CIDARA THERAPEUTICS

Rezafungin: Evidence and Experience to Date

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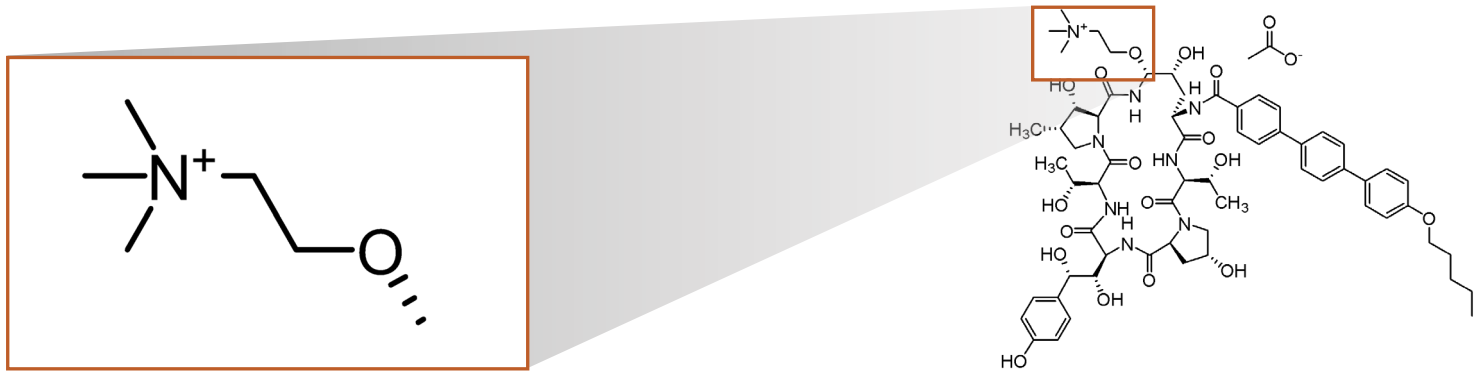
Rezafungin: A Novel Long-Acting Echinocandin



STRUCTURAL MODIFICATION ENHANCES STABILITY COMPARED WITH CURRENT ECHINOCANDINS[1], YIELDING IMPROVED CHEMICAL & BIOLOGICAL PROPERTIES FOR ONCE-WEEKLY DOSING

Design Features	Potential Benefit
Long-acting PK[2]	Once weekly dosing as in ongoing clinical trials[2]
Designed for high exposures[3,4]	Potential for improved efficacy
Observed absence of toxic degradation products[5]	Potential for improved safety
No DDIs[6] and favorable hepatic & renal safety[2,5]	Compatible with other medications

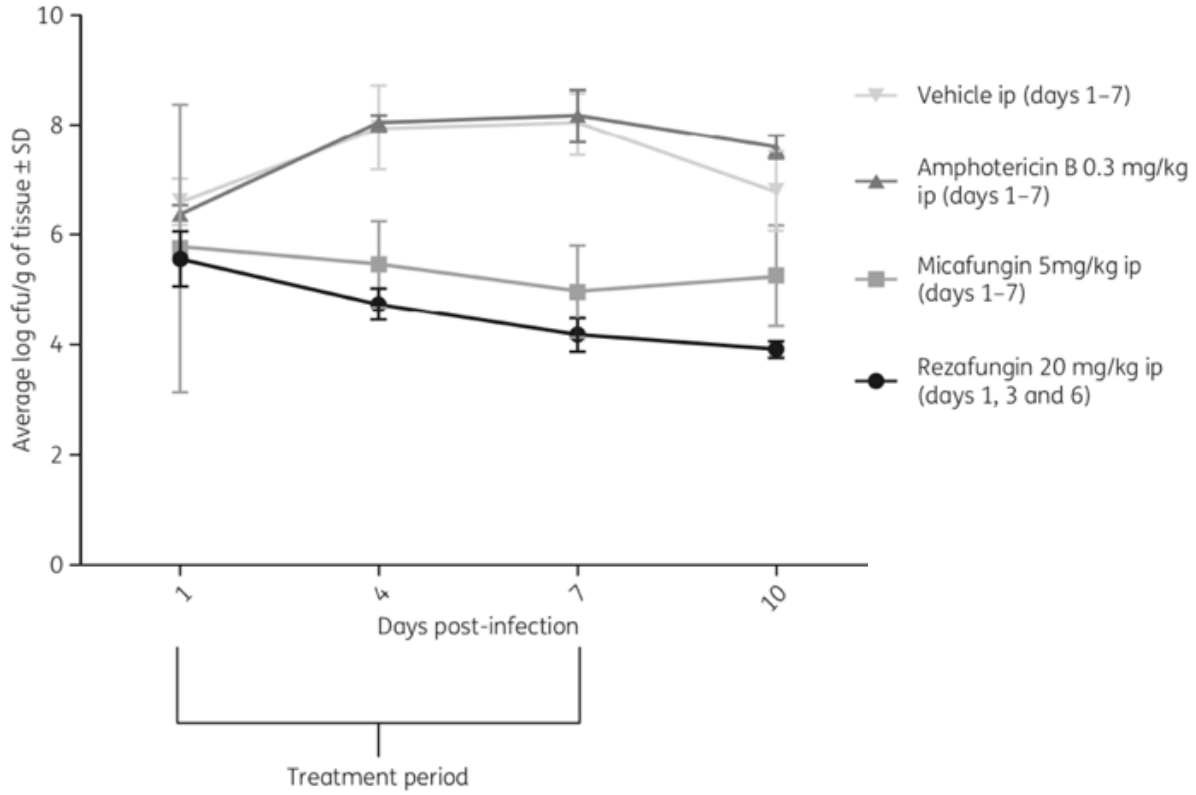
Enhanced stability allows for once-weekly dosing

1. Krishnan et al. J Antibiot (Tokyo). 2017;70:130-135; 2. STRIVE Ph2 Trial. Thompson et al. CID Sept 2020; 3. Lakota et al. AAC November 2017; 4. Zhao et al. AAC October 2017; 5. Ong et al. AAC November 2016; 6. Ong et al. EBMT March 2019.

Rezafungin: *In Vivo* Efficacy

Rezafungin Treatment in a *Candida auris* Mouse Model

KIDNEY TISSUE FUNGAL BURDEN ON DAYS 1, 4, 7, AND 10



Rezafungin-treated mice showed significantly lower *C. auris* fungal burden

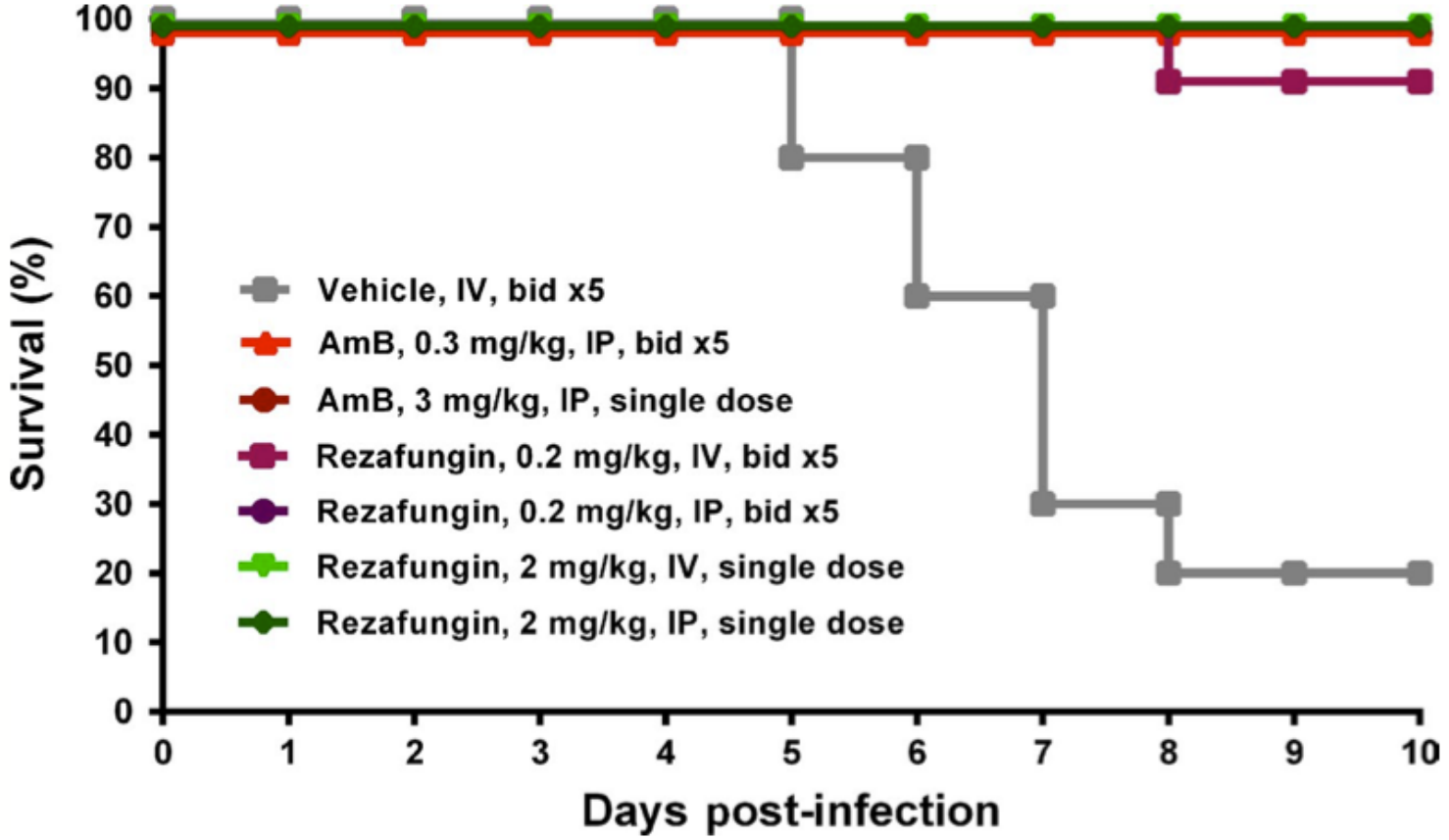
- vs amphotericin B, all days ($p<0.0001$)[a]
- vs micafungin, day 10 ($p=0.0128$)

Rezafungin significantly lowered *C. auris* burden in immunosuppressed mice

[a]p=0.023 on day 1 post-infection

Hager et al. J Antimicrob Chemother. 2018;73:2085-2088.

Rezafungin Treatment in an Invasive *Aspergillosis* Mouse Model

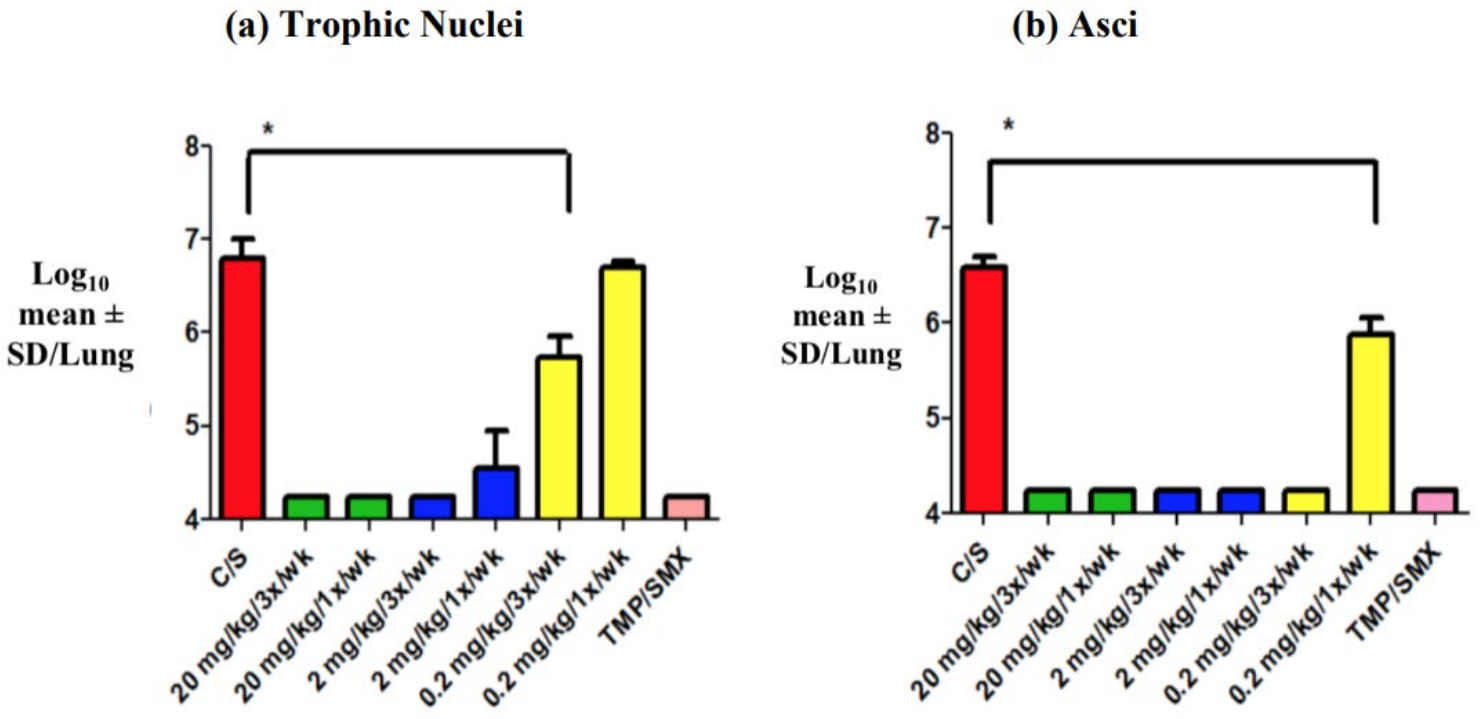


100% survival following single 2 mg/kg rezafungin dose (human equivalent=20 mg/kg), comparable to amphotericin B treatment

Miesel et al. Pharmacol Res Perspect. 2019;00:e00546.

Rezafungin Prophylaxis *In Vivo* Against *Pneumocystis*

KIDNEY BURDEN 6 WEEKS AFTER INOCULATION



Prophylaxis administered simultaneously with fungal inoculation.
*P<0.05 vs control.[1]

***In Pneumocystis* model, rezafungin significantly reduced trophic nuclei and asci counts at all tested doses.**

Comparable antifungal prophylaxis vs. TMP-SMX (gold standard) at human equivalent doses

TMP/SMX, trimethoprim-sulfamethoxazole; wk, week

1. Miesel L, Cushion MT, Ashbaugh A, et al. Efficacy of Rezafungin in Prophylactic Mouse Models of Invasive Candidiasis, Aspergillosis, and Pneumocystis Pneumonia. Antimicrob Agents Chemother. 2020 Dec 14:AAC.01992-20. doi: 10.1128/AAC.01992-20.

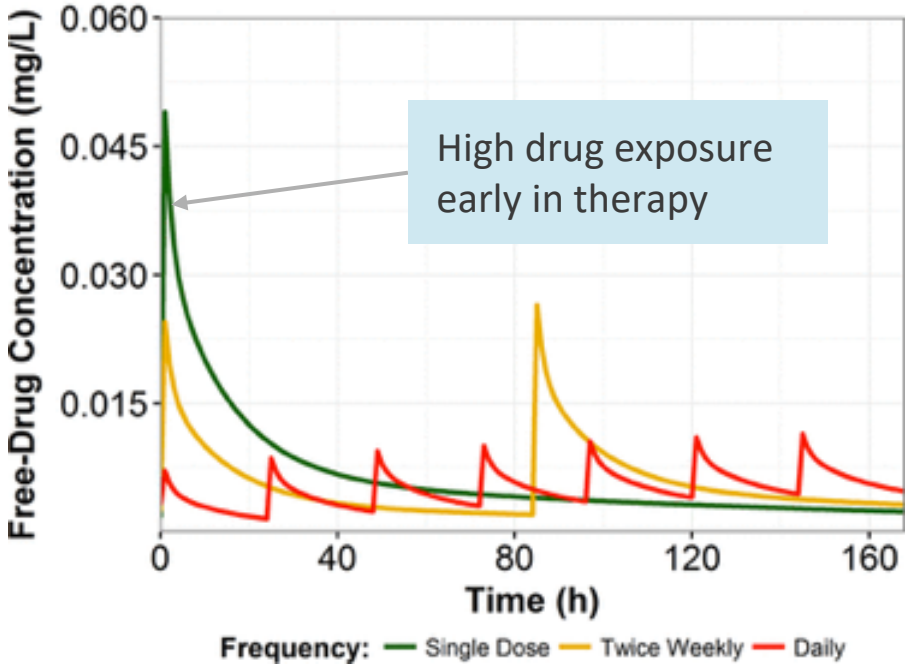
Rezafungin: PK/PD

PK, pharmacokinetic; PD, pharmacodynamic

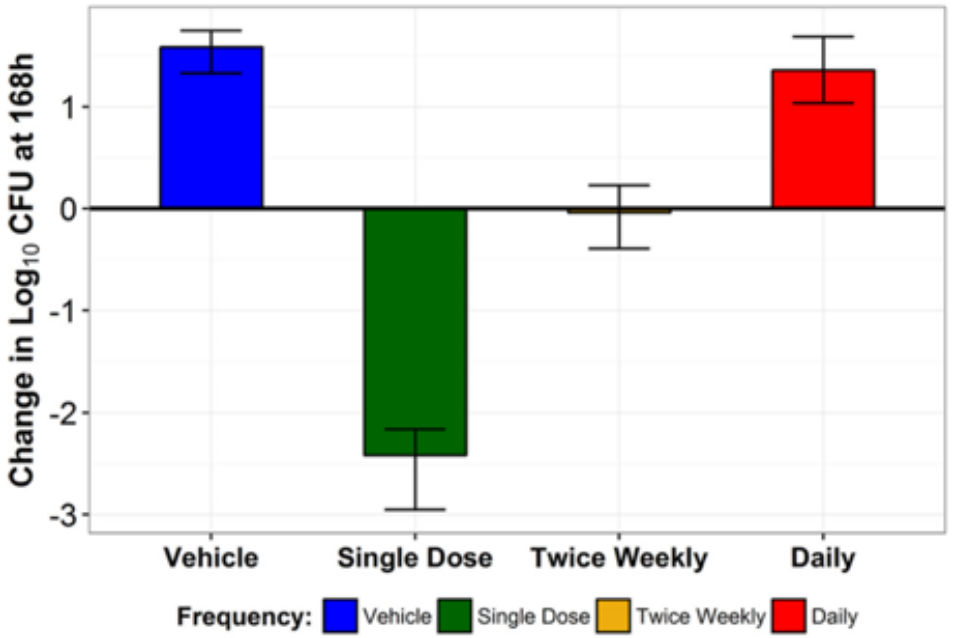
High Exposure for Sustained Fungicidal Activity

Exposure Shape Matters for Antifungal Efficacy

DOSE FRACTIONATION OF REZAFUNGIN 2 MG/KG IN NEUTROPENIC MICE (n=5/grp)



NEUTROPENIC MOUSE MODEL INFECTED WITH *Candida albicans* (isolate R303)



High drug exposure following once-weekly dosing resulted in greater fungal killing than divided doses

Lakota et al. Antimicrob Agents Chemother. 2017;61:e00758-17.

High Simulated Probabilities of PK-PD Target Attainment

Target Attainment Percent Probabilities Against C. albicans and C. glabrata at Steady State Based on Non-Clinical PK-PD Targets

MIC (µg/mL)	*C. albicans*[1,2]				MIC (µg/mL)	*C. glabrata*[1,2]			
	Anidulafungin	Caspofungin	Micafungin	Rezafungin		Anidulafungin	Caspofungin	Micafungin	Rezafungin
0.008	100[a,b]	100	99.4	100	**0.008**	100	100	100	100
0.015	99.1	100	71.2	100	**0.015**	100	100	100	100
0.03	52.7	100	10.1	100	**0.03**	99.2	100	97.5	100
0.06	0.90	97.9	0.1	100	**0.06**	54.3	100	49.9	100
0.12	0	76.7	0	100	**0.12**	0.95	100	3.40	100
0.25	0	35.7	0	100	**0.25**	0	100	0	100
0.5	0	12.1	0	100	**0.5**	0	97.0	0	100
1	0	4.4	0	76.5	**1**	0	73.2	0	100
2	0	1.35	0	1.00	**2**	0	33.9	0	100
4	0	0.25	0	0	**4**	0	11.3	0	100
8	0	0.05	0	0	**8**	0	4.35	0	100

Shading reflects relative probability of PK/PD target attainment in healthy people at Week 4

Rezafungin has high simulated probabilities of PK-PD target attainment against *C. albicans* and *C. glabrata*

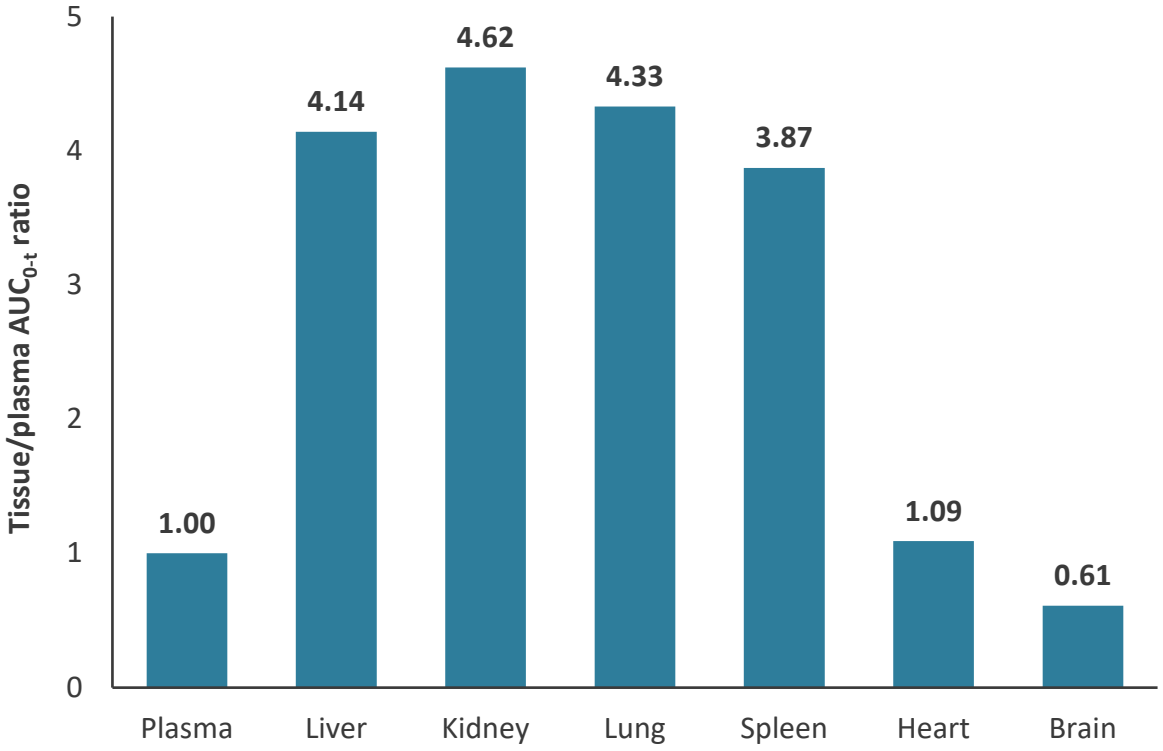
MIC, minimum inhibitory concentration; PK, pharmacokinetic; PD, pharmacodynamic

1. Bader et al. IDWeek 2017; poster 833; 2. Bader et al. Antimicrob Agents Chemother 62:e02614-17.

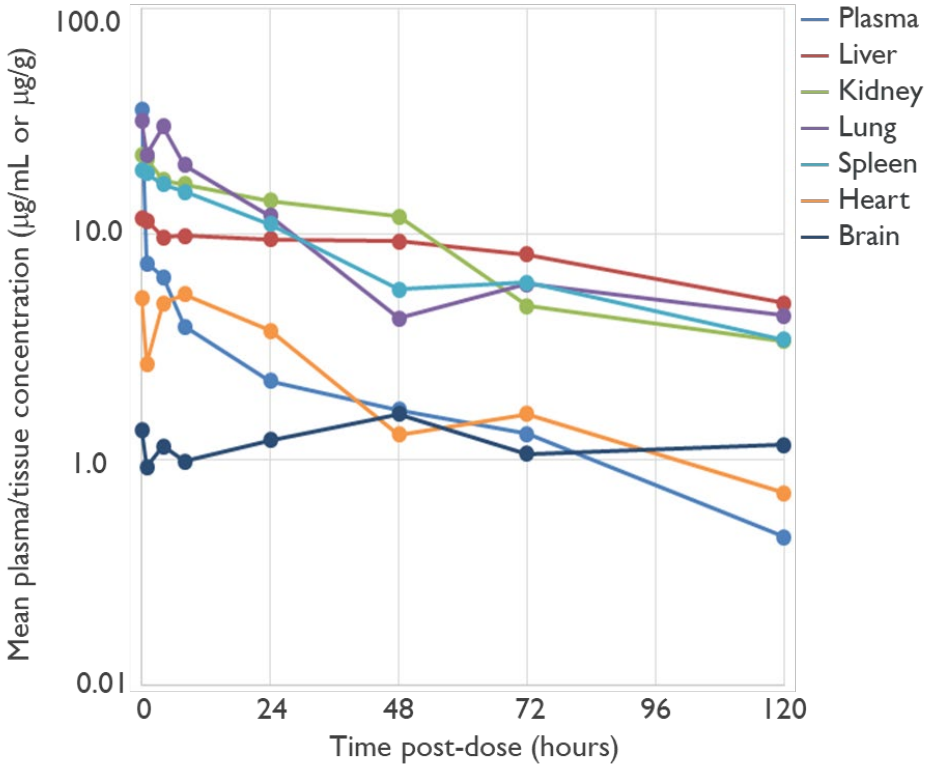
Significant and Sustained Tissue Distribution *In Vivo*

Rezafungin Tissue Distribution in Rat PK Models

RAT PK MODEL: UNIFORM TISSUE PENETRATION ACROSS LIVER, KIDNEY, LUNGS AND SPLEEN[1]



SIMILAR HALF-LIFE/ELIMINATION IN ORGANS[2]



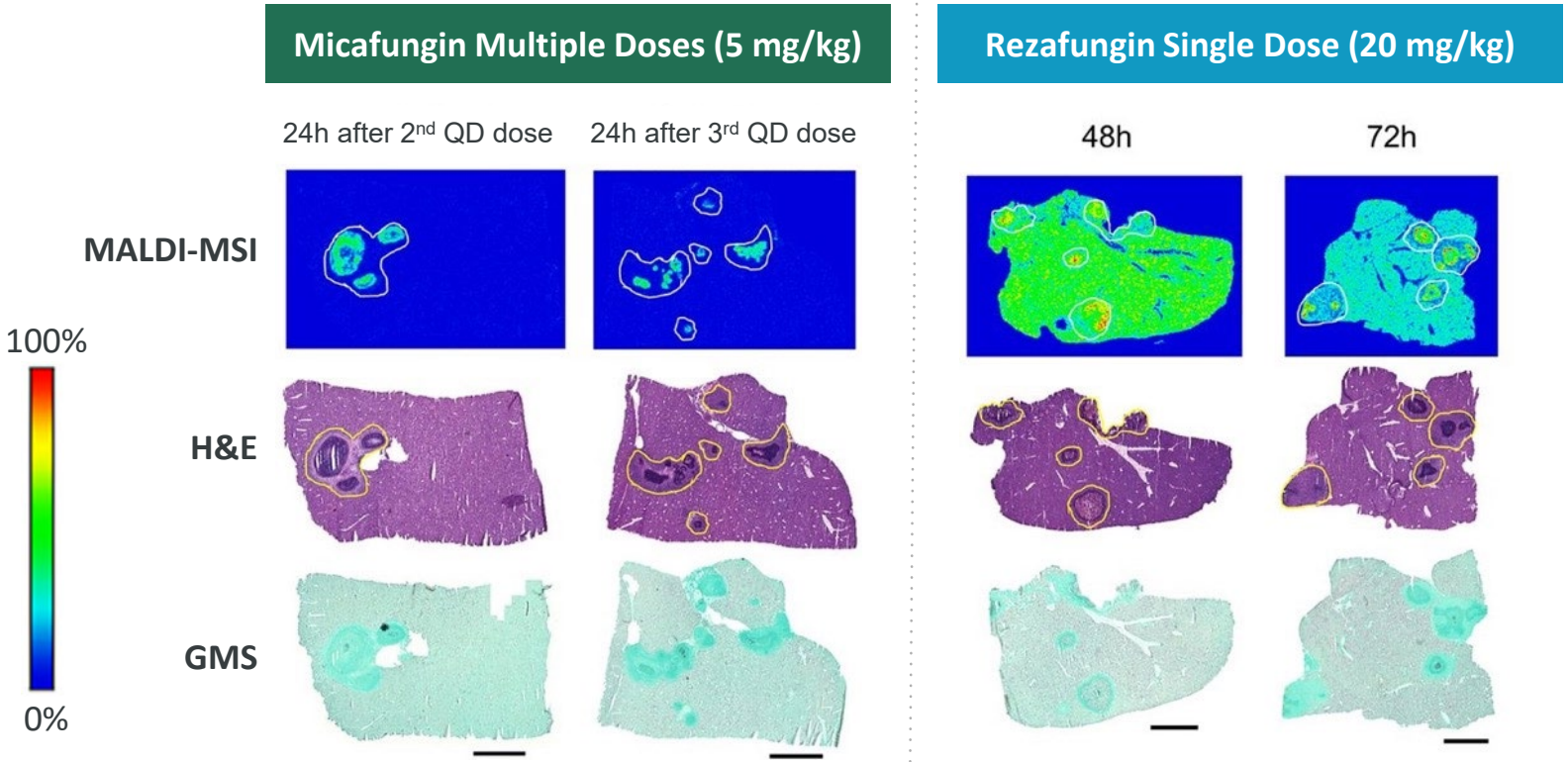
PK, pharmacokinetic

1. Ong et al. Antimicrob Agents Chemother. 2017;61:e01626-16; 2. Ong et al. Biol Blood Marrow Transplant. 2018;24:S291–S459

Deep Tissue Penetration With a Single Dose

Superior Penetration vs. Multiple Doses of Micafungin In Vivo

DRUG DISTRIBUTION IN LIVER[1]



Adapted from Zhao et al. 2017[1]

The signal intensity color bar is fixed for micafungin, with gradually increased intensity from blue (no signal) to red (max signal). Outlines highlight the lesion area on each tissue section.

Single dose rezafungin 20 mg/kg or 2-3 doses of micafungin 5 mg/kg on day 3 after *Candida albicans* infection.

MALDI-MS imaging to assess drug penetration at infection site .

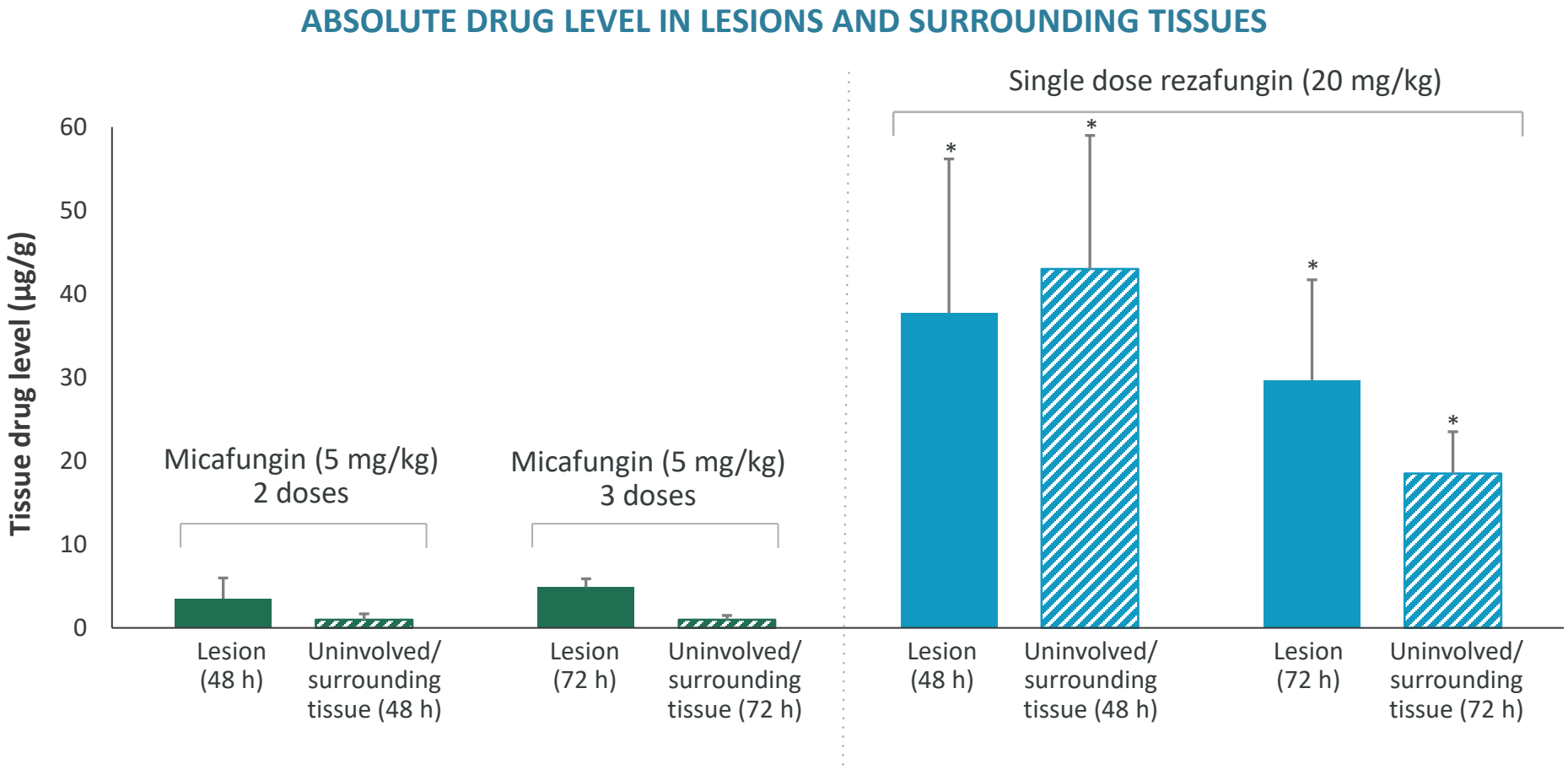
- **Multiple doses of micafungin did not reach tissue drug levels achieved with single dose rezafungin**
- **Rezafungin accumulated in necrotic areas of each lesion at 72 hours**

MALDI-MSI, matrix-assisted laser desorption ionization mass spectrometry imaging; H&E, haematoxylin and eosin; GMS, Gomori methenamine silver.

1. Zhao, et al. *Antimicrob Agents Chemother*. 2017;61(10).

Drug Accumulation at the Site of Infection

Superior Drug Accumulation vs. Multiple Doses of Micafungin In Vivo

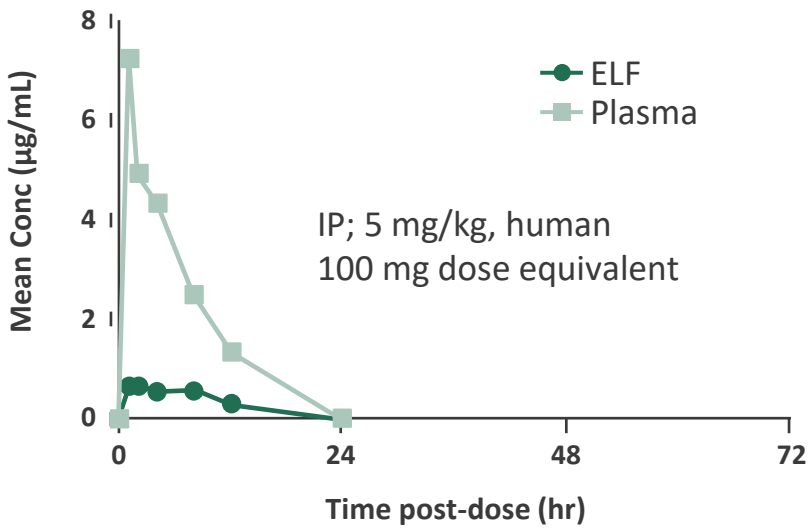


Superior tissue penetration and accumulation within liver fungal lesions vs. micafungin

*$p<0.001$
IC, invasive candidiasis ; h, hour; MALDI-MSI, matrix-assisted laser desorption ionization mass spectrometry imaging.
1. Zhao, et al. *Antimicrob Agents Chemother*. 2017;61(10).

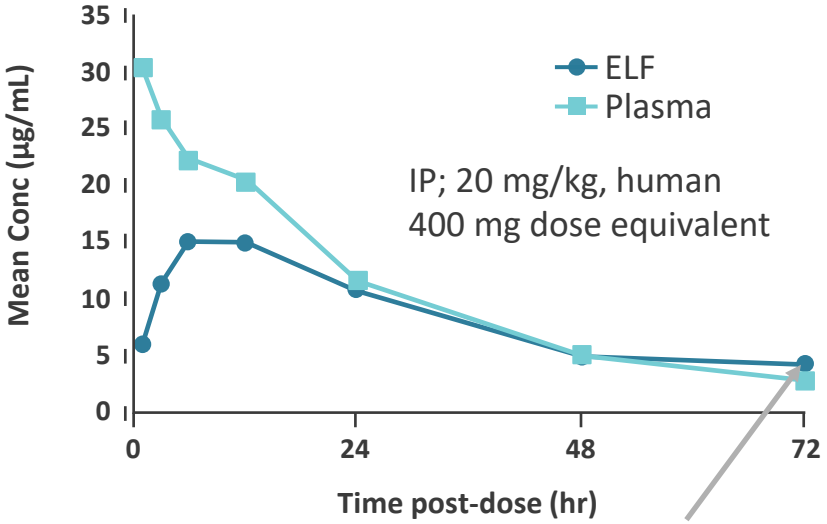
Rezafungin Distribution to Key Sites in Infection

MICAFUNGIN CONCENTRATIONS IN PLASMA AND EPITHELIAL LINING FLUID



Comparable levels in humans expected after 1 week due to rezafungin plasma half-life (133 hrs in human, 21 hrs in mouse).

REZAFUNGIN CONCENTRATIONS IN PLASMA AND EPITHELIAL LINING FLUID



Rezafungin concentrations >20-fold higher than MEC_{90} (0.015 µg/mL against *Aspergillus fumigatus* and *Aspergillus flavus* in plasma (3 µg/mL) and ELF (4 µg/mL) after 3 days.

Rezafungin demonstrated higher levels and longer duration in epithelial lining fluid vs. micafungin

IP, intraperitoneal; ELF, epithelial lining fluid; h, hour; MALDI-MSI, matrix-assisted laser desorption ionization mass spectrometry imaging.
Ong, et al. HTIDE, 2018; poster.

Rezafungin Demonstrated No Significant Drug-Drug Interactions in Phase 1

DRUG	POSSIBLE MECHANISM(S)	OBSERVATIONS	SUGGESTED ACTION
Tacrolimus	CYP3A4, P-gp	$\leftrightarrow C_{max}$ $\downarrow$AUC ~15%	No change in dose
Repaglinide	CYP2C8, OATP	$\leftrightarrow C_{max}$ $\uparrow$AUC ~15%	No change in dose
Metformin	OCT, MATEs	$\leftrightarrow C_{max}$ $\leftrightarrow$AUC	No change in dose
Rosuvastatin	BCRP, OATP	$\uparrow C_{max}$ ~12% $\uparrow$AUC ~15%	No change in dose
Pitavastatin	OATP	$\leftrightarrow C_{max}$ $\leftrightarrow$AUC	No change in dose
Caffeine	CYP1A2	$\leftrightarrow C_{max}$ $\leftrightarrow$AUC	No change in dose
Efavirenz	CYP2B6	$\leftrightarrow C_{max}$ $\leftrightarrow$AUC	No change in dose
Midazolam	CYP3A	$\leftrightarrow C_{max}$ $\leftrightarrow$AUC	No change in dose
Digoxin	CYP2B6	$\leftrightarrow C_{max}$ $\leftrightarrow$AUC	No change in dose

Single-center, open-label trial (N=26). Substrate drugs dosed alone for 3 weeks, then with rezafungin for 3 weeks.

No dose adjustments required when rezafungin is co-administered with these commonly used drugs.

C_{max}, maximum plasma concentration; AUC, area under the curve; CYP, cytochrome P450; OATP, organic anion transporting polypeptides; P-gp, P-glycoprotein; OCT, organic cation transporter; MATEs, multidrug and toxin extrusion protein; BCRP, breast cancer resistance protein

1. Ong et al. EBMT19 Poster B196. 2019.

Rezafungin: Phase 2 data

STRIVE

STRIVE Phase 2 Program: Candidemia & Invasive Candidiasis

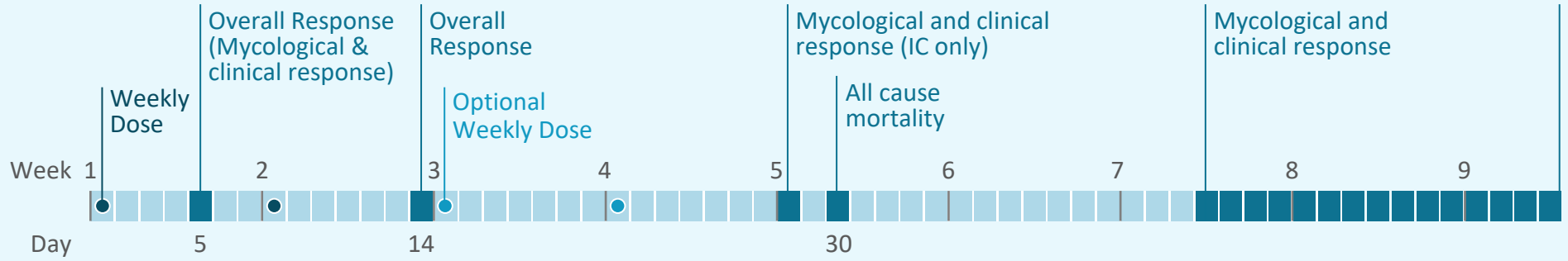
Trial Not Powered for Inferential Statistical Analysis

STRIVE

mITT N=183[1]

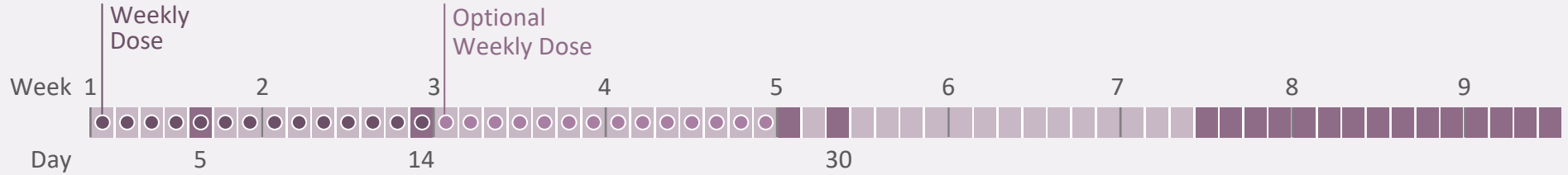
REZAFUNGIN
(N=122)

400/400 mg N=76
400/200 mg N=46



CASPOFUNGIN
(N=61)

70/50 mg



ANALYSIS POPULATIONS:

- Intent-to-treat (ITT) population: all randomized subjects
- Safety population: all subjects who received any amount of study drug
- Microbiological Intent-to-treat population (mITT): all subjects in safety population who had documented *Candida* infection

1. Thompson, et al. *Clin Infect Dis*. 2020, ciaa1380, https://doi.org/10.1093/cid/ciaa1380.

STRIVE Demographics and Baseline Characteristics

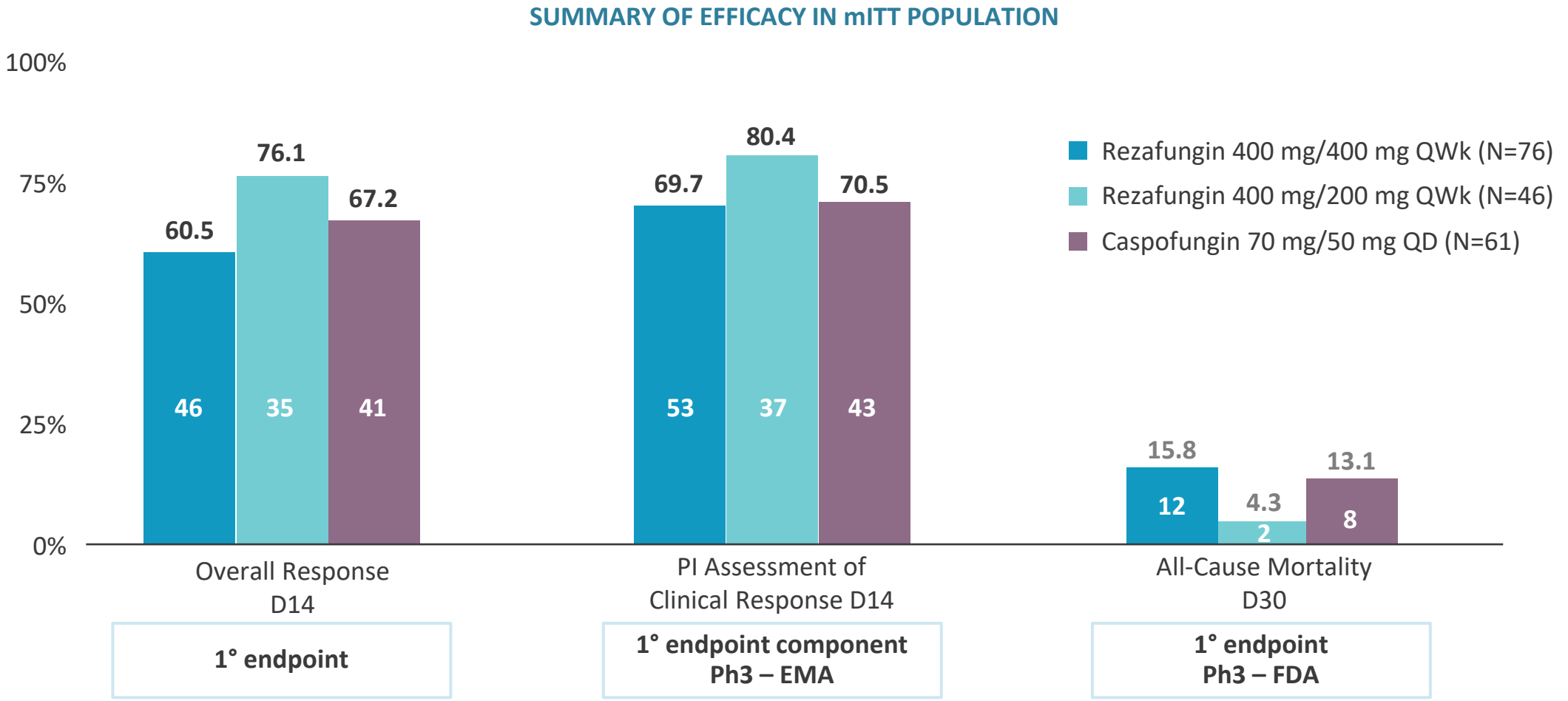
ITT Population

PARAMETER		Rezafungin 400 mg/400 mg QWk N= 81	Rezafungin 400 mg/200 mg QWk N= 57	Caspofungin 70 mg/50 mg QD N= 69
Age	Mean [Range]	60 y [24-88]	60 y [24-91]	59 y [24-93]
Diagnosis	Candidemia	76.5	80.7	81.2
	IC	23.5	19.3	18.8

[a]Numbers of subjects with scores not calculated/missing not shown.

- **~20% invasive candidiasis in overall population**
- **Treatment groups well balanced and matched**

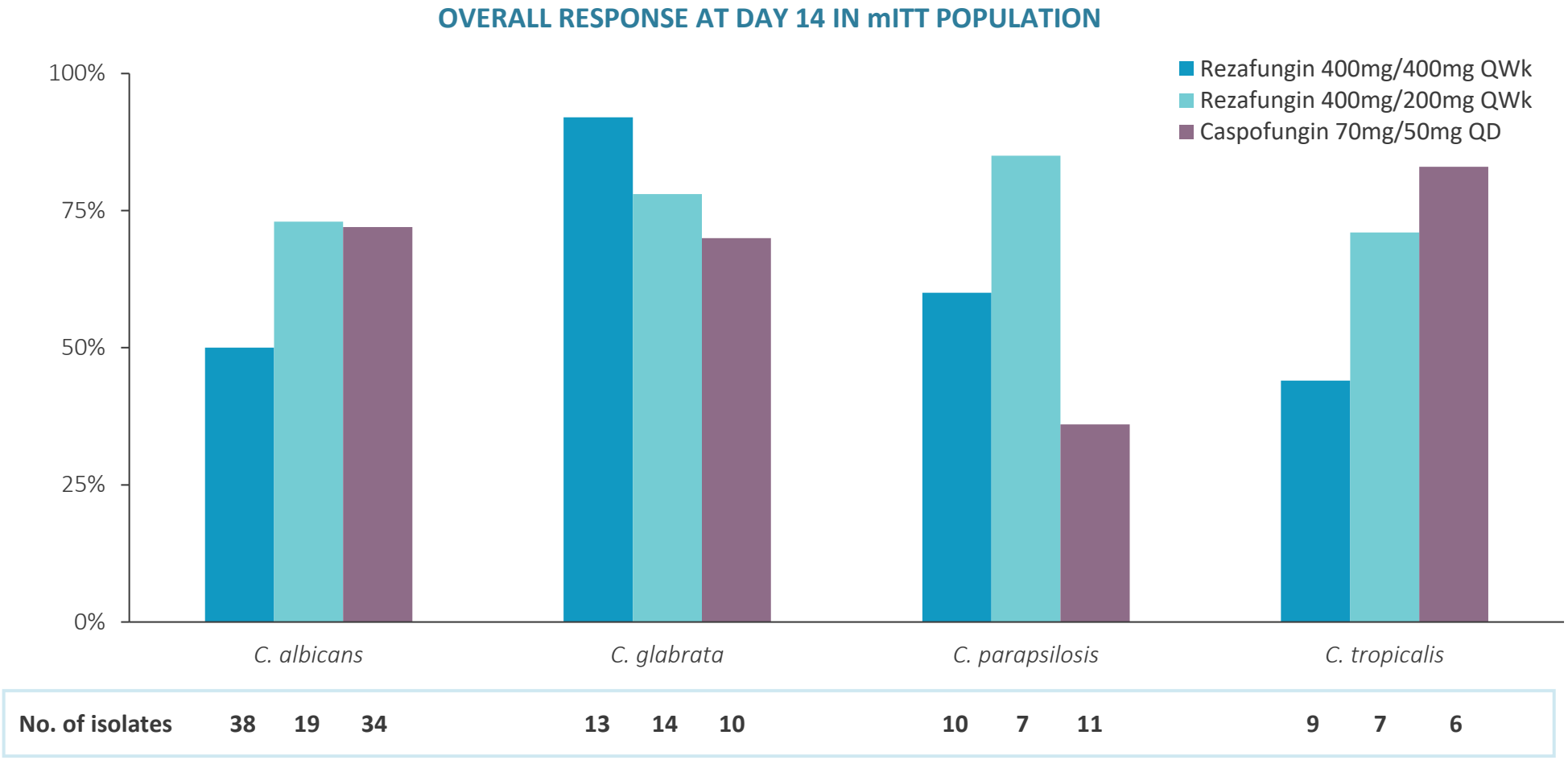
STRIVE Phase 2 Trial: Summary of Rezafungin Efficacy



Rezafungin demonstrated similar efficacy vs. caspofungin SOC

1. Thompson, et al. *Clin Infect Dis*. 2020, ciaa1380, https://doi.org/10.1093/cid/ciaa1380.

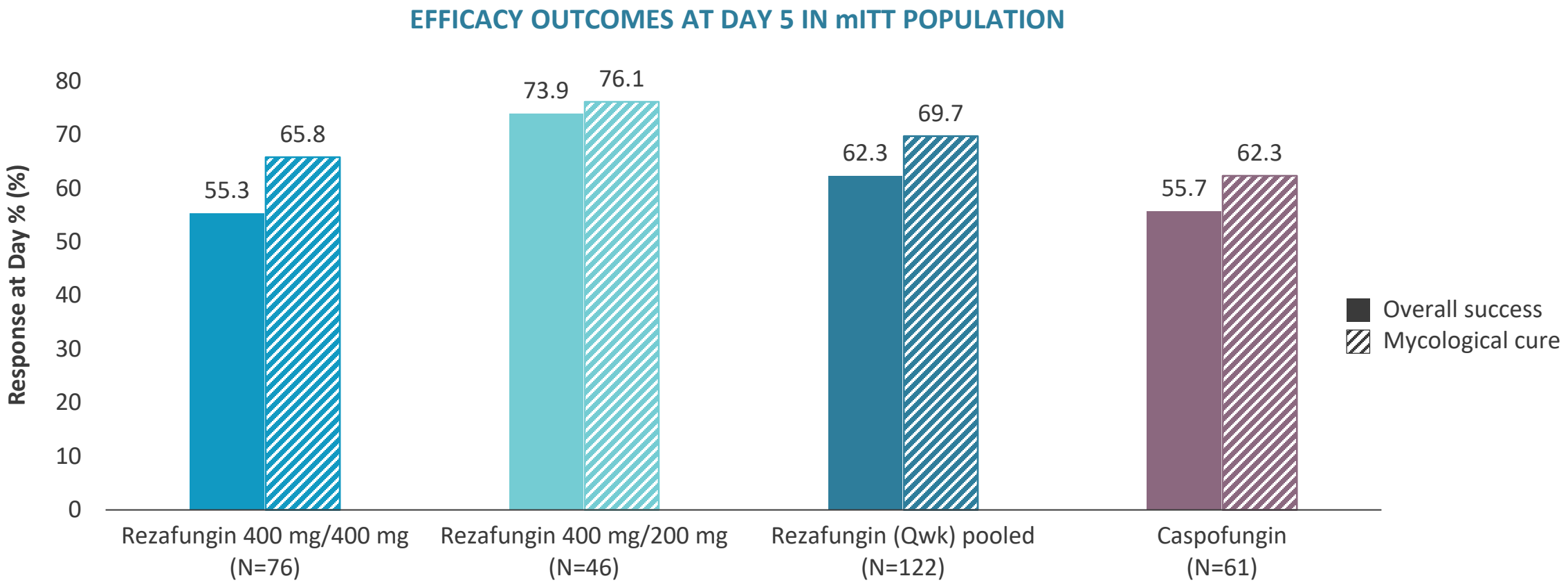
STRIVE Overall Response By *Candida* Species



Rezafungin efficacy compared with caspofungin SOC consistent in variety of *Candida* species

1. Thompson, et al. ID week 2020;poster 1284.

STRIVE Outcomes at Day 5



Day 5 outcomes reflect initial dose of 400 mg in both rezafungin-treated arms.

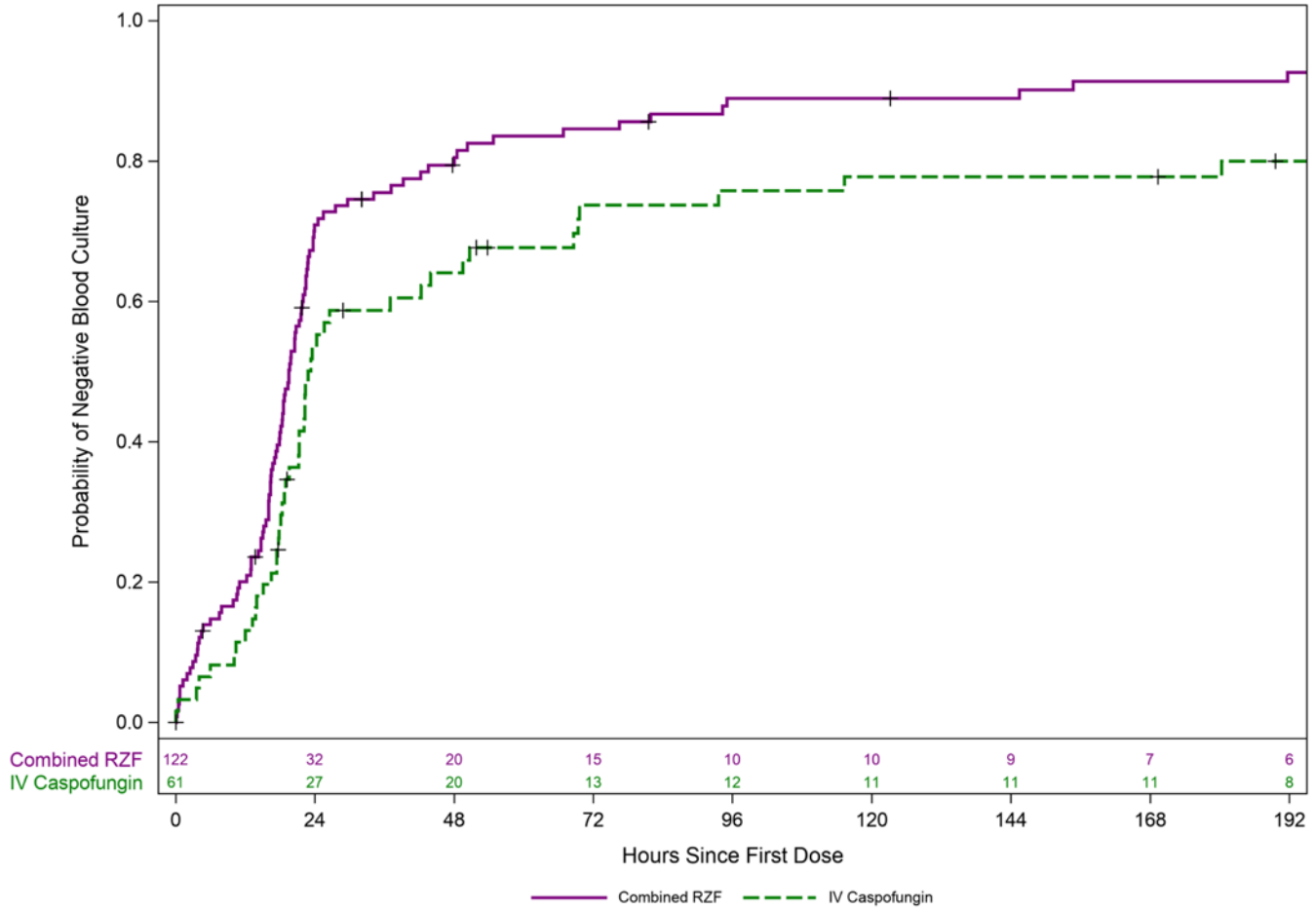
Rezafungin efficacy compared with caspofungin SOC evident in day 5 outcomes

mITT, microbiological intention-to-treat.

1. Thompson, et al. *Clin Infect Dis*. 2020, ciaa1380, https://doi.org/10.1093/cid/ciaa1380.

Rezafungin Showed Superiority on Time to Negative Blood Culture Over Caspofungin

TIME TO NEGATIVE BLOOD CULTURE (mITT POPULATION)



Maximum difference in probability of negative blood culture ~24 hours after first dose

Post-hoc log-rank test p = 0.02

mITT, microbiological intention-to-treat.

1. Thompson, et al. *Clin Infect Dis*. 2020, ciaa1380, https://doi.org/10.1093/cid/ciaa1380.

STRIVE Summary of Adverse Events

Safety Population

Adverse Event	Rezafungin 400 mg/400 mg QWk N=81	Rezafungin 400 mg Wk1/200 mg QWk N=53	All Rezafungin (Pooled) N=134	Caspofungin 70 mg/50 mg QD N=68
	n (%)			
≥1 TEAE	71 (87.7)	49 (92.5)	120 (89.6)	55 (80.9)
Severe	29 (35.8)	17 (32.1)	46 (34.3)	26 (38.2)
Study drug–related	7 (8.6)	6 (11.3)	13 (9.7)	9 (13.2)
Serious AE	35 (43.2)	28 (52.8)	63 (47.0)	29 (42.6)
Study drug–related	1 (1.2)	1 (1.9)	2 (1.5)	2 (2.9)

TEAE (treatment-emergent adverse event)=AE that occurs after first dose of study drug is administered.

1. Thompson et al. Clin Infect Dis 2020, ciaa1380, https://doi.org/10.1093/cid/ciaa1380.

STRIVE Treatment-Emergent Adverse Events (≥10%)

Safety Population

TEAE, Preferred Term	Rezafungin 400 mg/400 mg QWk N=81	Rezafungin 400 mg Wk1/200 mg QWk N=53	All Rezafungin (Pooled) N=134	Caspofungin 70 mg/50 mg QD N=68
	n (%)			
Hypokalemia	13 (16.0)	9 (17.0)	22 (16.4)	9 (13.2)
Diarrhea	7 (8.6)	11 (20.8)	18 (13.4)	10 (14.7)
Vomiting	6 (7.4)	8 (15.1)	14 (10.4)	5 (7.4)
Pyrexia	9 (11.1)	4 (7.5)	13 (9.7)	6 (8.8)
Anemia	6 (7.4)	7 (13.2)	13 (9.7)	4 (5.9)
Nausea	4 (4.9)	8 (15.1)	12 (9.0)	6 (8.8)
Abdominal Pain	5 (6.2)	6 (11.3)	11 (8.2)	5 (7.4)
Septic Shock	9 (11.1)	1 (1.9)	10 (7.5)	3 (4.4)

No concerning trends with rezafungin safety

TEAE, treatment-emergent adverse event.

1. Thompson et al. Clin Infect Dis 2020, ciaa1380, https://doi.org/10.1093/cid/ciaa1380.

Rezafungin Overall Phase 3 Development Plan

	PHASE 3 TREATMENT TRIAL	PHASE 3 PROPHYLAXIS TRIAL
	ReSTORE	ReSPECT
Potential Indication	Treatment of candidemia & invasive candidiasis	Prophylaxis against *Aspergillus*, *Candida* & *Pneumocystis* in allogeneic blood and marrow transplant patients
Trial Size	218 patients[1] (20% NI margin)	462 patients[2] (12.5% NI margin)
Overall Objective	Improve outcomes, allow early hospital discharge and enable transition to outpatient use Expect topline data by end of 2021	Transform post-blood & marrow transplant standard of care Trial Ongoing

1. clinicaltrials.gov NCT03667690 accessed 5 Feb 2021. 2. clinicaltrials.gov NCT04368559 accessed 5 Feb 2021.

Rezafungin: Phase 3 Treatment Trial

Study design:[1]

A Phase 3, international, prospective, multicenter, randomized, double-blind study

Study aims:[1]

Evaluate the efficacy and safety of once weekly IV rezafungin vs. caspofungin followed by optional oral fluconazole step-down in the treatment of candidemia and/or IC

Primary efficacy endpoint:[1]

- US FDA: demonstrate noninferiority in subjects randomized to rezafungin for injection compared to subjects randomized to caspofungin for ACM at Day 30 (±2 days) in the mITT population
- EMA: demonstrate noninferiority in subjects randomized to rezafungin for injection compared to subjects randomized to caspofungin for global cure and mycological eradication at Day 14 (±1 day) in the mITT population

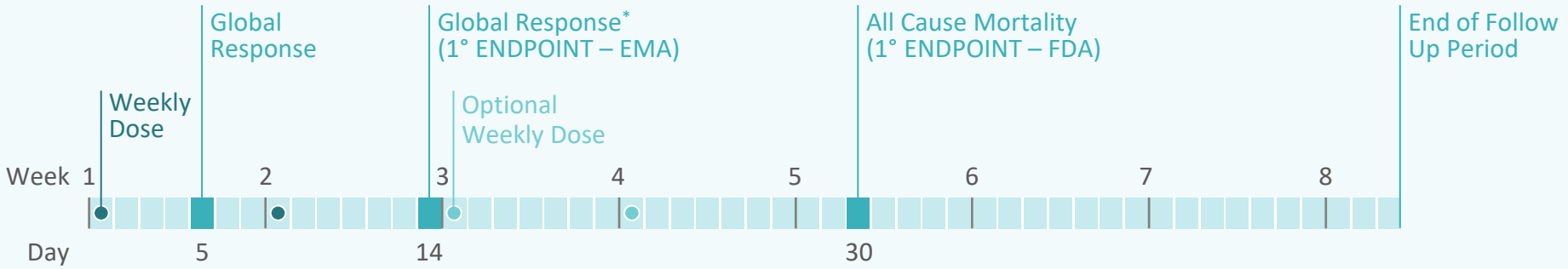
IV, intravenous; ACM, all-cause mortality; IC, invasive candidiasis; US FDA, United States Food and Drug Administration; EMA, European Medicines Agency; mITT, microbiological intent to treat

1. clinicaltrials.gov NCT 03667690 accessed 5 Feb 2021.

ReSTORE Phase 3 Trial Design Mirrors Strive Phase 2 Trial

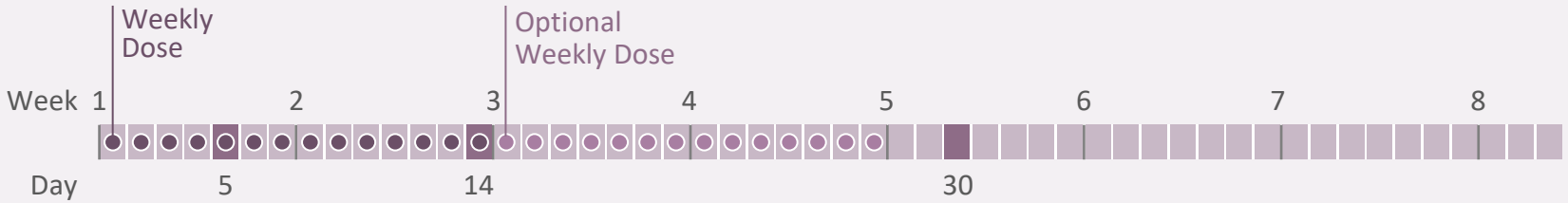
REZAFUNGIN
(N=92)

400/200 mg



CASPOFUNGIN†
(N=92)

70/50 mg

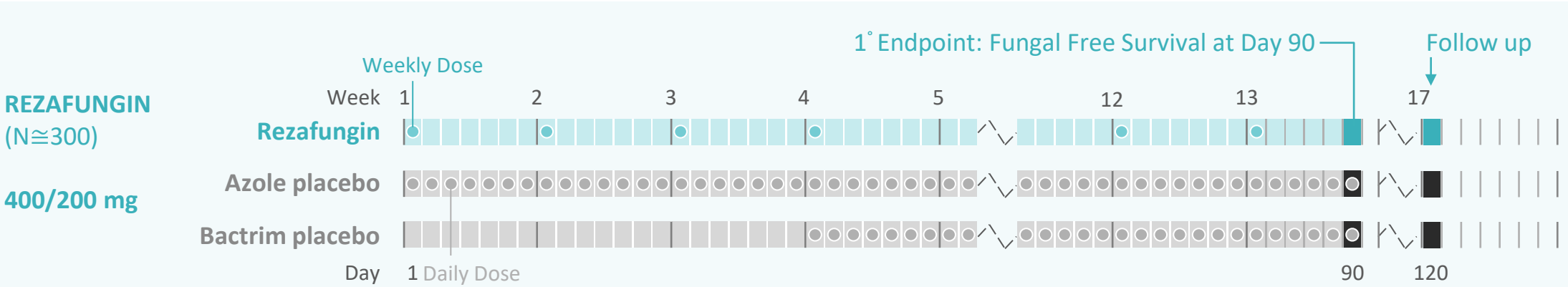


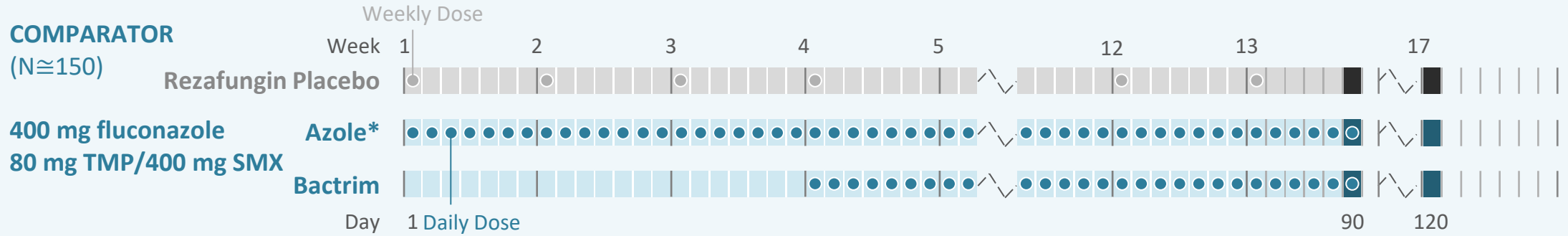
*Global Response=Clinical Response (as assessed by the Primary Investigator), Mycological Response and Radiological Response (for qualifying invasive candidiasis patients only).
†Caspofungin followed by optional oral fluconazole step-down therapy.

Clinicaltrials.gov NCT 03667690 accessed 5 Feb 2021.

Rezafungin: Phase 3 Prophylaxis Trial

ReSPECT Phase 3 Prophylaxis Trial Design





*Fluconazole to start in all patients. 300 mg posaconazole optional in patients who develop GVHD per label.
Clinicaltrials.gov NCT04368559 accessed 4 Feb 2021.

Rezafungin for Treatment and Prophylaxis

Unique Properties of a Next-Generation Echinocandin

- **Potent and Broad-Spectrum activity against *Candida*, *Aspergillus*, and *Pneumocystis***
  includes *C. auris,* subset of azole- and echinocandin-resistant isolates,[1-5] *Aspergillus* activity includes azole-resistant species
- **Enhanced PK**
  extended half-life (~130 hours), once-weekly front-loaded dosing, and greater tissue penetration compared with MCF[6-10]
  - Front-loaded dosing may improve early outcomes, TTNBC, and day 5 outcomes compared with caspofungin[11]
- **Safety and DDI profile of the echinocandin class**
  spares myelosuppression, TDM, hepatic & renal toxicity, non-compliance, and complications of managing/avoiding DDIs[12]
- **Dosing & Administration**
  inpatient and outpatient use dosed once-weekly, earlier hospital discharge, multiple formulations

Phase 3 Development of rezafungin 400 mg/200 mg QWk dose

- Treatment of candidemia and IC up to 4 weeks
- Prophylaxis of *Candida*, *Aspergillus*, and *Pneumocystis* in alloBMT setting, with and without GVH - 90 days

alloBMT, allogeneic blood and marrow transplant; DDI, drug-drug interaction; GVH, graft versus host; IC, invasive candidiasis; MCF, micafungin; PK, pharmacokinetics; QWk, once weekly; TDM, therapeutic drug monitoring; TTNBC, time to negative blood culture.

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Rezafungin Poster Presentations at ICHS 2021

- Efficacy and Safety By Renal Function in the Phase 2 STRIVE Trial of Rezafungin in Treatment of Candidemia and Invasive Candidiasis
- Safety and Efficacy of Rezafungin in Immunocompromised Patients: Analysis of Outcomes from the Phase 2 STRIVE Trial of Rezafungin for Treatment of Candidemia and Invasive Candidiasis
- Fungal Eradication With Extended Rezafungin Treatment In a Murine Model Of *Pneumocystis* Pneumonia