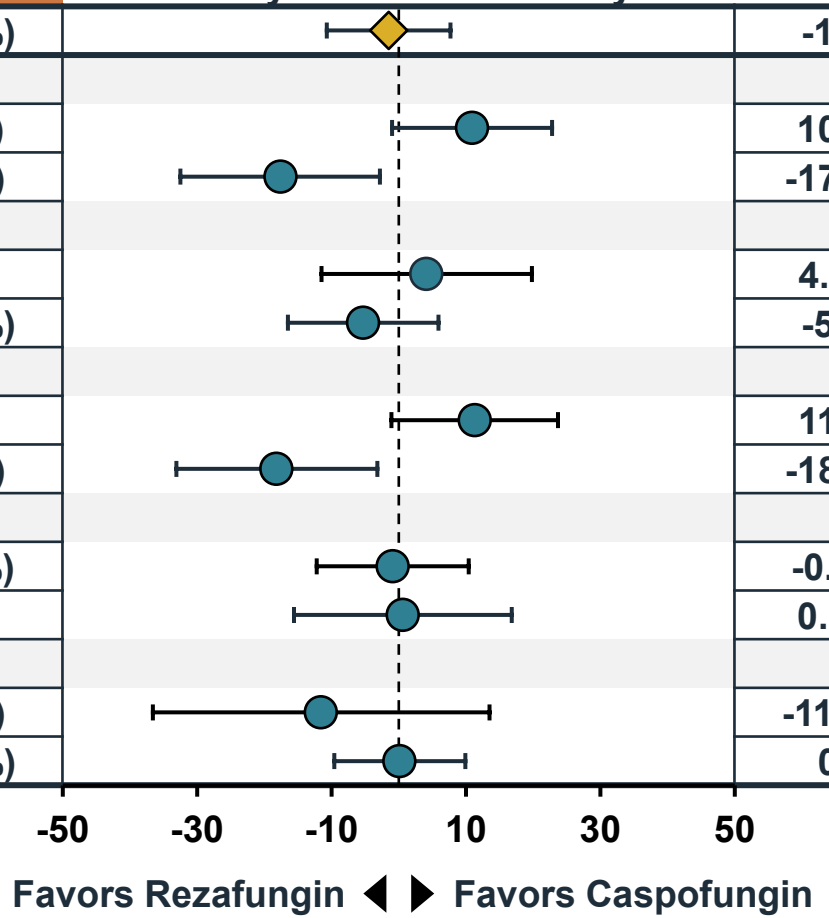
Candida Species		Rezafungin (N = 93)		Caspofungin (N = 94)	
		n / N	%	n / N	%
C. albicans	Global cure	21 / 39	53.8%	23 / 40	57.5%
	Mycological eradication	23 / 39	59.0%	24 / 40	60.0%
C. glabrata	Global cure	16 / 24	66.7%	14 / 25	56.0%
	Mycological eradication	20 / 24	83.3%	15 / 25	60.0%
C. tropicalis	Global cure	14 / 20	70.0%	10 / 17	58.8%
	Mycological eradication	15 / 20	75.0%	10 / 17	58.8%
C. parapsilosis	Global cure	6 / 8	75.0%	11 / 17	64.7%
	Mycological eradication	6 / 8	75.0%	14 / 17	82.4%

mITT Population

Pooled Analyses for Subgroups

Pooled: Subgroup Analysis of 30-Day ACM

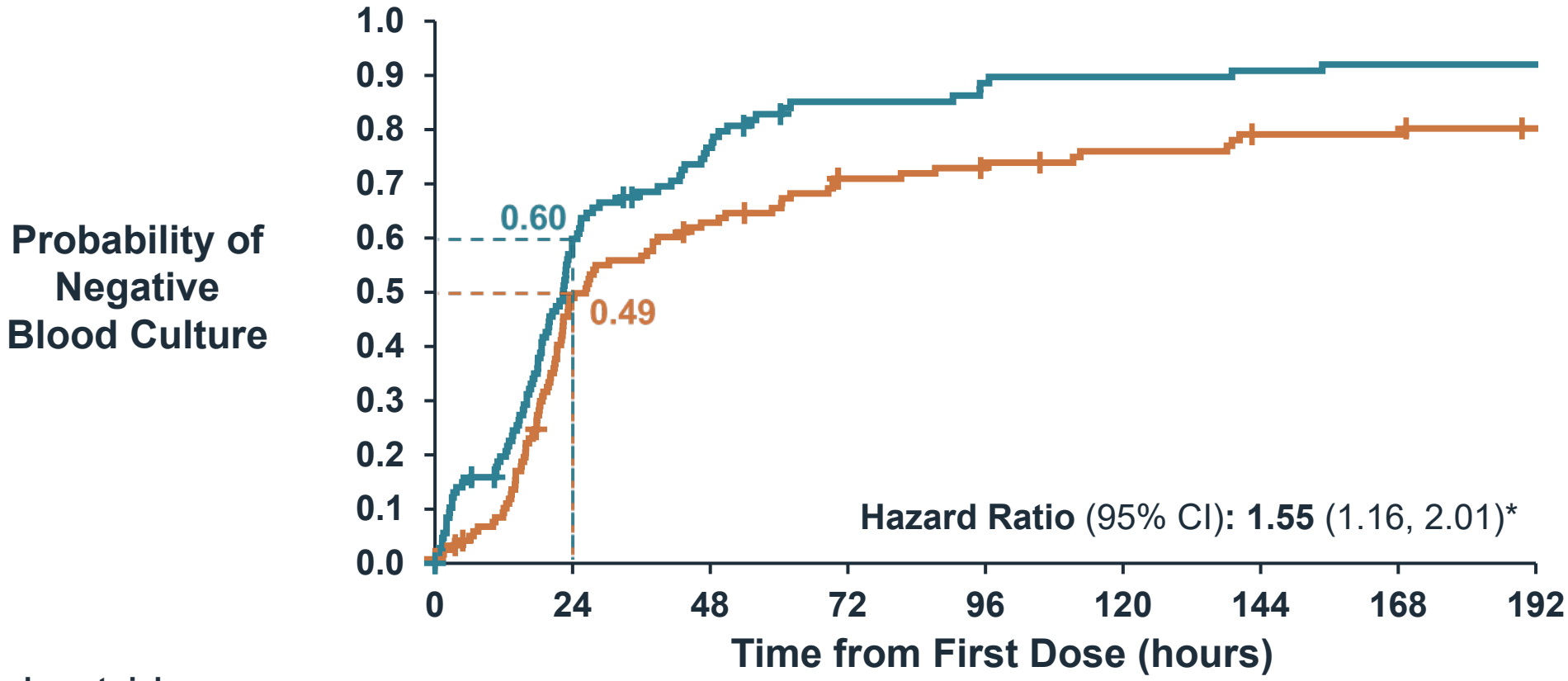
	Rezafungin 400 / 200 mg (N = 139)	Caspofungin 70 / 50 mg (N = 155)	Difference (95% CI)*
Overall	26 / 139 (19%)	30 / 155 (19%)	**-1.5** (-10.7, 7.7)
Age			
< 65 years	18 / 82 (22%)	10 / 92 (11%)	**10.9** (-1.0, 22.8)
≥ 65 years	8 / 57 (14%)	20 / 63 (32%)	**-17.6** (-32.5, -2.8)
Region			
North / South America	6 / 43 (14%)	4 / 46 (9%)	**4.1** (-11.5, 19.8)
Other Regions	20 / 96 (21%)	26 / 109 (24%)	**-5.3** (-16.5, 5.9)
Renal impairment			
≥ 60 mL/min (normal / mild)	17 / 75 (23%)	9 / 83 (11%)	**11.3** (-1.1, 23.7)
< 60 mL/min (moderate / severe)	7 / 54 (13%)	18 / 59 (31%)	**-18.2** (-33.1, -3.2)
Diagnosis			
Candidemia only	22 / 100 (22%)	26 / 115 (23%)	**-0.9** (-12.2, 10.4)
Invasive candidiasis	4 / 39 (10%)	4 / 40 (10%)	**0.6** (-15.6, 16.8)
Modified APACHE II score			
≥ 20	5 / 21 (24%)	10 / 26 (39%)	**-11.6** (-36.6, 13.5)
< 20	19 / 116 (16%)	20 / 126 (16%)	**0.1** (-9.6, 9.9)



mITT Population

*Adjusted (for study and part) confidence interval for the weighted treatment difference

Pooled: Kaplan-Meier Estimate of Time to Negative Blood Culture



Number at risk									
Rezafungin (400 / 200 mg)	109	42	23	13	10	9	8	7	7
Caspofungin (70 / 50 mg)	122	59	42	30	27	23	19	19	16

mITT Population with positive blood culture before randomization
*Adjusted (for study and part) hazard ratio and confidence interval

Efficacy Conclusions

- ReSTORE demonstrated
  - Rezafungin was non-inferior (20% NI margin) to caspofungin for 30-day all-cause mortality (primary endpoint)
  - Rates of global cure at day 14 (key secondary endpoint) high and comparable between treatment groups
- Endpoints support evidence of efficacy
  - Global cure at other visits
  - Mycological eradication
  - Overall cure
  - Time to negative blood culture

Clinical Safety

Taylor Sandison, MD, MPH
Chief Medical Officer
Cidara Therapeutics

Safety Populations

- N = 312 exposed to ≥ 2 infusions of rezafungin at proposed commercial dose or higher

	Rezafungin			
	400 / 200 mg or Higher	400 / 400 mg	400 / 200 mg	Caspofungin
Phase 1 or Compassionate Use	80	-	-	-
Phase 2 - STRIVE	-	81	53	68
Phase 3 - ReSTORE	-	-	98	98
Pooled Safety Dataset	-	-	151	166

Pooled: Treatment Duration

	Rezafungin 400 / 200 mg (N = 151)	Caspofungin 70 / 50 mg (N = 166)
Median treatment duration, days (range)		
IV and oral therapy combined	**14** (1–28)	**14** (1–28)
IV therapy	**14** (1–28)	**14** (1–28)
Patients on oral therapy, %	**28%**	**36%**
Median treatment duration, days (range)	**10** (1–24)	**9** (2–21)

Pooled: Overview of Adverse Events

	Rezafungin 400 / 200 mg (N = 151)	Caspofungin 70 / 50 mg (N = 166)
Adverse Events	91%	83%
Severe AE	49%	51%
SAE	55%	49%
AE leading to interruption of study drug	2%	2%
AE leading to discontinuation of study drug	9%	9%
AE resulting in death	23%	24%

Pooled: Common Adverse Events Reported

	Rezafungin 400 / 200 mg (N = 151)	Caspofungin 70 / 50 mg (N = 166)
Patients with ≥ 1 Adverse Events	**91%**	**83%**
Preferred Term (≥ 5% of Rezafungin Patients)		
Hypokalemia	15%	10%
Pyrexia	12%	7%
Diarrhea	11%	10%
Anemia	10%	8%
Vomiting	9%	4%
Nausea	9%	5%
Hypomagnesemia	8%	3%
Pneumonia	8%	4%
Abdominal pain	7%	5%
Septic shock	7%	7%
Sepsis	7%	5%
Constipation	5%	5%
Hypophosphatemia	5%	3%

Pooled: Similar Rates of Severe AEs

	Rezafungin 400 / 200 mg (N = 151)	Caspofungin 70 / 50 mg (N = 166)
Patients with ≥ 1 Severe AE	**49%**	**51%**
Preferred Term (≥ 2%)		
Septic shock	7%	7%
Pneumonia	5%	1%
Sepsis	3%	4%
Acute kidney injury	1%	2%

Pooled: Similar Rate and Pattern of Serious Adverse Events

	Rezafungin 400 / 200 mg (N = 151)	Caspofungin 70 / 50 mg (N = 166)
Patients with ≥ 1 SAE	**55%**	**49%**
Preferred Term (≥ 2%)		
Septic shock	6%	6%
Multiple organ dysfunction syndrome	3%	2%
Sepsis	3%	4%
Pneumonia	3%	2%
Bacteremia	3%	1%
Cardiac arrest	2%	0.6%
Respiratory failure	1%	3%
Acute respiratory failure	1%	2%

Pooled: Serious Adverse Events by System Organ Class

System Organ Class	Rezafungin 400 / 200 mg (N = 151)		Caspofungin 70 / 50 mg (N = 166)	
	n	%	n	%
Infections and infestations	35	23%	40	24%
Cardiac disorders	11	7%	8	5%
Respiratory, thoracic and mediastinal disorders	10	7%	19	11%
Gastrointestinal disorders	10	7%	13	8%
General disorders and administration site conditions	8	5%	7	4%
Neoplasm benign, malignant and unspecified (incl cyst and polyps)	7	5%	4	2%
Vascular disorders	7	5%	1	0.6%
Injury, poisoning and procedural complications	5	3%	3	2%
Nervous system disorders	5	3%	2	1%
Renal and urinary disorders	4	3%	4	2%
Metabolism and nutrition disorders	2	1%	5	3%
Hepatobiliary disorders	2	1%	3	2%
Blood and lymphatic system disorders	2	1%	2	1%
Skin and subcutaneous tissue disorders	2	1%	0	0
Death NOS	1	0.7%	0	0
Immune system disorders	0	0	1	0.6%
Investigations	0	0	1	0.6%
Musculoskeletal and connective tissues disorders	0	0	1	0.6%

Pooled: Similar Rates of AEs Leading to Study Drug Discontinuation

	Rezafungin 400 / 200 mg (N = 151)	Caspofungin 70 / 50 mg (N = 166)
Patients with ≥ 1 AE Leading to Study Drug Discontinuation	**9%**	**9%**
Preferred Term (≥ 1%)		
Infusion related reaction	1%	0
Chorioretinitis	0	1%
Endophthalmitis	0	1%

Pooled: Similar Incidence of AEs Leading to Death

	Rezafungin 400 / 200 mg (N = 151)	Caspofungin 70 / 50 mg (N = 166)
Patients with ≥ 1 AE Leading to Death	**23%**	**24%**
Preferred Term (> 1 patient)		
Septic shock	5%	6%
Multiple organ dysfunction syndrome	3%	2%
Sepsis	2%	2%
Cardiac arrest	2%	1%
Respiratory failure	1%	2%
Shock	1%	0
COVID-19 pneumonia	0	1%

- Mortality rate similar to previous clinical trials in this vulnerable population

Adverse Events of Special Interest

Photosensitivity

Neurologic AESIs

Infusion-Related Reactions

Summary of Rezafungin Nonclinical Nervous System Findings in Nonhuman Primates

- No neuropathology findings in 4-week study (9 × clinical exposure)
- 13-week studies
  - High dose not tolerated (60/45 mg/kg, 15 × clinical exposure)
    - Tremors, hunched posture, poor condition
  - 30 mg/kg well tolerated (9 × clinical dose) - no adverse effects
  - Non-adverse finding - Schwann cell phospholipidosis (hyperplasia at higher doses)
  - No definitive evidence of rezafungin axonal / nerve fiber degeneration or myelinopathy up to highest tolerated dose

Summary of Rezafungin Longer-Term Nonclinical Nervous System Findings

- 6-month nonhuman primate blinded study
  - Non-adverse finding - Schwann cell phospholipidosis and at high dose (6 × clinical exposure) hyperplasia with recovery
  - No evidence of definitive rezafungin-related tremors or nerve/myelin degenerative changes following a detailed evaluation of neurobehavior and CNS/PNS pathology
- Conclusion
  - Overall risk of neurological toxicity with rezafungin is low

Four Rezafungin-Treated Patients Experienced Mild Events of Tremor That Resolved Without Sequelae

Age / Sex	Underlying Diagnosis	Severity Resolution	Independent Neurologist Assessment	Comments
67 / M	Seizure	Mild, Resolved without sequalae	Not related	Recent cerebral infarction
28 / F	Hypocalcemia	Mild, Resolved without sequalae	Not related	Tumor lysis syndrome, caused by chemotherapy for lymphoma
84 / F	Fluid shifts with use of diuretics	Mild, Resolved without sequalae	Possibly related	May have contributed to electrolyte abnormalities
77 / F	Hypokalemia	Mild, Resolved without sequalae	Related	Based on class effects of echinocandins

Pooled: Neuropathy Events Low in Both Arms

	Rezafungin 400 / 200 mg (N = 151)		Caspofungin 70 / 50 mg (N = 166)	
	n	%	n	%
Any Neuropathy AESI	**2**	**1%**	**4**	**2%**
Preferred Term				
Intensive care unit acquired weakness	1	0.7%	1	0.6%
Peroneal nerve palsy	1	0.7%	0	0
Polyneuropathy	0	0	2	1%
Neuropathy peripheral	0	0	1	0.6%

Pooled: Few Infusion-Related Reactions

	Rezafungin 400 / 200 mg (N = 151)		Caspofungin 70 / 50 mg (N = 166)	
	n	%	n	%
Any Infusion-related Reaction AESI	**4**	**3%**	**1**	**0.6%**
Preferred Term				
Infusion-related reaction	3	2%	0	0
Infusion-related hypersensitivity reaction	1*	0.7%	0	0
Adverse drug reaction	1*	0.7%	0	0
Anaphylactic shock	0	0	1	0.6%

*Same patient

Conclusions: Similar Safety Profile to Other Echinocandins

- Treatment groups had similar incidence and type of AEs
- Incidence of SAEs reflected severity of disease under study along with high rate of comorbidities
- Death rates as expected in highly vulnerable population
- Adverse events of special interest were uncommon
- Few neurological AEs, mostly mild, transient, and reversible

Clinical Perspective

Cornelius (Neil) J. Clancy, MD

Professor of Medicine,
Associate Chief of Infectious Diseases

University of Pittsburgh

Unmet Need: Perspective on Currently Available Treatments

- Candidemia and invasive candidiasis remain serious medical conditions with high mortality
- *Candida* species 2nd leading pathogen among bloodstream infections[1]
- WHO includes *Candida* species as global threats[2]
  - Critical or high priority pathogens
  - Need medical advances to treat these infections
- Once-daily echinocandins trusted first-line treatments for *Candida* infections, but opportunities for improvements remain

1. Magill, 2018; 2. WHO, 2022

Unique Pharmacologic Profile

Stability and long half-life allows for once-weekly administration

- Potentially reducing need for inpatient management and continuous indwelling catheter, reducing exposures to potential infusion-related complications

Front loaded PK profile

- Potential for faster microbial clearance
- Sustained therapeutic exposures maximize anti-*Candida* activity and minimize underdosing, a concern for critically ill patients
- Deep tissue penetration supported by animal models

No or low risk of clinically meaningful drug-drug interactions

Microbiological Profile Addresses Increasing *Candida* Resistance

Improved activity to manage resistant pathogens

- *C. glabrata* target attainment
  - Successful clinical treatment of *fks* mutant *C. glabrata*
- *C. auris* efficacy (animal model)
  - CLSI provisional breakpoint (only antifungal)

Earlier mycological clearance observed in blood cultures

Less potential for resistance development due to high initial drug exposure, less potential for underdosing

Safety Results Align with Expectations for an Echinocandin

- Echinocandins have well-established safety profile and are well tolerated
- Safety data for rezafungin aligns with class
- AEs mostly mild and transient
- Patients able to remain on treatment
- SAEs and AEs leading to death at comparable rates between groups
  - Types of AEs expected in this very sick population
- Neurological AEs limited and reversible
- Benefits continue to outweigh potential risks

Clinical Scenarios Support Positive Benefit-Risk Profile

Expanded Access Example 1

- Patient with multidrug-resistant *Candida glabrata* vascular graft infection
- Patient had exhausted options across all antifungal drug classes
  - 3-year history of continuous antifungal use
    - Micafungin; Fluconazole; Micafungin; Lipid amphotericin B (LAB); Posaconazole; Micafungin; LAB + 5-FC
- *C. glabrata* resistant to azoles and micafungin
  - Fks2 D666Y mutation conferring resistance to all approved echinocandins
- Rezafungin used for > 2 year
  - No significant AEs, including no neurological AEs
  - Successful suppression of invasive candidiasis

Adeel, 2021

Clinical Scenarios Support Positive Benefit-Risk Profile

Expanded Access Example 2

- Patient underwent liver transplant, complicated by peritonitis and multiple abdominal abscesses
  - *Candida krusei*
- Worsening of abscesses despite treatment with micafungin
- Rezafungin requested due to improved distribution and tissue penetration
- Infection cleared after 12 weeks treatment with rezafungin
  - Administered once weekly in outpatient transplant clinic
- No neurological AEs

Pechacek, 2022

Clinical Scenario Where Patient Could Benefit from Having Rezafungin

Hospital Setting Example 1

- 32-year-old man with active injection drug use and past history of *C. glabrata* and *S. aureus* vertebral osteomyelitis
  - Received 8 weeks of micafungin, then fluconazole
- Admitted now with azole-resistant *C. glabrata* bloodstream infection and native aortic valve endocarditis
- Cared for by multi-disciplinary endovascular infection team
  - Treated initially with micafungin, underwent aortic value replacement
  - Echinocandin planned for at least 6 weeks post-operative
  - Placement is sought in facility or program that can address drug use
  - Need for active antifungal regimen that can avoid PICC line or port

Clinical Scenario Where Patient Could Benefit from Having Rezafungin

Hospital Setting Example 2

- 54-year-old woman with multiple sclerosis admitted to hospital twice with pneumonia
- Receiving antibiotics through a central venous catheter
  - Developed *C. glabrata* bloodstream infection
- Treated with micafungin
- Central line not discontinued for 3 days due to concerns about poor vascular access
  - Blood cultures still positive for *C. glabrata*
- Likely need at least 14 days of echinocandin treatment
  - Assuming blood cultures clear after central line is discontinued
- Rezafungin might offer treatment option
  - Avoid need for daily micafungin and venous access procedure by interventional radiology

Rezafungin Is a Next Generation Echinocandin for Treatment of Candida Infections

- Part of a well-established class of drugs that is the current standard of care for treatment of *Candida* infections.
- Consistent efficacy and safety data across two clinical studies compared to an approved echinocandin
- Demonstrated favorable risk-benefit balance for patients with candidemia and invasive candidiasis
- Improved pharmacokinetic profile – no DDIs and once weekly administration enables flexible IV catheter management
- Offers a treatment option for candidemia and invasive candidiasis to address patients' specific clinical and pharmacologic needs.

Rezafungin for Injection Limited Use Indication for the Treatment of Candidemia and Invasive Candidiasis in Adult Patients

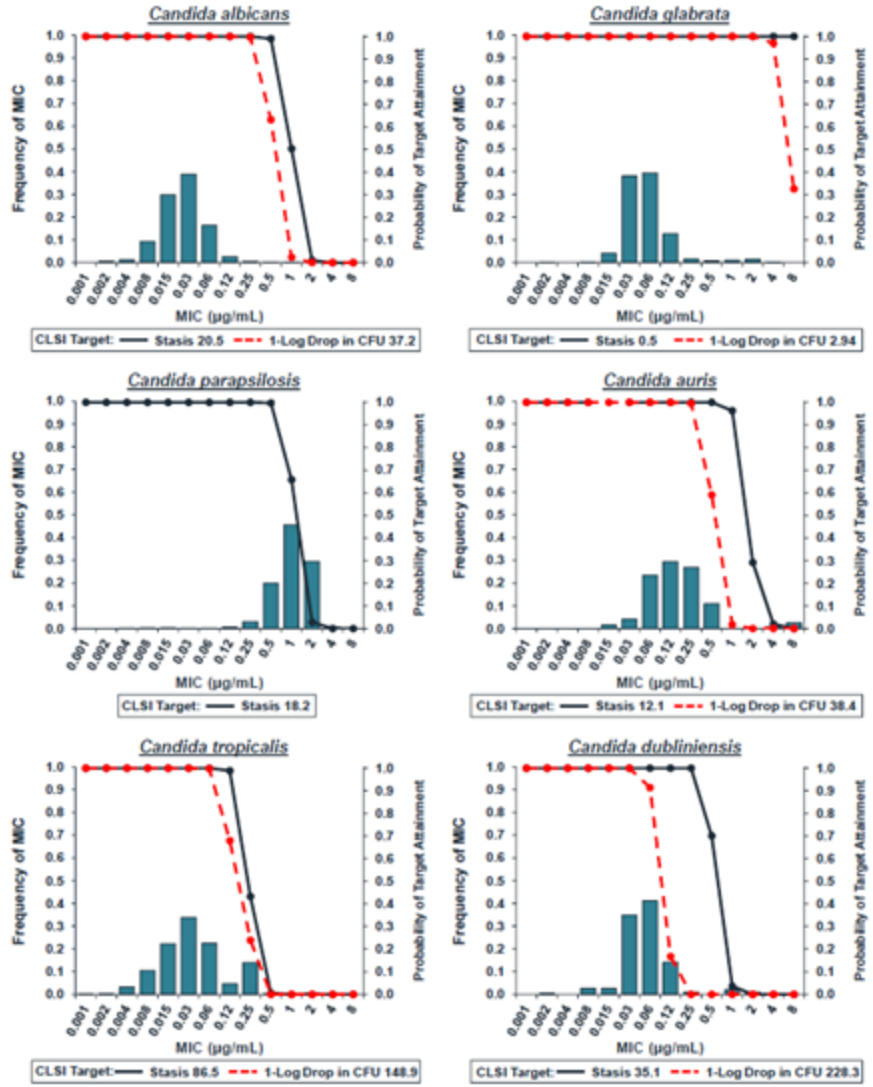
January 24, 2023

Cidara Therapeutics

Antimicrobial Drugs Advisory Committee

Back-up Slides

Figure 16: Probability of PK/PD Target Attainment Overlaid on Rezafungin MIC Distributions (CLSI Methodology) for Candida Species



Rezafungin Showed Efficacy in Reducing Fungal Burden in Kidneys of *C. auris* Infected Mice

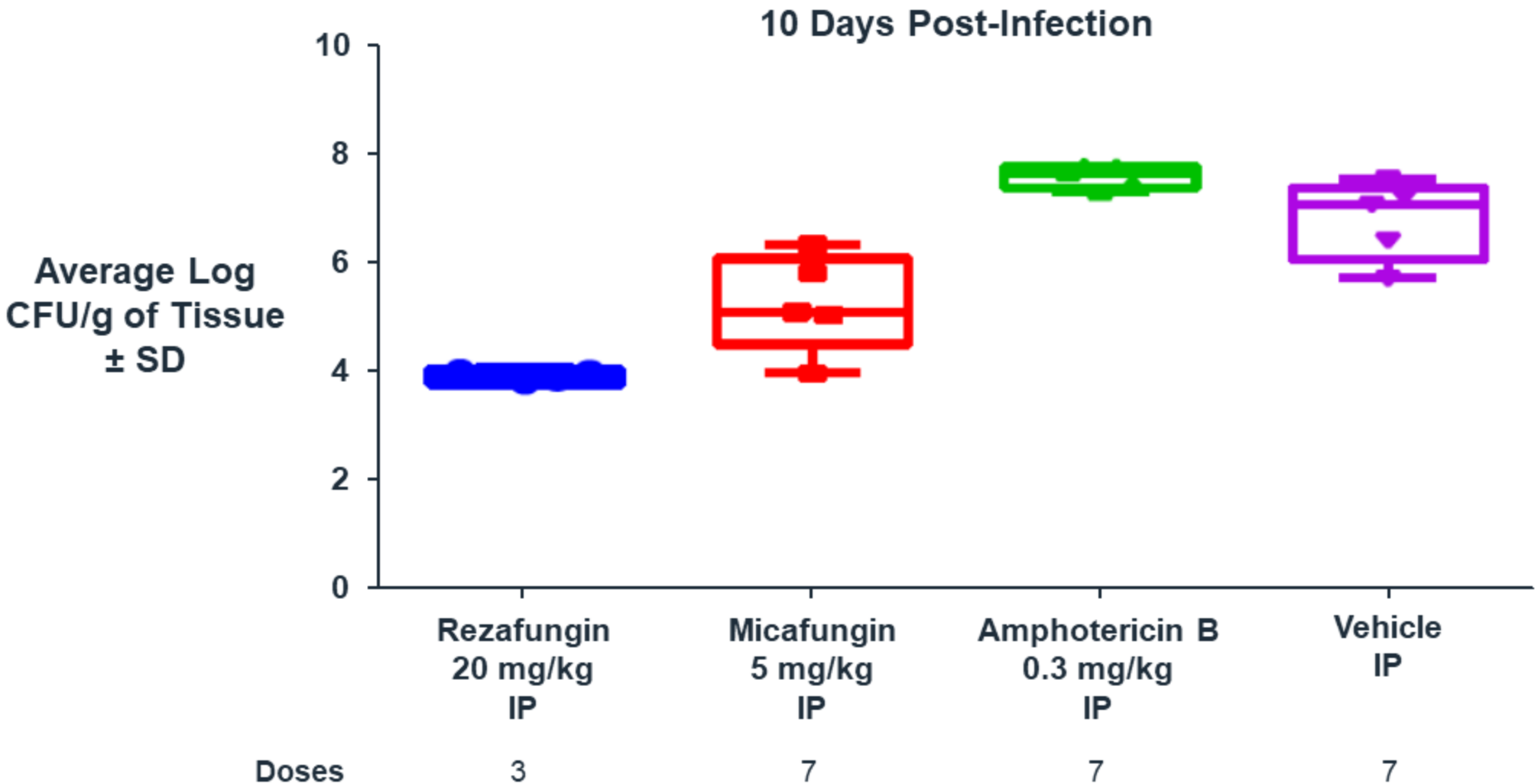
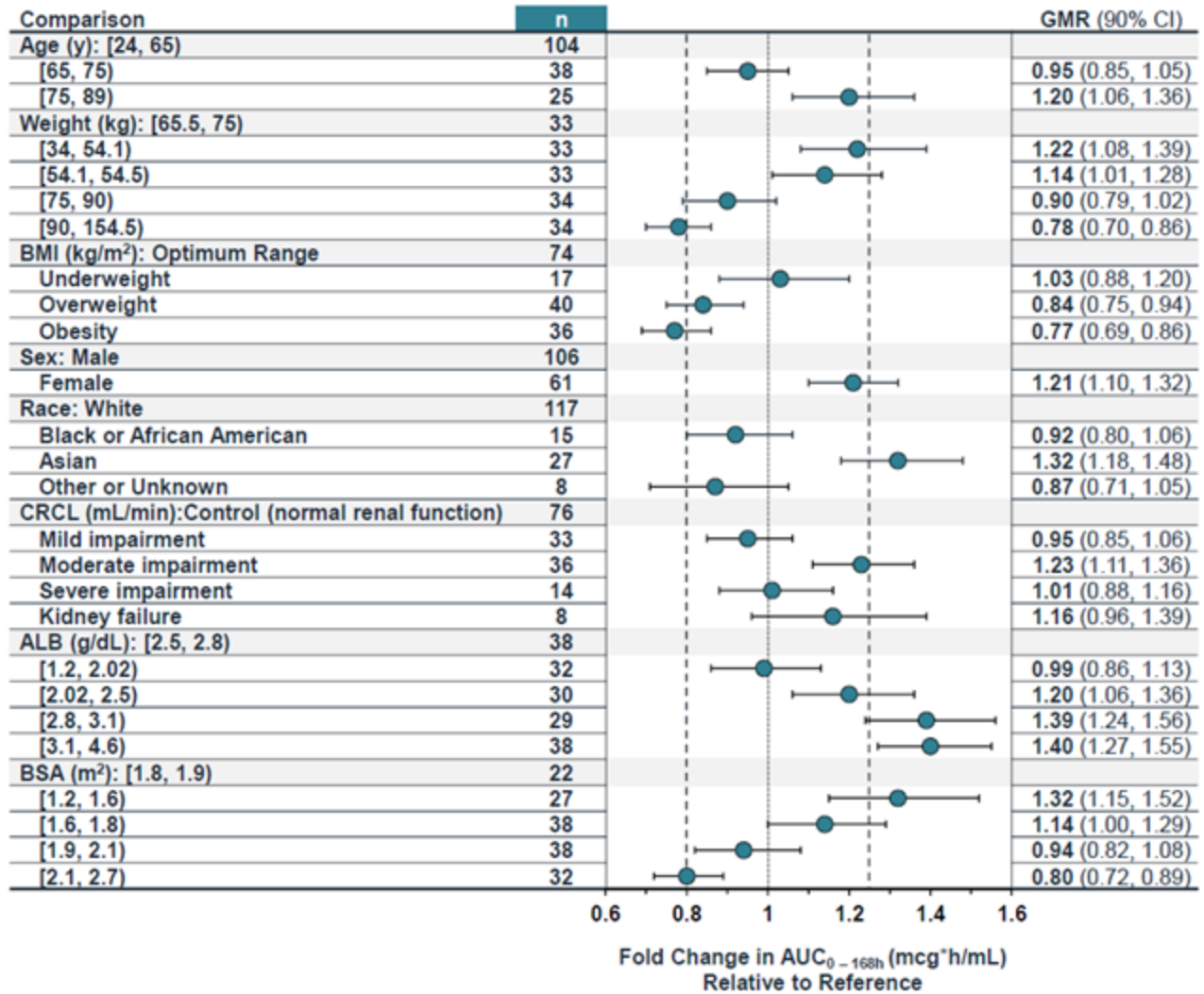
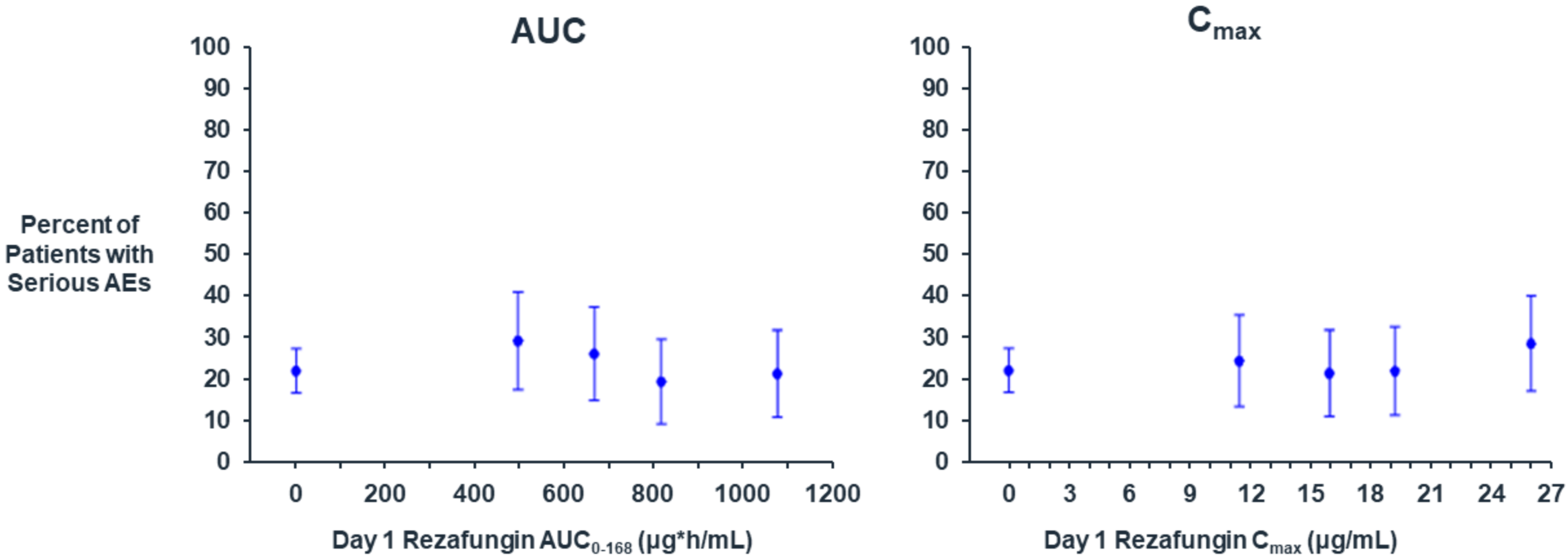


Figure 13: Forest Plots Illustrating the Impact of Covariate Effects on Rezafungin Exposure Following a Single 400 mg Dose in Patients Enrolled in STRIVE and ReSTORE



Rezafungin Exposure Response: Does Not Correlate with Safety

Percent of Patients With Serious Adverse Events Versus Rezafungin Exposure Measures



Clinical Data for Rezafungin Differentiation

- Tissue distribution and IC:
  - STRIVE Overall Response and ReSTORE Global Response showed high success rates at Day 14 for rezafungin

	Rezafungin (400 / 200 mg) n / N1 (%)	Caspofungin n / N1 (%)
STRIVE Overall Success	**10 / 10 (100%)**	**10 / 13 (77%)**
ReSTORE Global Cure	**16 / 29 (55%)**	**14 / 27 (52%)**
Pooled 30-day ACM	**4/39 (10%)**	**4/40 (10%)**

  - Expanded access patient with multiple abdominal abscess failed micafungin but was cured with rezafungin (Pecachek, JAC, 2022)

FICI Summary of Rezafungin Antifungal Combinations

Fractional Inhibitory Concentration Index (FICI)

- FICI = (MIC of RZF in the presence of Drug 2/MIC of RZF alone) + (MIC of Drug 2 in presence of RZF/MIC of Drug 2 alone)

	MIC[1]				MIC[2]		
Strain	**AMB**	**FLU**	**POSA**	**5FC**	**FLU**	**POSA**	**5FC**
C. albicans **ATCC 90028**	1.03	2.00	0.57	2.00	-	-	-
C. glabrata **ATCC 2001**	0.57	0.52	1.03	2.00	0.73	0.37	0.62
C. parapsilosis **ATCC 22019**	0.75	3.00	0.51	0.52	0.80	0.53	
C. krusei **ATCC 6258**	2.00	2.00	3.00	0.77	0.75	2.00	0.50
C. tropicalis **ATCC 750**	2.00	0.63	3.00	2.00	-	-	2.00
C. auris **B11211**	2.00	0.56	0.75	0.63	0.19	0.09	2.00

Synergy (≤ 0.50) Additivity (> 0.50 - ≤ 1) Indifference (> 1 - ≤ 4) Antagonistic (> 4)

[1]MIC endpoint: 100% AMB; 50 – 80% FLU, POSA, 5FC
[2]MIC endpoint: 100% FLU, POSA, 5FC
-, endpoint not available; RZF, rezafungin; AMB, amphotericin B; FLU, fluconazole; POSA, posaconazole; 5FC, flucytosine

Four Rezafungin-Treated Patients Experienced Mild Events of Tremor That Resolved Without Sequelae - BMI

Patient	Age / Sex	BMI, kg/m^2 (Percentile*)	Independent Neurologist Assessment
1	67 / M	35.3 (90.4)	Not related
2	28 / F	21.1 (27.1)	Not related
3	84 / F	27.3 (66.0)	Possibly related
4	77 / F	30.6 (77.8)	Related

*Percentiles are among 400 / 200 mg Rezafungin group only

All-Cause Mortality: ≥ 65 Years of Age by Sex

	Rezafungin 400 / 200 mg (N = 139)		Caspofungin 70 / 50 mg (N = 155)	
	n / N1	%	n / N1	%
Pooled Analysis				
Male	7 / 39	18%	12 / 38	32%
Female	1 / 18	6%	8 / 25	32%

	Rezafungin 400 / 200 mg (N = 93)		Caspofungin 70 / 50 mg (N = 94)	
	n / N1	%	n / N1	%
ReSTORE				
Male	6 / 27	22%	7 / 23	30%
Female	1 / 11	9%	5 / 15	33%

Clinical Treatment of *fks* Mutant *Candida* Isolates with Rezafungin

- All 3 patients with *fks* mutant isolates treated to date with rezafungin have been successes:

#	Origin	*Candida* spp.	Fks alteration	MIC (µg/mL) / CLSI interpretation*				Notes
				RZF	CAS	MCF	ANF	
1	ReSTORE - rezafungin arm	*C. glabrata*	F659V	0.5 / S	0.25 / I	0.06 / S	0.5 / R	success for 30-Day ACM and Day 14 mycological eradication
2	Expanded Access	*C. glabrata*	D666Y	2 / NS	0.5 / R	0.5 / R	1 / R	successfully treated/suppressed infection; treatment ongoing for >2 yrs
3	Expanded Access	*C. glabrata*	F659del	1 / NS	0.5 / R	1 / R	2 / R	successfully cleared infection following 2 weeks of therapy

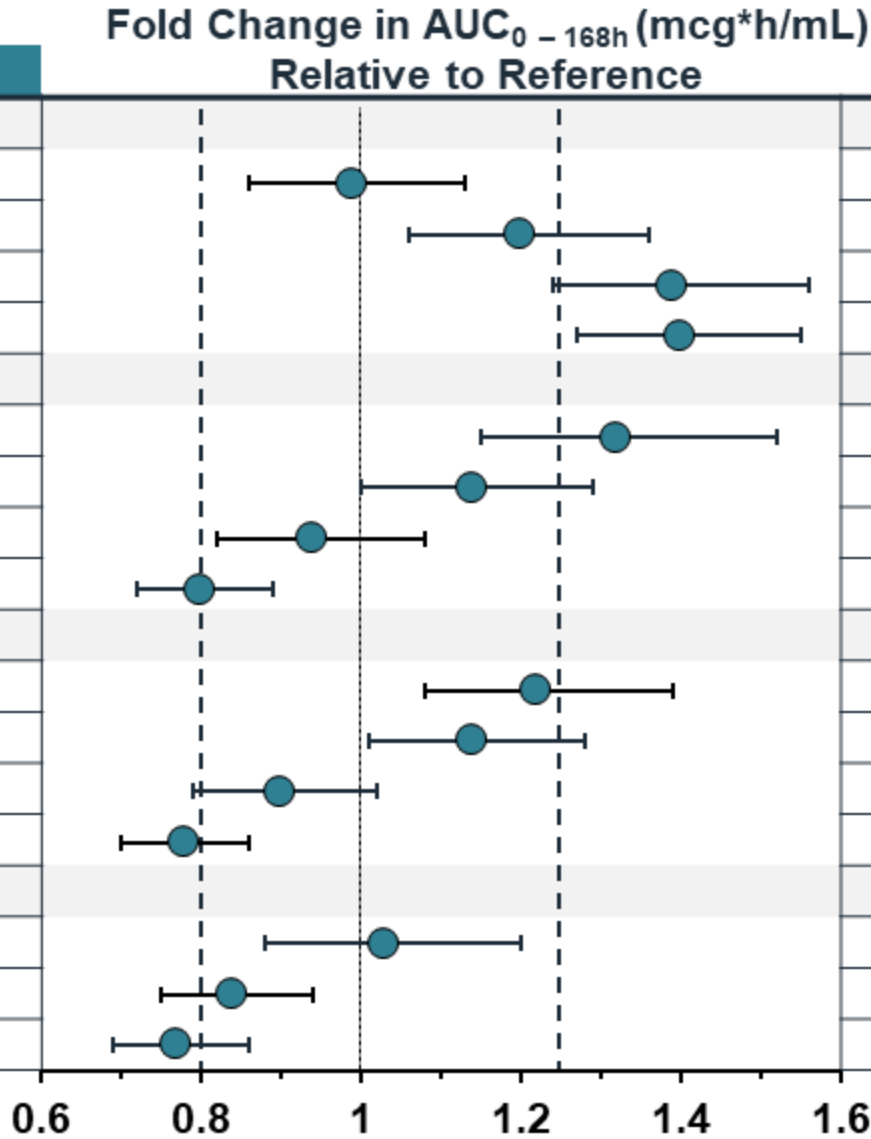
RZF = rezafungin; CAS = caspofungin; MCF = micafungin; ANF = anidulafungin; S = susceptible; I = intermediate; R = resistant;
NS = nonsusceptible (rezafungin I and R breakpoints not yet established); del = deletion
*CLSI M27M44S Ed3 2022

ReSTORE: 30-Day ACM by Prior Echinocandin Use (mITT Population)

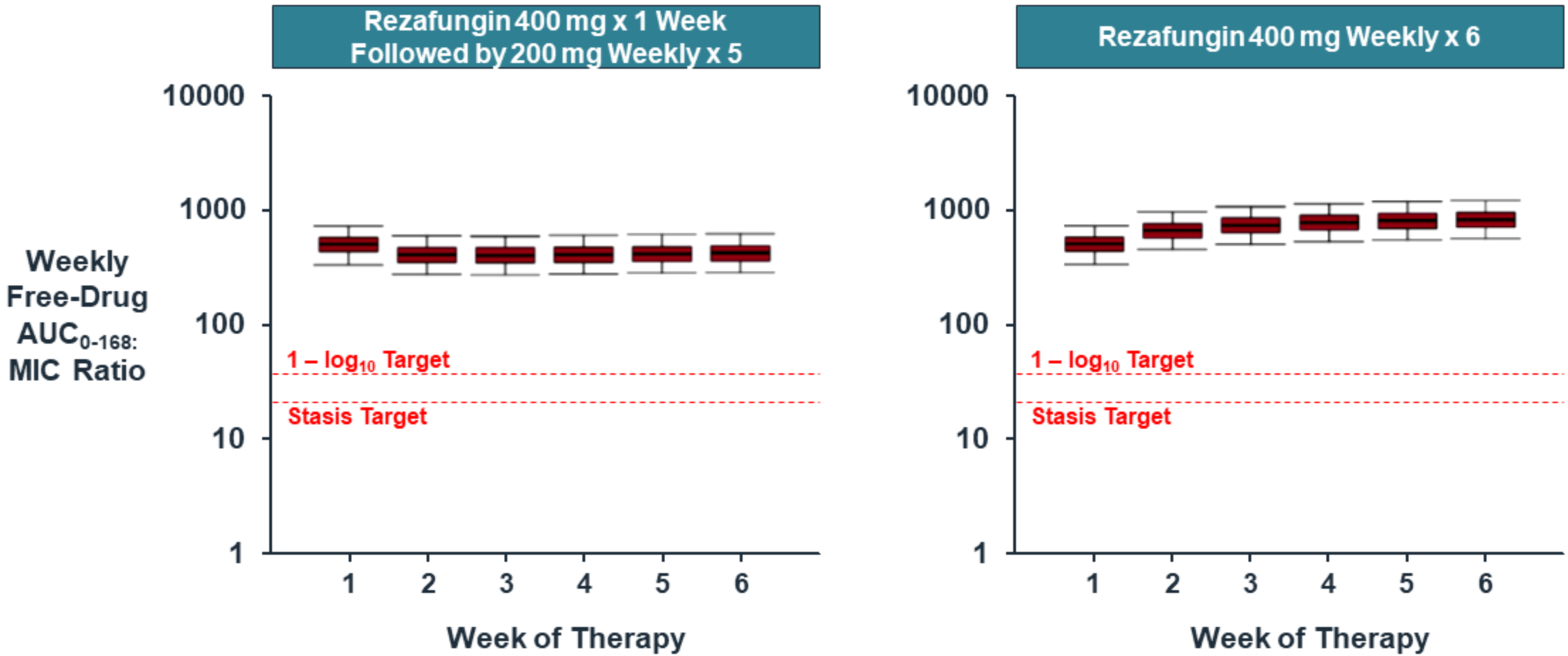
	Rezafungin (N = 93) n (%)	Caspofungin (N = 94) n (%)
Prior Echinocandin	52 (56)	36 (38)
Deceased / Unknown	13 (25)	8 (22)
No Prior Echinocandin	41 (44)	58 (62)
Deceased / Unknown	9 (22)	12 (21)

Impact of Covariate Effects on Rezafungin Exposure (Single 400 mg Dose)

Comparison	n	GMR (90% CI)
ALB (g/dL): [2.5, 2.8)	38	
[1.2, 2.02)	32	**0.99** (0.86, 1.13)
[2.02, 2.5)	30	**1.20** (1.06, 1.36)
[2.8, 3.1)	29	**1.39** (1.24, 1.56)
[3.1, 4.6)	38	**1.40** (1.27, 1.55)
BSA (m^2): [1.8, 1.9)	22	
[1.2, 1.6)	27	**1.32** (1.15, 1.52)
[1.6, 1.8)	38	**1.14** (1.00, 1.29)
[1.9, 2.1)	38	**0.94** (0.82, 1.08)
[2.1, 2.7)	42	**0.80** (0.72, 0.89)
Weight (kg): [65.5, 75)	33	
[34, 54.1)	33	**1.22** (1.08, 1.39)
[54.1, 65.5)	33	**1.14** (1.01, 1.28)
[75, 90)	34	**0.90** (0.79, 1.02)
[90, 154.5)	34	**0.78** (0.70, 0.86)
BMI (kg/m^2): Optimum Range	74	
Underweight	17	**1.03** (0.88, 1.20)
Overweight	40	**0.84** (0.75, 0.94)
Obesity	36	**0.77** (0.69, 0.86)



Phase 3 Dose Selection



Bader et al., AAC 2018

Rate of AEs and SAEs were Similar Between Rezafungin and Caspofungin Cohorts

	Rezafungin 400 / 400 mg (N = 81)	Rezafungin 400 / 200 mg (N = 151)	Caspofungin 70 / 50 mg (N = 166)
Adverse Events	88%	91%	83%
Severe AE	35%	49%	51%
SAE	43%	55%	49%
AE leading to interruption of study drug	0	2%	2%
AE leading to discontinuation of study drug	7%	9%	9%
AE resulting in death	16%	23%	24%