REZAFUNGIN FOR INJECTION
FOR TREATMENT OF CANDIDEMIA AND INVASIVE CANDIDIASIS

SPONSOR BRIEFING DOCUMENT

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE

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TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACM	all-cause mortality
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APACHE II	Acute Physiology and Chronic Health Evaluation II
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BMI	body mass index
BSA	body surface area
CDC	Centers for Disease Control and Prevention
CDE	Center for Drug Evaluation
CFU	colony-forming units
CI	confidence interval
CLSI	Clinical and Laboratory Standards Institute
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury
DRC	Data Review Committee
ECG	electrocardiogram
ELF	epithelial lining fluid
EMA	European Medical Agency
EOP2	End of Phase 2
EOT	End of Treatment
EU	European Union
FDA	Food and Drug Administration
FKS	wild-type gene encoding the 1,3-β-D-glucan synthase catalytic subunit

fks	gene encoding a mutant 1,3-β-D-glucan synthase catalytic subunit
Fks	1,3-β-D-glucan synthase catalytic subunit encoded by *FKS* genes
ICU	intensive care unit
IC_{50}	half-maximal inhibitory concentration
IP	Intraperitoneal injection
IRB	institutional review board
ITT	Intent-to-Treat
IV	intravenous
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LE	Long-Evans
LFTs	liver function tests
LLOQ	lower limit of quantification
LSC	liquid-scintillation counting
MAD	multiple-ascending dose
MALDI-MSI	matrix-assisted laser desorption ionization mass spectrometry imaging
MDR	multidrug-resistant
MEC	minimum effective concentration
$MEC_{50/90}$	minimum effective concentration to inhibit 50% and 90% of isolates tested, respectively
MIC	minimum inhibitory concentration
$MIC_{50/90/100}$	minimum inhibitory concentration to inhibit 50%, 90%, and 100% of isolates tested, respectively
mITT	microbiological or modified Intent-to-Treat
NDA	New Drug Application
NOAEL	no-observed-adverse-effect level
NI	noninferiority
OLT	orthotopic liver transplant
PAFE	post-antifungal effect
PD	pharmacodynamic(s)
PICC	peripherally inserted central catheter
PK	pharmacokinetic(s)
pre-NDA	pre-New Drug Application [meeting]
PT	preferred term
QIDP	qualified infectious disease product
QT	QT interval on ECG study

QWBA	quantitative whole-body autoradiography
SAD	single-ascending dose
SAE	serious adverse event
SOC	system organ class
spp.	species
$t_{½}$	terminal half-life
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States

1 EXECUTIVE SUMMARY

1.1 Introduction

Cidara Therapeutics, Inc. (Cidara), is seeking approval of rezafungin for injection (hereafter referred to as rezafungin) for the treatment of candidemia and invasive candidiasis in adult patients. Rezafungin is an addition to the well-established echinocandin class of antifungals, which are commonly used for first-line treatment of fungal infections.

The active ingredient of rezafungin, rezafungin acetate, is derived from anidulafungin, an echinocandin approved by the Food and Drug Administration (FDA). A structural modification confers improved molecular stability and pharmacokinetics (PK). Rezafungin's enhanced molecular stability, high front-loaded exposure, and improved distribution and longer half-life, allowing for once-weekly dosing, have the potential to fill current treatment gaps.

As demonstrated through the Phase 2 and Phase 3 clinical studies, rezafungin provides patients with candidemia and invasive candidiasis a new echinocandin antifungal treatment with comparable efficacy and safety to commonly used echinocandins, while addressing important unmet needs and key limitations of existing echinocandins.

1.2 Background and Unmet Need

Candidemia and invasive candidiasis are rare, serious, and life-threatening infections. According to the Centers for Disease Control and Prevention (CDC), the average rate of new infections is approximately 9 per 100,000 people, and there are approximately 25,000 cases per year (CDC 2021).

These infections occur in patients who are already sick with other diseases and are associated with high morbidity and mortality. Patients who are at risk of invasive fungal infections include the critically ill, immunosuppressed, post-surgical, and those with central venous catheters. Invasive infection with *Candida* in this already vulnerable patient population often results in severe illness and death.

In a recent analysis of a large United States (US) patient database, *Candida* infections accounted for 40% of all invasive fungal infections (Menzin 2009). Patients with these invasive infections can suffer from a range of comorbidities on top of their underlying condition, including fever and septic shock. Candidemia and invasive candidiasis are associated with a long length of hospital stay, with an estimated additional 3 to 13 days of hospitalization after diagnosis. Additionally, the mortality rate in patients with these infections is greater than 40% (Wisplinghoff 2004, Falagas 2006, Pfaller 2007, Labelle 2008, Pfaller 2010, Slavin 2010, Andes 2012, Mikulska 2012, Mylonakis 2015).

Echinocandins are recommended as first-line antifungal agents by practice guidelines for the treatment of candidemia and invasive candidiasis due to their well-established efficacy and safety profile and strong fungicidal activity (Pappas 2016). Currently

approved echinocandins include caspofungin, micafungin, and anidulafungin. Azoles are also used as antifungal treatment, but are known to have significant toxicity, including hepatotoxicity and severe skin reactions, as well as interactions with other drugs commonly used in patients with invasive *Candida* infections.

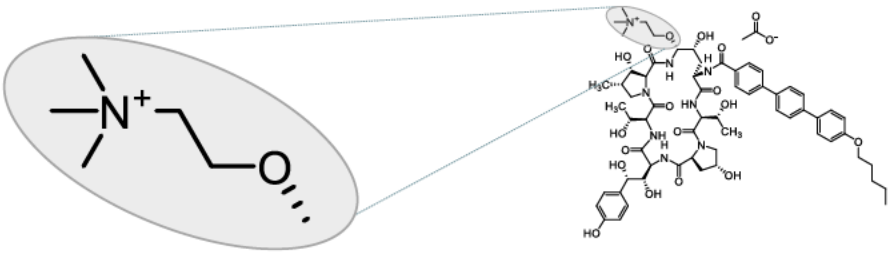
Gaps in treatment continue to exist, particularly for patients with the highest unmet need, such as the critically ill and elderly (Hall 2013, Sinnollareddy 2015, Lempers 2016, van der Elst 2017, Maseda 2018, Mainas 2020). There are specific concerns with current echinocandins about underdosing, the ability to reach deep tissue infections, toxicity, and resistance. Additionally, the shifting predominance of invasive *Candida* infections to non-*albicans* species and increasing resistance to existing treatments is becoming problematic, especially for *C. glabrata* and *C. auris*. The CDC has labeled these emerging pathogens as serious global health threats and predicts more outbreaks in the coming years. Improved and additional antifungals are needed to treat these life-threatening infections that have rising rates of resistance to azoles and the marketed echinocandins.

No new antifungal agents have been approved for treatment of candidemia and invasive candidiasis since anidulafungin in 2007. So, while *Candida* pathogens have continued to evolve and to withstand antifungal therapy as detailed above, the physician's arsenal of antifungal agents has not changed for over 15 years. There is an urgent need for new effective antifungals with a well-understood safety and PK profile to treat these serious and often fatal infections.

1.3 Rezafungin Overview

Rezafungin was discovered in an effort to develop an orally administered echinocandin. The structural modifications, primarily the addition of the choline moiety on the cyclic hexapeptide ring, yielded improved molecular stability and biological properties (Figure 1).

Figure 1: Rezafungin Structure



Improved stability, in terms of both reduced metabolism and degradation relative to other echinocandins, resulted in a long half-life which allows for once-weekly intravenous (IV) dosing. The dosing schedule generates a front-loaded exposure allowing rezafungin's potential therapeutic benefits to be maximized. These benefits include improved cidality, and greater tissue distribution as assessed relative to micafungin.

As an echinocandin, rezafungin has a similar broad spectrum of activity as other echinocandins that inhibit 1,3-β-D-glucan synthetase, an essential component of fungal cell wall synthesis, further described in Section 3.

1.4 Rezafungin Development Program

The clinical development of rezafungin has considered guidance from the FDA and the European Medical Agency (EMA), as well as scientific advice from national authorities in the European Union (EU) and in consultation with China's Center for Drug Evaluation (CDE).

The FDA has designated rezafungin as a qualified infectious disease product (QIDP). This designation was created to spur the development of drugs for serious or life-threatening infections. Rezafungin also has fast track and orphan drug status. Based on orphan designation for candidemia and invasive candidiasis, rezafungin qualifies for, and Cidara requested, a waiver for pediatric studies.

Beginning with a Pre-IND meeting in 2015, Cidara met with the FDA more than 15 times to discuss rezafungin development. Rezafungin was developed under FDA's 2017 streamlined development guidance titled *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases.* Under the recent May 2022 updated guidance, *Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers*, the pathway is now called flexible clinical development. As per FDA guidance, the safety database should include at least 300 subjects exposed to the commercial dose or higher.

At an End of Phase 2 (EOP2) meeting in July 2018, agreement was reached on the Phase 3 study design for ReSTORE which, together with STRIVE as a supporting Phase 2 study, would form the basis for the New Drug Application (NDA) for treatment of candidemia and invasive candidiasis. A 20% noninferiority (NI) margin for an endpoint of 30-day all-cause mortality (ACM) and the associated sample size, was deemed adequate for a limited use indication for treatment of candidemia and invasive candidiasis. The primary endpoint of ACM at Day 30 is a first for an echinocandin development program and was supported by a key secondary endpoint of global response at Day 14. The global cure secondary endpoint is similar to the primary endpoint for previous pivotal trials for the approved echinocandins (Kuse 2007; Reboli 2007). However, in previous trials, the time of assessment occurred at end of IV therapy or at the end of all study treatment, rather than fixed at Day 14 as in the ReSTORE study.

In a Pre-NDA interaction earlier this year, the FDA agreed it was reasonable to proceed with an NDA, based on STRIVE and ReSTORE, for a treatment indication.

The efficacy and safety data supporting the rezafungin NDA come primarily from 2 similarly designed global double-blind randomized controlled clinical studies:

- STRIVE, a Phase 2 study, and
- ReSTORE, a Phase 3 study.

Both studies were conducted in patients with confirmed candidemia or invasive candidiasis and compared rezafungin to caspofungin, an established echinocandin (Thompson 2021; Thompson 2022). ReSTORE and STRIVE are adequate and well-controlled investigations that provide substantial evidence of effectiveness. The similarity in study designs allowed for the pooling of efficacy and safety data in the NDA, as agreed with the FDA in Sept 2021.

ReSPECT, a single multinational pivotal Phase 3 study for the prevention of invasive fungal disease in adults undergoing allogeneic blood and marrow transplant, is currently ongoing. Target enrollment is 462, and the study is approximately 45% enrolled.

ReSTORE-China is ongoing with target enrollment of 56 patients as agreed with Chinese Regulatory Agency. The trial is approximately 50% enrolled.

Additional rezafungin studies are described in Sections 4.2 and 5.

1.5 Submitted Indication and Dose

As there is a lack of precedent for a limited use indication for an antifungal, Cidara submitted the NDA with the following indication:

> Rezafungin is an echinocandin antifungal indicated for the treatment of candidemia and invasive candidiasis in patients 18 years of age or older.

Rezafungin is dosed weekly. A loading dose of 400 mg IV in Week 1 is followed by a 200 mg IV dose thereafter.

1.6 Efficacy

1.6.1 Phase 2 Study: STRIVE

Design

STRIVE is a Phase 2 multicenter, randomized, two-part, double-blind study that established the appropriate dosing regimen of rezafungin while evaluating its efficacy and safety. Patients 18 years and older with confirmed candidemia or invasive candidiasis were eligible for enrollment. Patients with septic arthritis in a prosthetic joint, osteomyelitis, endocarditis, myocarditis, meningitis, endophthalmitis, central nervous system infection, neutropenia, elevated liver enzymes (> 10 × the upper limit of normal [ULN]) or severe hepatic impairment were excluded.

As illustrated in Figure 2, in Part A, patients were randomized 1:1:1 to:

- Rezafungin 400/400 mg: IV rezafungin 400 mg on Days 1 and 8 with an optional 400 mg dose on Day 15 and (for invasive candidiasis patients only) Day 22;
- Rezafungin 400/200 mg: IV rezafungin 400 mg on Day 1, 200 mg on Day 8 with an optional 200 mg dose on Day 15 and (for invasive candidiasis patients only) Day 22; or
- Caspofungin 70 mg IV as a loading dose, followed by 50 mg IV daily

Part B comprised 2 randomization periods. In Part B1, patients were randomized 2:1 to:

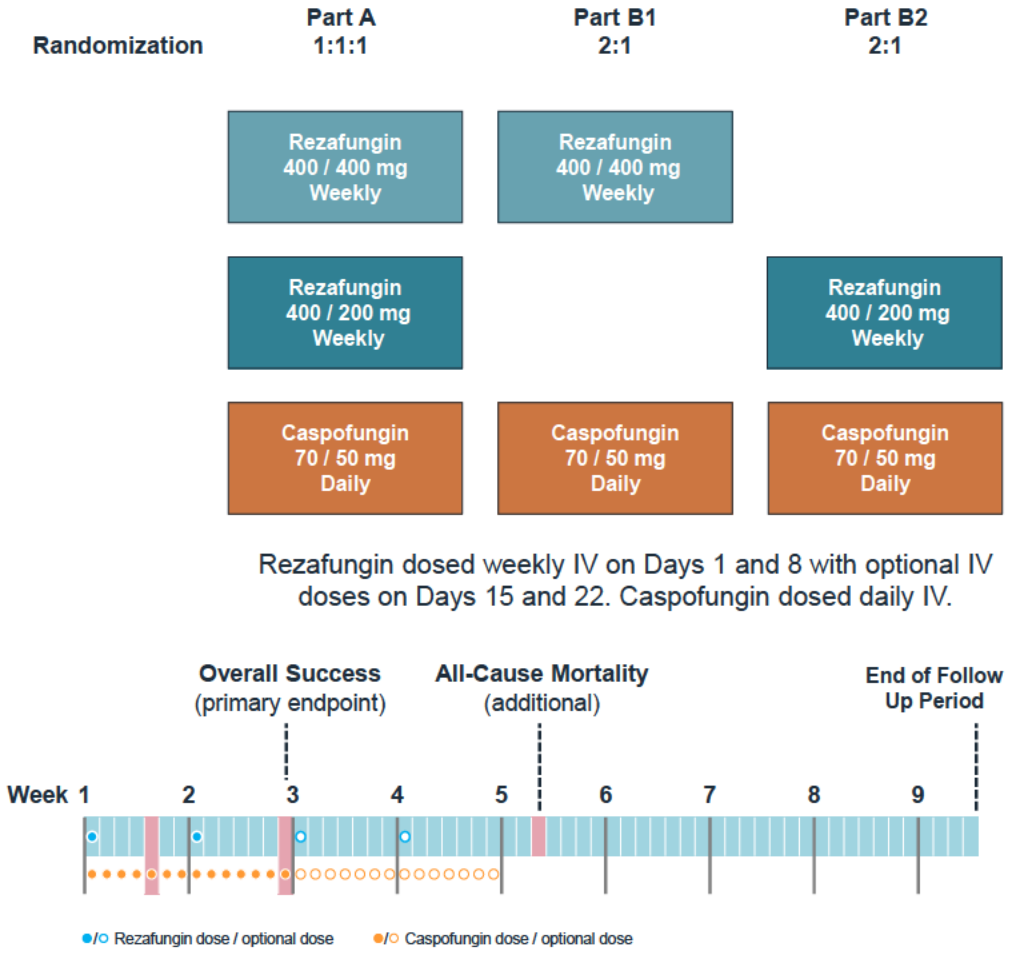
- IV rezafungin 400/400 mg; or
- IV caspofungin 70/50 mg.

Following an unblinded review of data from Part A, it was determined that both doses showed evidence of efficacy and safety and PK data indicated that either dose regimen would provide adequate exposures in patients. Thus, in Part B2, patients were randomized 2:1 to:

- IV rezafungin 400/200 mg; or
- IV caspofungin 70/50 mg.

In all parts, to maintain the blind, patients randomized to rezafungin also received daily saline injections. After at least 3 days of treatment, patients in the caspofungin group could be switched to oral fluconazole stepdown therapy; to maintain the blind, patients in the rezafungin group could be switched to oral placebo (see Section 6.1.2).

Figure 2: STRIVE Study Design



The primary efficacy endpoint in STRIVE was overall success at Day 14 in the microbiological Intent-to-Treat (mITT) population. Overall success was defined as mycological success (eradication/presumed eradication) plus resolution of attributable systemic signs of candidemia and/or invasive candidiasis that were present at baseline. The mITT Population was defined as all patients who received at least one dose of study drug and had a documented *Candida* infection based on a blood culture, or specimen from another sterile site, within 96 hours prior to randomization.

Secondary endpoints included mycological response and Investigator assessment of clinical response. ACM was an additional endpoint.

Patients

The mITT Population included 76 patients in the rezafungin 400/400 mg group, 46 in the rezafungin 400/200 mg group, and 61 in the caspofungin group. Baseline characteristics, including age, sex, race, diagnosis, modified Acute Physiology and

Chronic Health Evaluation II (APACHE II) score, and renal impairment category, were generally balanced between treatment groups.

Table 1: STRIVE Patient Demographics and Baseline Characteristics (mITT Population)

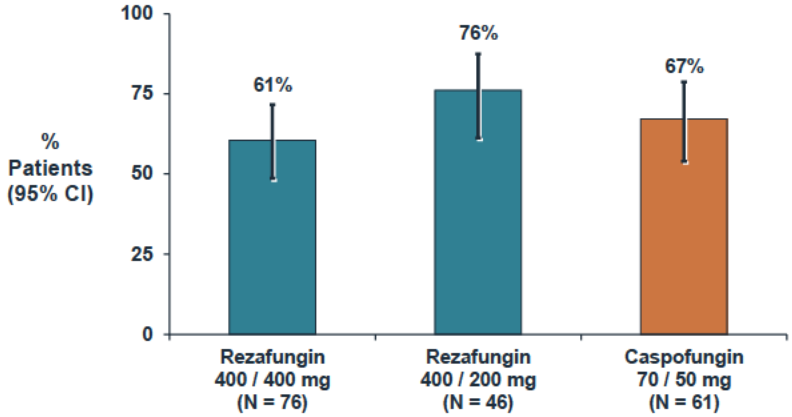
Characteristic	Rezafungin 400/400 mg (N=76)	Rezafungin 400/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Age, mean (min, max)	60 (24, 88)	60 (26, 91)	59 (24, 93)
Sex, Male, n (%)	42 (55)	28 (61)	34 (56)
Race, n (%)			
White	66 (87)	36 (78)	51 (84)
Black	6 (8)	6 (13)	4 (7)
Other	4 (5)	4 (9)	6 (10)
Diagnosis, n (%)			
Candidemia only	57 (75)	36 (78)	48 (78)
Invasive candidiasis	19 (25)	10 (22)	13 (21)
Modified APACHE II score, n (%)	74	45	58
≥ 20	16 (21)	9 (20)	9 (15)
< 20	58 (76)	36 (78)	49 (80)
Renal Impairment category, n (%)			
< 60 (moderate/severe)	17 (22.4)	18 (39.1)	23 (37.7)

APACHE II: Acute Physiology and Chronic Health Evaluation II; mITT: microbiological Intent-to-Treat

Results

The 2 rezafungin treatment groups achieved overall success rates of 61% (400/400 mg) and 76% (400/200 mg) at Day 14, compared to 67% of patients receiving caspofungin (Figure 3). Secondary endpoints aligned with these findings (see Section 6.1.7.2).

Figure 3: STRIVE Day 14 Overall Success Rate (mITT Population)



CI: confidence interval; mITT: microbiological Intent-to-Treat

The ACM rate at Day 30 in the mITT Population was 24% in the rezafungin 400/400 mg group, 9% in the rezafungin 400/200 mg group, and 16% in the caspofungin group.

The lowest effective rezafungin dose of 400 mg followed by 200 mg once-weekly was selected for Phase 3 based on the positive efficacy data from Part A of Phase 2 and after confirming that either dose regimen would provide adequate exposures in patients relative to nonclinical PK/pharmacodynamic (PD) targets. See Section 6.2 on Phase 3 dose selection.

Since Part B enrollment of Phase 2 was enrolling rezafungin 400/400 mg patients while the Part A data were being locked and analyzed, the final dosing decision for Phase 3 also prompted the switch from 400/400 mg (STRIVE B1) to 400/200 mg (STRIVE B2) in the Phase 2 study.

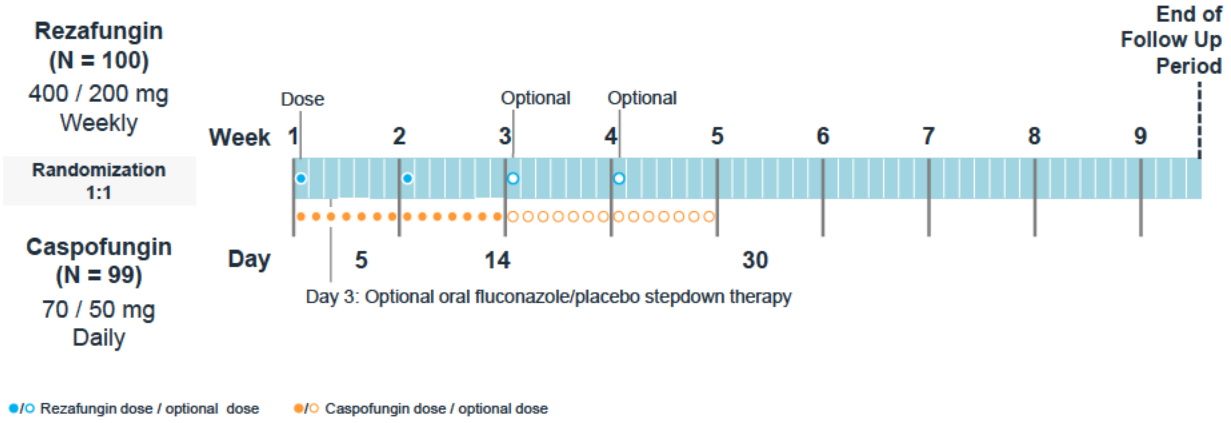
1.6.2 Phase 3 Study: ReSTORE

Design

ReSTORE was a Phase 3 multicenter, randomized, double-blind study. Patients 18 years and older with an established mycological diagnosis of candidemia and/or invasive candidiasis and ≥ 1 attributable systemic sign at baseline were enrolled. Exclusion criteria were similar to the STRIVE study with the exception that patients with severe neutropenia were eligible in ReSTORE.

Patients were randomized 1:1 to IV rezafungin 400/200 mg or IV caspofungin (Figure 4). After at least 3 days of treatment, patients in the caspofungin group could be switched to oral fluconazole. Patients in the rezafungin group were given daily IV placebo on days they did not receive rezafungin until stepdown occurred (if it did), at which point they received daily oral placebo and continued weekly IV rezafungin. Patients were followed through Day 59.

Figure 4: ReSTORE Study Design



The primary endpoint was Day 30 ACM, which was defined as patients who died on or before Day 30 or with unknown survival status at Day 30. The NI margin of 20% was based on the determination of the treatment effect from studies of no or inadequate treatment and previous clinical trials of echinocandins. The 20% margin was chosen as this maintains a portion of the treatment effect, was applicable for this high unmet need population in the context of a limited use indication and enrollment feasibility in an orphan indication. The NI margin was agreed upon with the FDA.

Secondary outcomes included global cure (defined as mycological eradication/presumed eradication, clinical cure, and radiologic cure [for patients with documented invasive candidiasis by radiologic/imaging at baseline]) by visit, which was assessed by a blinded, independent Data Review Committee (DRC), and mycological response, which was determined programmatically. Additional secondary and exploratory endpoints are described in Section 6.3.4.

The analysis population for the efficacy endpoints was the modified Intent-to-Treat (mITT), which included all randomized patients who received at least one dose of study drug and had a documented *Candida* infection from a blood culture or culture from another normally sterile site within 96 hours before randomization. Note that this is the same definition as used in the STRIVE study for the microbiologic ITT Population.

Patient Population

The mITT Population in ReSTORE included 93 patients in the rezafungin group and 94 patients in the caspofungin group. Demographics and baseline characteristics are summarized in Table 2.

Table 2: ReSTORE Patient Demographics and Baseline Characteristics (mITT Population)

Characteristic	Rezafungin 400 / 200 mg (N=93)	Caspofungin 70 / 50 mg (N=94)
Age, mean (min, max)	60 (19, 89)	62 (20, 91)
Sex, Male, n (%)	62 (67)	56 (60)
Race, n (%)		
White	59 (63)	55 (59)
Asian	23 (25)	31 (33)
Black	5 (5)	4 (4)
Other/Not reported	5 (5)	3 (3)
Geographic Region, n (%)		
North/South America	26 (28)	24 (26)
Europe/Israel/Turkey	38 (41)	37 (39)
Asia-Pacific/China/Taiwan	29 (31)	33 (35)
Diagnosis, n (%)		
Candidemia only	64 (69)	67 (71)
Invasive candidiasis	29 (31)	27 (29)
Modified APACHE II score, n (%)	92	94
≥ 20	12 (13)	17 (18)
< 20	80 (86)	77 (82)
Renal impairment category, n (%)	88	83
< 60 mL/min (moderate/severe)	36 (39)	36 (38)
ICU at time of dosing, n (%)	29 (31)	37 (39)
Mechanical ventilation, n (%)	16 (17)	28 (30)
Modified APACHE II score, median (min, max)	12.0 (0, 40)	11.5 (0, 37)
APACHE II and absolute neutrophil count (ANC)*, n (%)		
≥ 20 or ANC < 500 µ/L	22 (24)	21 (22)
< 20 and ANC ≥ 500 µ/L	71 (76)	73 (78)

APACHE II: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; mITT: microbiological Intent-to-Treat
*randomization stratification factor

Baseline pathogens were comparable between treatment groups. The most common pathogens were *C. albicans, C. glabrata, C. tropicalis,* and *C. parapsilosis (*see Table 25*)*. Nearly all (99.5%) pathogens were susceptible to rezafungin and caspofungin.

Results

Rezafungin was noninferior to caspofungin for the primary endpoint of Day 30 ACM in the mITT Population (Table 3). The percentage of patients who were either known to be

deceased or with unknown survival status was 23.7% for the rezafungin group and 21.3% for the caspofungin group. The treatment difference was 2.4% with an upper limit of the 95% confidence interval (CI) of 14.4, which is below the NI margin of 20%. Unknown survival status was low at 3.2% in both treatment groups.

Table 3: ReSTORE All-Cause Mortality at Day 30 (-2 days) (mITT Population)

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

CI: confidence interval; mITT: modified Intent-to-Treat
a. Patients who died on or before Day 30, or with unknown survival status.
b. Two-sided 95% CI for the observed treatment difference in death rates, rezafungin minus caspofungin, was calculated using the unadjusted methodology of Miettinen and Nurminen.

Approximately 60% of patients in both groups achieved the key secondary endpoint of global cure by Day 14 (Table 4). The results of the other secondary endpoints provided supportive evidence of the efficacy of rezafungin (see Section 6.3.8.3).

Table 4: ReSTORE Global Response as Assessed by Data Review Committee at Day 14 (±1 day) (mITT Population)

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

CI: confidence interval; DRC: data review committee; mITT: modified Intent-to-Treat
Notes: Two-sided 95% CI for the observed differences in cure rate (rezafungin treatment group minus caspofungin treatment group) was calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of patients in the mITT Population in each treatment group as the denominator

Rates of indeterminate response were 10.8% in the rezafungin and 8.5% in the caspofungin group. The primary reason for an indeterminate response was lost to follow-up or withdrew consent (5 patients in each treatment group).

Global cure rates were similar between treatment groups at each of the other visits (Day 5, Day 30), End of Treatment [EOT, within 2 days of the last dose of study drug], and Follow-up [Days 52–59]).

The rates of mycological eradication at Days 5 and 14 were also high and comparable between groups. At Day 5, 68.8% of patients in the rezafungin group and 61.7% in the

caspofungin group achieved mycological eradication. At Day 14, 67.6% and 66.0% of patients achieved eradication. Additional results from ReSTORE, which show the consistency across secondary endpoints, are provided in Section 6.3.8.

1.6.3 Pooled Efficacy Data

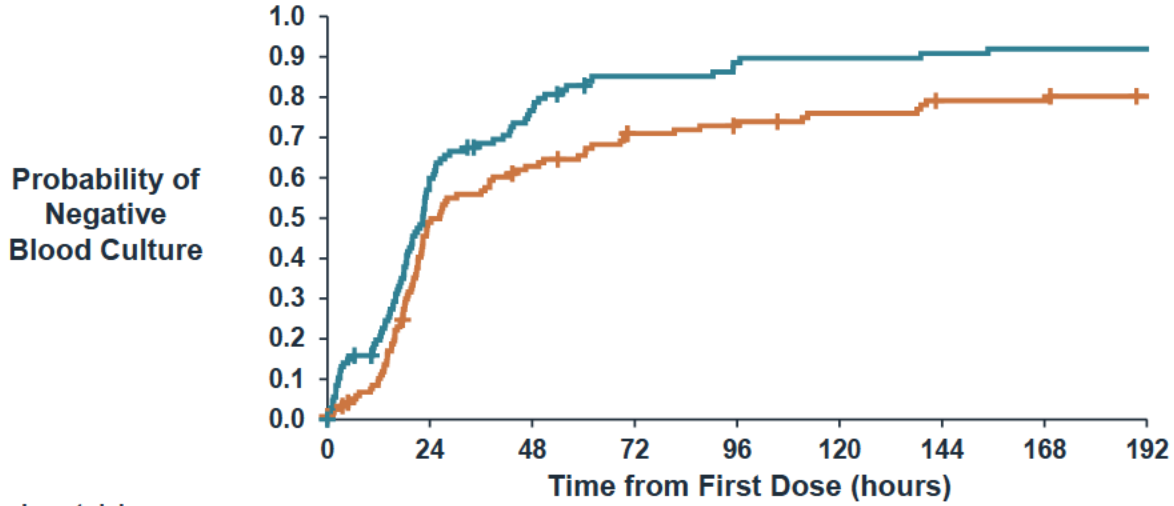
Given the similarities between the studies, additional analyses were performed by pooling data from STRIVE (rezafungin 400/200 mg only) and ReSTORE.

The ACM rate was similar between treatment groups in subgroups defined by demographic and baseline characteristics, with the exception of age and renal impairment (see Figure 25).

Among the pooled groups, the rate of patients with mycological eradication at Day 5 was 73.4% and 64.5% in the rezafungin and caspofungin groups, respectively (see Table 34). Mycological eradication rates at Day 14 were similar to the results at Day 5.

An additional efficacy endpoint of time to first negative blood culture was examined in patients with a positive blood culture before randomization. Based on the Kaplan-Meier curve, the median time to first negative blood culture was 22.3 hours and 26.3 hours in the rezafungin and caspofungin groups, respectively (Figure 5), and at 24 hours, the percentage of patients with a negative blood culture was 60% and 49%, respectively Figure 6 (see Table 35). These data suggest rezafungin may provide earlier clearance of *Candida* from blood in patients with candidemia.

Figure 5: Pooled STRIVE and ReSTORE Kaplan-Meier Estimate of Time to Negative Blood Culture



mITT: modified Intent-to-Treat
Note: mITT Population with positive blood culture before randomization

1.7 Safety

1.7.1 Safety Populations and Exposure

Across the clinical development program, a total of 312 individuals received rezafungin at the proposed dose of 400/200 mg or higher administered for at least 2 weeks.

Given the similar study designs and enrolled patients, and in agreement with the FDA, data were pooled from the Phase 2 and 3 studies to better inform the safety profile. This Pooled Safety Population included 151 patients treated with the rezafungin 400/200 mg dose and 166 patients treated with caspofungin.

The median duration of therapy, IV and oral combined, in both treatment groups was 14 days, with a range of 1–28 days. In the rezafungin group 27.8% of patients received oral therapy compared with 35.5% of caspofungin patients.

1.7.2 Overview of Adverse Events

As expected in this seriously ill hospitalized population, nearly all patients in both treatment groups experienced at least 1 adverse event (AE; Table 5). Severe AEs and serious AEs (SAEs) occurred in approximately half of patients in each group. In both groups, approximately 2% of patients had AEs that led to interruption of study drug, and 9% of patients experienced AEs leading to discontinuation of study drug.

Table 5: Summary Overview of Adverse Events (Pooled Safety Population)

Number of Patients with ≥ 1:	Rezafungin 400/200 mg (N=151) n (%)	Caspofungin 70/50 mg (N=166) n (%)
Adverse Events	138 (91.4)	138 (83.1)
Severe	74 (49.0)	85 (51.2)
AE leading to interruption of study drug	3 (2.0)	4 (2.4)
AE leading to discontinuation of study drug	14 (9.3)	15 (9.0)
Serious adverse event	83 (55.0)	81 (48.8)
Serious adverse event resulting in death	35 (23.2)	40 (24.1)

AE: adverse event

The most commonly reported AEs included hypokalemia, pyrexia, and diarrhea, all of which are expected in this population. As shown in Table 39, there were imbalances observed in rates of AEs, but there is no known pathophysiological reason for rezafungin to cause these to a greater degree than caspofungin.

Septic shock was reported as the most common severe AE and SAE in both treatment groups. With the exception of pneumonia, percentages of patients with severe AEs were similar between treatment groups.

In the rezafungin treatment group, the only AE leading to discontinuation of study drug that was reported in 2 patients was infusion-related reaction. In the caspofungin group, AEs leading to discontinuation of study drug that occurred in 2 patients were chorioretinitis and endophthalmitis.

Through Day 59, the incidence of SAEs resulting in death was similar in both treatment groups: 23% of patients in the rezafungin group and 24% of patients in the caspofungin group. The most common AE leading to death was septic shock, followed by multiorgan dysfunction syndrome and sepsis – all of which occurred in a similar percentage across treatment groups. The observed mortality rate is not unusual for this seriously ill population with multiple comorbidities and is similar to what has been reported in previous clinical trials for this indication.

1.7.3 Safety Topics of Interest

AEs of special interest (AESIs) in the rezafungin clinical trials included infusion-related reactions, photosensitivity, and neurological events. These events were selected as they are either known echinocandin class effects or were identified as a potential risk through early nonclinical or Phase 1 studies.

Overall, infusion-related reactions occurred in 4 rezafungin-treated patients and 1 caspofungin-treated patient (Table 6). One infusion-related hypersensitivity reaction reported as “rash and significant wheezing during study drug infusion” occurred in a patient while receiving saline placebo on Day 3. The “adverse drug reaction” was a rash that occurred during saline placebo infusion in the same patient on Day 4. One additional rezafungin patient with infusion-related reaction experienced the event during a Day 3 placebo infusion. Two infusion-related reactions in rezafungin-treated patients, and one in caspofungin-treated patients occurred during administration of active study drug.

Table 6: Summary of Infusion-Related Reaction Adverse Events of Special Interest (Pooled Safety Population)

Category	Rezafungin 400/200 mg (N=151) n (%)	Caspofungin 70/50 mg (N=166) n (%)
Any infusion-related reaction AESI	4 (2.6)	1 (0.6)
Preferred Term		
Infusion-related reaction	3 (2.0)	0
Infusion-related hypersensitivity reaction*	1 (0.7)	0
Adverse drug reaction*	1 (0.7)	0
Anaphylactic shock	0	1 (0.6)

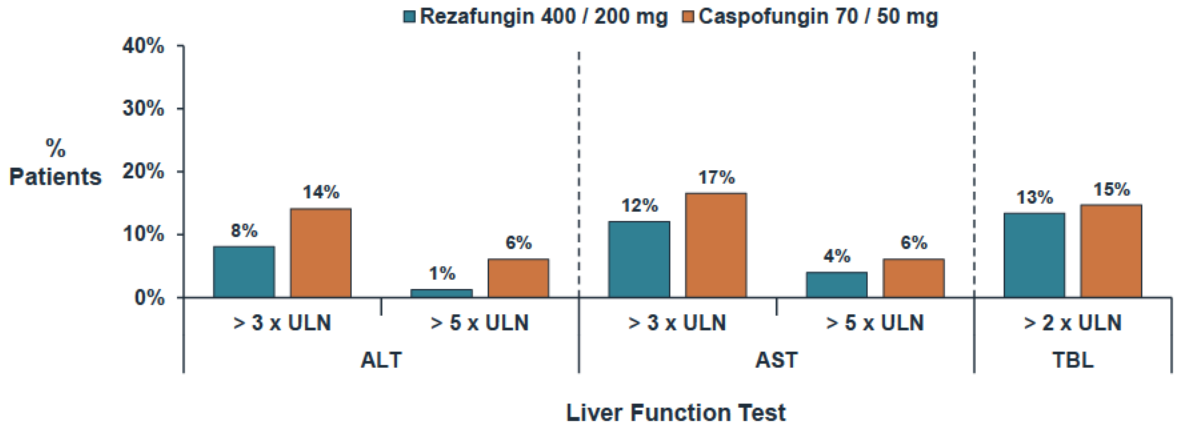
*same patient
AESI: adverse event of special interest

Four patients in the rezafungin group experienced “tremor,” and no patients reported tremor in the caspofungin group. All 4 of these events were Grade 1 and resolved. An independent neurologist assessed these 4 AEs for relatedness to rezafungin. Two were considered definitely not related due to other underlying causes. One event was deemed possibly related to rezafungin. This patient, who was no longer in the hospital, experienced fluid shifts due to diuretic use. This may have contributed to unreported electrolyte abnormalities. Finally, one event of tremor was considered to be related to rezafungin secondary to rezafungin causing hypokalemia. The tremor resolved after replacement of potassium.

There was a low incidence of neuropathy in both treatment groups. The number of neuropathy AEs was higher in the caspofungin treatment group, occurring in 4 patients in the caspofungin group and 2 in the rezafungin group. None were related to either study treatment.

Given the known class effects of echinocandins, a thorough evaluation of liver enzyme abnormalities was performed to assess the potential hepatotoxicity of rezafungin. Two-grade increases from baseline in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin were less common in the rezafungin group than in the caspofungin group (Figure 6). Analysis of the safety database demonstrated that there were no cases of serious hepatocellular drug-induced liver injury (DILI) in either treatment group. The screening laboratory criteria for potential serious hepatocellular DILI cases are bilirubin > 2 × ULN and ALT or AST > 3 × ULN and alkaline phosphatase (ALP) < 2 × ULN. After excluding patients who already met these criteria at baseline, 3 rezafungin-treated patients met the screening laboratory criteria post-baseline; however, these were determined to not be cases of serious hepatocellular DILI due to the presence of alternative causes (e.g., traumatic injury to liver, sickle cell crisis, and sepsis and congestive hepatopathy). In patients without elevations in total bilirubin prior to initiation of study drug, 1/134 (0.7%) patients developed elevations in AST or ALT and total bilirubin following treatment with rezafungin and 3/148 (2.0%) developed elevations in AST or ALT and total bilirubin following treatment with caspofungin. Additional details are provided in Section 7.12 Table 47 and Appendix Section 10.7.

Figure 6: Liver Enzyme Abnormalities at any time Post-Baseline (Pooled Safety Population)



ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal

1.8 Benefit-Risk Summary

While echinocandins are the current first-line therapy for candidemia and invasive candidiasis, gaps in treatment continue to exist. Thus, there is need for new effective antifungals to address the gaps.

Rezafungin is an echinocandin whose front-loaded exposure maximizes its therapeutic potential from a PK/PD standpoint with increased in vivo molecular stability and earlier concentration-dependent killing with once-weekly dosing. Rezafungin can provide a meaningful alternative for patients and physicians in this rare disease that continues to be associated with high mortality.

Rezafungin was noninferior to caspofungin for Day 30 ACM (primary endpoint) in the pivotal Phase 3 trial. High and similar global cure rates (key secondary endpoint) were observed in the treatment groups. Additionally, exploratory endpoints suggest faster clearance of *Candida* from the blood with rezafungin. Both the STRIVE and ReSTORE trials showed improvement in mycological outcomes at Day 5 compared to caspofungin. Given that early appropriate antifungal therapy is associated with improvement in outcomes, the ability of rezafungin to shorten the time to *Candida* clearance may provide benefit to patients and may reduce the risk of developing resistance. Additional benefits of rezafungin include no potential for drug-drug interactions and no need for dosing adjustments in special populations (renal or hepatic impairment).

Echinocandins have a well-established safety profile and, in general, are well tolerated. Importantly, the safety data observed for rezafungin aligns with expectations of an echinocandin. AEs were mostly mild and transient, resolving while patients remained on treatment. SAEs leading to death occurred at comparable rates between treatment groups and were the types of events expected in this hospitalized, seriously ill patient population with multiple comorbidities. Lower levels of increased liver enzymes were

observed for those treated with rezafungin, and no events of serious hepatocellular DILI occurred in rezafungin- or caspofungin-treated patients.

Based on consistent clinical efficacy and safety data across 2 global randomized controlled clinical studies, together with a microbiologic and PK profile that addresses current treatment gaps, rezafungin demonstrates a favorable benefit-risk profile in patients with candidemia and invasive candidiasis.

The patient population that is most likely to benefit from rezafungin are adult patients with candidemia or invasive candidiasis, including those who are critically ill, who are symptomatic, and have traditional risk factors for candidemia and/or deep tissue (intra-abdominal and peritoneal) invasive candidiasis. Rezafungin offers patients an echinocandin with once-weekly dosing and front-loaded exposure associated with earlier mycological clearance, that lacks drug-drug interactions, requires no dose adjustment (e.g., for those with renal or hepatic dysfunction), and better enables continuity of care.

2 BACKGROUND ON CANDIDEMIA AND INVASIVE CANDIDIASIS

Summary

- Candidemia and invasive candidiasis are rare, serious, and life-threatening infections affecting the bloodstream and / or deep tissues.
- *Candida* infections account for 40% of all invasive fungal infections and are associated with high excess length of stay and attributable mortality (Menzin 2009).
- Candidemia/invasive candidiasis affects patients already suffering from other comorbidities, such as critical illness, immunosuppression, recent surgery, and any disease syndrome requiring a central venous catheter, which predispose them to acquiring these infections.
- *Candida* species is a leading pathogen among bloodstream infections, with *C. albicans* and *C. glabrata* being the most common in the US.
- *C. glabrata* and *C. auris* are associated with high rates of antifungal resistance, including resistance to the currently approved echinocandins.
- Echinocandins are the recommended first-line agents for the treatment of candidemia and invasive candidiasis.
- Limitations of current anti-*Candida* treatments include underdosing, drug-drug interactions, hepatotoxicity, resistance, poor deep tissue distribution, and patient access due to once-daily dosing.
- Observations suggest the need for early and high therapeutic exposures of echinocandins for *Candida* pathogens with higher minimum inhibitory concentrations (MICs).
- Due to the gaps with current therapies, there is an urgent need for new antifungals that can achieve higher exposures in deep tissues and organs, overcome resistance issues, and support dosing in hospital and outpatient settings.

2.1 Overview of Invasive *Candida* Infections

Candidemia and other forms of invasive candidiasis (e.g., intra-abdominal abscess) are among the most serious fungal infections in the US (Menzin 2009, Vincent 2009, Pfaller 2010, Azie 2012, Brown 2012, Arendrup 2013, Tsay 2020).

2.2 Epidemiology of *Candida* Infections

In a 2015 CDC survey of US acute care hospitals, *Candida s*pecies was the second leading pathogen among bloodstream infections (Magill 2018). A large, nationwide, surveillance study of more than 24,000 bloodstream infections from 49 US hospitals over a 7-year period (1995–2002) found *Candida* species to be the fourth most frequent among pathogens isolated from bloodstream infections, led by coagulase-negative staphylococci, *Staphylococcus aureus,* and *Enteroco*ccu*s s*pecies (*E. faecalis, E. faecium*) (Wisplinghoff 2004). Yet, the impact of candidemia may be underrepresented by incidence alone. Indeed, among all pathogens isolated in this study, associated crude mortality in this study was highest for *Candida* species, followed by *Pseudomonas aeruginosa*, *Acinetobacter baumannii, Enterococcus* species, and *Klebsiella* species. Among the most common *Candida* species isolated from these nosocomial infections, the majority were *C. albicans*, followed by *C. glabrata, C. parapsilosis,* and *C. tropicalis.* Crude mortality rates were, in rank order, highest for *C. glabrata* (50.1%), then *C. tropicalis* (43.1%), *C. albicans* (36.6%), and *C. parapsilosis* (27.9%).

In a recent analysis of a large US patient database, *Candida* infections accounted for 40% of all invasive fungal infections and were associated with the longest length of stay and attributable mortality (Menzin 2009). In fact, the mortality rate in patients with candidemia has been reported to be > 40%, which exceeds rates for invasive aspergillosis in some populations (Wisplinghoff 2004, Falagas 2006, Pfaller 2007, Labelle 2008, Pfaller 2010, Slavin 2010, Andes 2012, Mikulska 2012, Mylonakis 2015). In comparison, *S. aureus*, the most common bacterial pathogen in bloodstream infections (Diekema 2019), showed recent declines in incidence, with an overall in-hospital mortality of 18% in the US (Kourtis 2019).

A recent retrospective cohort study compared > 600 candidemia patients to > 6,000 matched controls and noted a crude mortality rate of 42.4% and an attributable mortality due to candidemia of 28.4% (Mazi 2022). Additionally, in the same study, the highest risk for mortality occurred among patients considered to have the lowest risk of acquiring candidemia, and thus were frequently missed or left untreated for a longer period prior to diagnosis. It has been well established that any delay in initiation of appropriate antifungal therapy results in increased morbidity and mortality (Garey 2006, Kollef 2012). Additionally, early treatment is emphasized in the US and global practice guidelines. Timely initiation of antifungal therapy with a rapidly fungicidal agent will provide a valuable therapeutic benefit.

2.3 Risk Factors and Signs and Symptoms

Risk factors for candidemia and invasive candidiasis include:

- Central venous catheters
- Active malignancy
- Broad-spectrum antibiotic therapy
- Diabetes mellitus
- Immunosuppression
- Major surgery
- Total parenteral nutrition
- Transplant recipient
- Trauma
- End-stage renal disease/dialysis
- Burns
- Pancreatitis

Signs of infection that might be attributable to candidemia and/or invasive candidiasis at baseline include fever, hypothermia, hypotension, tachycardia, tachypnea, and local signs of inflammation (erythema, edema, heat, and pain at the site of infection).

2.4 Current Treatment Options

2.4.1 Echinocandins: First-Line Therapy for Candidemia and Invasive Candidiasis

The Infectious Diseases Society of America recommends that echinocandins (anidulafungin, caspofungin, and micafungin) are the first-line antifungal agents for the treatment of candidemia and invasive candidiasis, except when affecting the central nervous system, the eyes, or the urinary tract (Pappas 2016). The recommendation is based on the established safety profile and fungicidal activity of echinocandins compared to the static effect of azoles. Additionally, the trend towards better outcomes for echinocandins versus other antifungals observed in individual studies and combined analyses of candidemia and invasive candidiasis studies support the use of echinocandins. Despite this, there is an opportunity to address gaps with the currently available echinocandins.

2.4.2 Shortcomings of Marketed Treatments: Pharmacokinetics and Toxicity

When the first-generation echinocandins were developed more than 20 years ago, modern pharmacometrics methods were not widely utilized, leaving gaps with standard dosing and therapeutic exposure (Andes 2011, Bader 2018b). Today, there are specific concerns about underdosing in some populations such as the critically ill and elderly (Hall 2013, Sinnollareddy 2015, Lempers 2016, van der Elst 2017, Maseda 2018, Mainas 2020). There are also concerns regarding the optimal dosing across *Candida* species (Andes 2011). A recent study examined the target attainment of the 3 marketed echinocandins to examine the likelihood of achieving clinical success and determined that while wild-type organisms may be covered with current dosing, therapeutic exposures are unlikely to be achieved for *Candida* species with elevated MIC values (Bader 2018a). This is especially concerning given the increasing rates of reduced

susceptibility to echinocandins observed across all *Candida* species, particularly in *C. glabrata* and *C. auris* (Alexander 2013, Lockhart 2017).

There are also concerns regarding the ability of the marketed echinocandins to reach deep tissue infections, specifically intra-abdominal and peritoneal candidiasis (Howard 2011, Grau 2015, Welte 2021). These observations suggest the need for an echinocandin with higher therapeutic exposures for *Candida* pathogens with higher MICs and for invasive candidiasis of the deep tissues and organs (Boonstra 2017, Luque 2019, Maseda 2018). There have been attempts to increase the approved dose of currently marketed echinocandins to improve patient outcomes (Hiemenz 2005, Sirohi 2006, Hall 2011). However, the risk of toxicity increases with higher doses and offsets possible therapeutic benefit. Each of the 3 marketed echinocandins is associated with liver toxicity and necrosis, as shown in nonclinical development studies, and with hepatotoxicity in patients (Cancidas Prescribing Information, Mycamine Prescribing Information, Eraxis Prescribing Information). Therefore, higher exposures of these echinocandins, beyond approved doses, could lead to increased risk of hepatotoxicity.

The azole class of drugs, also used to treat candidemia and invasive candidiasis as second-line agents, is associated with hepatotoxicity, as well as severe skin reactions (e.g., Stevens Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms, etc.), and are more likely to be discontinued due to toxicity or drug-drug interactions, compared to the echinocandin class (Wang 2010, Wang 2015).

2.4.3 Increasing Threat and Resistance of Candida

The need for new antifungal agents is underscored by pathogen-related trends in *Candida* species during the past 15 years. The shifting predominance to non-*albicans* species and increasing resistance to azoles and echinocandins has become increasingly problematic over the past few years, especially in *C. glabrata, C. auris, and C. parapsilosis* (Pfaller 2019, Ricotta 2021, Escribano and Guinea 2022, Demirci-Duarte 2021).

C. glabrata is the second most common species of *Candida* observed in candidemia and invasive candidiasis infections and is more frequently isolated among patients aged ≥ 65 years compared with relatively younger patients (Vallabhaneni 2015, Pfaller 2022). In addition to its increasing prevalence, *C. glabrata* distinguishes itself among *Candida* species as difficult to diagnose and treat (Fernandez 2009, Kwon 2021). *C. glabrata* is the only common *Candida* species that has a haploid genome and other genetic factors resulting in a predisposition to drug resistance-conferring mutations. Rates of *C. glabrata* resistance to fluconazole (5.6%–15.7%) and cross-resistance with newer triazoles, as well as emerging echinocandin resistance (1.7%–3.5%) indicate the reality of *C. glabrata* as an opportunistic threat on the rise (Pfaller 2012b, Vallabhaneni 2015, Arastehfar 2020, Tortorano 2021).

The CDC recently warned that fluconazole-resistant *Candida* infections have the potential to pose a serious threat to public health (CDC 2013, CDC 2016). Echinocandin resistance occurs as a result of mutations in *FKS* genes encoding “hot spot” regions of 1,3-β-D-glucan synthase that are involved in echinocandin binding, leading to higher MICs (Garcia-Effron 2009). This increase in MIC as a direct result of *fks* mutations has been identified as an independent risk factor for echinocandin failure in *C. glabrata* infections (Shields 2012).

C. auris has emerged as a global mycological phenomenon and quickly presented a public health issue in the US and elsewhere (Vallabhaneni 2016, Lockhart 2017). Several nosocomial outbreaks have occurred over the past few years, resulting in a mortality rate of 30–60% (Chowdhary 2017). C. *auris is a* haploid organism predisposed to resistance-conferring mutations, similar to C. *glabrata. Br*oad resistance of C. *auris to a*zoles and polyenes (e.g., amphotericin B) has been noted and resistance to echinocandins has also been reported, though to a lesser degree (Kordalewska 2018).

The CDC estimates that the rates of *C. auris* resistance to azoles are ~90% and to amphotericin B are ~30%, while echinocandin resistance overall is < 5% (CDC 2020). Because of the near universal resistance to azoles for *C. auris* observed in surveillance studies, echinocandins are considered the first-line therapy; however, this is complicated by the fact that the Clinical and Laboratory Standards Institute (CLSI) has not established *C. auris* breakpoints for the marketed echinocandins (Chowdhary 2016, Kordalewska 2018). The CDC has labeled this emerging pathogen as a serious global health threat and predicted more outbreaks in the coming years. Improved and additional antifungal options are needed to treat these deadly infections, with increasing rates of resistance to azoles and the marketed echinocandins.

2.5 Medical Need for Additional Antifungals

As pathogen-related challenges have evolved, so have patient-related needs. Candidemia and invasive candidiasis are serious and life-threatening infections, particularly in more vulnerable patient populations such as the elderly, post-surgical, post-transplantation, and those with other immunosuppressive conditions (Kontoyiannis 2010, Pappas 2010), critically ill, and other hospitalized patients with serious medical conditions (Wisplinghoff 2004, Andes 2012, Magill 2014, Tsay 2020). For example, the growing elderly population (described by some as “the silver tsunami”) (Comlossy 2013, Bluethmann 2016), is now not only larger, but also older, with a poorer prognosis in treating candidemia than that of the younger population (Ramos-Martínez 2017, Zatta 2020). The elderly and other highly vulnerable patient populations frequently have multiple comorbidities treated with numerous medications, increasing the possibility of drug-drug interactions. Some antifungal agents, especially the azoles, have significant interactions with other drugs through the cytochrome P450 3A4 (CYP3A4) pathway (Czyrski 2021, Brüggemann 2022). The marketed echinocandins also have some interaction risk, especially with commonly used immunosuppressants or oncology drugs in patients with an already increased risk for invasive fungal infections

(Cancidas Prescribing Information, Mycamine Prescribing Information, Butts 2018). These interactions may result in increased toxicity and may also lead to reduced efficacy of the antifungal as well as the drugs used to treat the underlying comorbidities.

Echinocandins are the recommended first-line therapy for candidemia and invasive candidiasis (Pappas 2016); however, there are concerns for underdosing, potential for drug-drug interactions, and hepatotoxicity. The emerging threats of *C. auris* and azole-resistant *C. glabrata* have increased the urgent need for new therapeutic solutions, and yet no new antifungal agents have been approved for treatment of candidemia and invasive candidiasis since 2007 (CDC 2013, Executive Office of the President 2014, The White House 2014). For these reasons and because of the persistently high associated mortality, increasing antifungal resistance, and a growing list of contraindicated medications to be used with the current antifungal treatment options, there is an urgent need to develop new therapeutic options with well-understood efficacy, safety, microbiological, and dosing profiles to treat these serious and often fatal infections (Pfaller 2012a, Alexander 2013, Arendrup 2013, Ostrosky-Zeichner 2013).

3 PRODUCT DESCRIPTION

Summary

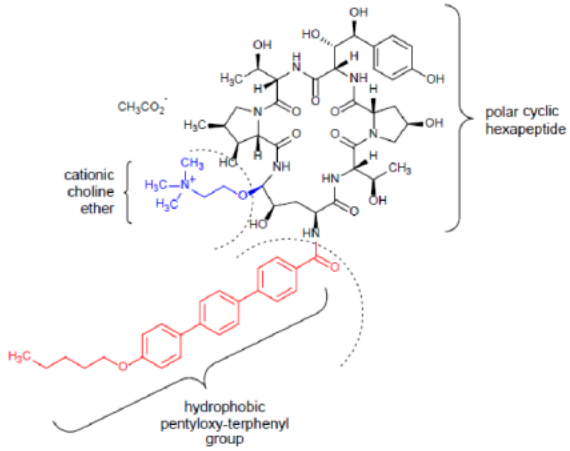
- Rezafungin is a well-understood echinocandin antifungal drug developed to treat candidemia and invasive candidiasis.
- Rezafungin is designed to achieve an improved chemical stability and pharmacokinetics profile, which offer patients and clinicians options beyond those of currently marketed antifungal agents.

3.1 Product Overview

Rezafungin is a semisynthetic echinocandin antifungal drug derived from anidulafungin (another echinocandin). The active pharmaceutical ingredient is rezafungin acetate. The drug exhibits antifungal activity against *Candida* species in both in vitro and in vivo nonclinical studies.

Rezafungin acetate fits the classical description of a cationic amphiphilic drug (drugs such as amiodarone, chlorpromazine, and tamoxifen) since it possesses a cationic polar head group (cyclic hexapeptide with choline ether) and a hydrophobic tail (pentyloxy-terphenyl group) as shown in Figure 7.

Figure 7: Chemical Structure of Rezafungin Acetate



Cationic (Blue), Polar (Black), and Hydrophobic (Red) sections of the Molecule

3.2 Submitted Indication and Dosing

As there is a lack of precedent for a limited use indication for an anti-fungal, Cidara submitted the NDA with the following indication:

> Rezafungin is an echinocandin antifungal indicated for the treatment of candidemia and invasive candidiasis in patients 18 years of age or older.

Rezafungin is dosed weekly. A loading dose of 400 mg IV in Week 1 is followed by a 200 mg IV dose thereafter.

Rezafungin is supplied as a single-dose vial containing 200 mg of rezafungin. For the 400 mg dose, aseptically reconstitute 2 vials with 9.5 mL of sterile Water for Injection each, to provide a concentration of 20 mg/mL in each vial. For the 200 mg dose, aseptically reconstitute 1 vial with 9.5 mL of sterile Water for Injection, to provide a concentration of 20 mg/mL.

3.3 Mechanism of Action

Antifungals in the echinocandin drug class inhibit the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall that is not present in mammalian cells (Sucher 2009). Rezafungin is designed to achieve improved chemical stability and optimized pharmacokinetic profile (James 2017). These 2 adaptations, in turn, yield properties that differentiate rezafungin from other echinocandins and potentially offer patients and clinicians options beyond those of currently marketed antifungal agents.

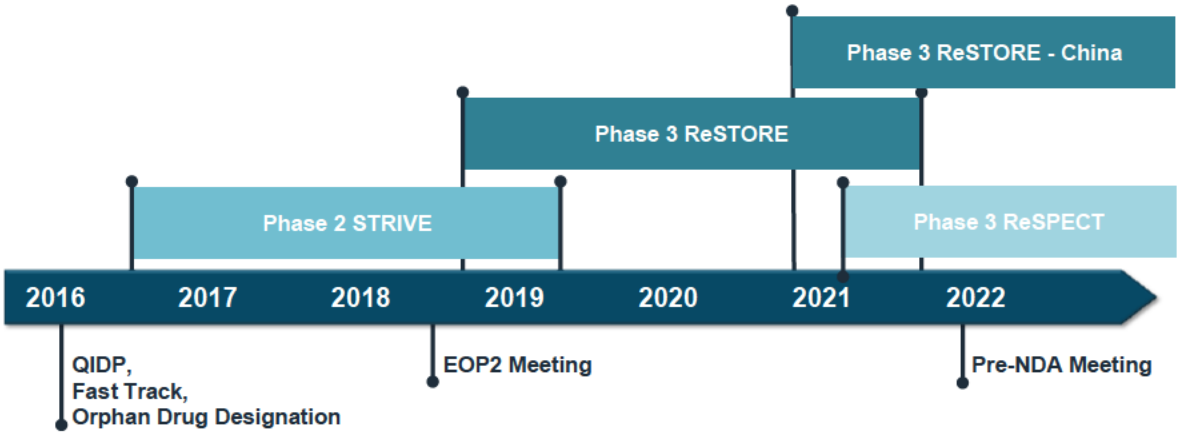
4 REGULATORY AND DEVELOPMENT HISTORY

4.1 Regulatory Milestones

Cidara has worked collaboratively with regulatory agencies, including the FDA and the EMA, and received scientific advice from national authorities in the EU and China's CDE.

The rezafungin development program timeline is illustrated in Figure 8.

Figure 8: Rezafungin Regulatory and Clinical Development Timeline



EOP: end of phase; NDA: New Drug Application; QIDP: qualified infectious disease product

The FDA has designated rezafungin as a QIDP. This designation was created to spur the development of drugs for serious or life-threatening infections. Rezafungin also has fast track and orphan drug status. Based on orphan designation for candidemia and invasive candidiasis, rezafungin qualifies for, and Cidara requested, a waiver for pediatric studies.

Beginning with a Pre-IND meeting in 2015, Cidara met with the FDA more than 15 times to discuss rezafungin development. Rezafungin was developed under FDA's 2017 streamlined development guidance titled *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases.* Under the recent May 2022 updated guidance, *Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers*, the pathway is now called flexible clinical development. As per FDA guidance, the safety database should include at least 300 subjects exposed to the commercial dose or higher.

At an EOP2 meeting in July 2018, agreement was reached on the Phase 3 study design for ReSTORE which, together with STRIVE as a supporting Phase 2 study, would form the basis for the NDA for treatment of candidemia and invasive candidiasis. For ReSTORE, a 20% NI margin for an endpoint of 30-day all-cause-mortality and the associated sample size, was deemed adequate to obtain a limited use indication for treatment of candidemia and invasive candidiasis. The primary endpoint of ACM at

Day 30, with a data driven non-inferiority margin, is a first for an echinocandin development program for candidemia/invasive candidiasis and was supported by a secondary endpoints of global cure at Day 14 and mycological eradication at Day 5 and Day 14.

At a Type C meeting held September 2021, agreement was reached on the plan for integrating Phase 2 STRIVE and Phase 3 ReSTORE safety and efficacy data of the clinical study data package in the NDA for the treatment of candidemia and invasive candidiasis. In a Pre-NDA interaction earlier this year, the FDA agreed it was reasonable to proceed with an NDA submission, based on STRIVE and ReSTORE, for a treatment indication.

4.2 Clinical Development Program

The current rezafungin clinical development program consists of 8 Phase 1 safety, PK/PD, and other clinical pharmacology studies in healthy volunteers or special populations and 3 clinical studies. The 2 clinical studies supporting the proposed indication are:

- STRIVE, a Phase 2 study and
- ReSTORE, a Phase 3 study.

Both studies evaluated the clinical safety and efficacy of rezafungin in the treatment of candidemia and invasive candidiasis.

ReSTORE China is ongoing to enroll Chinese patients (n=56) as agreed with the CDE.

An ongoing Phase 3 study (ReSPECT) is being conducted to evaluate the safety and efficacy of rezafungin for the prophylaxis of invasive fungal disease (candidemia and invasive candidiasis, invasive aspergillosis, *Pneumocystis jirovecii* pneumonia) in high-risk patients (allogeneic blood and marrow transplantation patients). In ReSPECT, rezafungin is administered once weekly for 13 weeks.

In addition, there are currently 4 US patients enrolled in an expanded access program with dosing duration extending to 90 weeks. Each of the patients responded to treatment, as described in Appendix Section 10.2.

Overall exposure to rezafungin in the clinical program is summarized in Table 7.

Table 7: Rezafungin Exposure in Clinical Program

Category	Number of Participants*
Participants/patients who received at least a single dose	412
Participants/patients who received rezafungin 400/200 mg dose or higher	312
Patients who received rezafungin 400/200 mg dose or higher	236

* includes 4 patients enrolled in the expanded access program

5 PHARMACOLOGY AND MICROBIOLOGY

Summary

- Rezafungin structural modifications yield improved chemical and biological properties, which translate to demonstrable advantages in dosing and pharmacokinetics compared to existing echinocandins.
- Rezafungin PK following IV administration is characterized by a volume of distribution of 33–48 L, which is similar to total body fluid volume; rezafungin is highly bound (97.4%) to human plasma proteins.
- Rezafungin undergoes minimal metabolism. In vitro studies show that rezafungin is stable across species after incubation with liver and intestinal microsomes and with hepatocytes, suggesting little or no biotransformation.
- Fecal excretion is the major route of elimination, accounting for approximately 74.3% of the recovered radioactivity, with 25.7% in urine.
- Population PK analyses showed no dose adjustment is required for any special patient population.
- In vitro and clinical studies rule out the possible effects of rezafungin on inhibition or induction of drug metabolizing enzymes or inhibition of drug transporters.
- Rezafungin's in vitro anti-*Candida* activity and resistance potential were similar to those of the approved echinocandins.
- Rezafungin exhibits some degree of cross-resistance to all *fks* mutations that confer reduced susceptibility to echinocandins but may be better able to treat mutant strains and lower the potential for resistance development compared to other echinocandins due to higher exposure and favorable target attainment.
- Concentration-dependent killing and prolonged post-antifungal effects of rezafungin have been demonstrated.
- At doses up to 1,400 mg (3.5 times the proposed 400 mg dose), rezafungin does not prolong or shorten the QTc interval.

5.1 Pharmacology

5.1.1 Studies in Human Biomaterials

In vitro, rezafungin was stable across species after incubation with liver and intestinal microsomes and with hepatocytes, suggesting little or no biotransformation.

Rezafungin did not cause meaningful inhibition (half-maximal inhibitory concentration [IC_{50}] values of > 25 µM) of human CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). Rezafungin was not a time-dependent inhibitor of the same 7 major human CYP isoforms when tested up to its solubility limit of 25 µM. There was no evidence of CYP induction (as measured by < 2-fold increase in mRNA expression) for CYP1A2 and CYP2B6 in all 3 donors tested, and, in the case of CYP3A4, in 2 of 3 donors tested. For CYP3A4, 1 out of the 3 donors tested showed a 2.68-fold induction of mRNA expression at the highest feasible concentration (3 µM) tested.

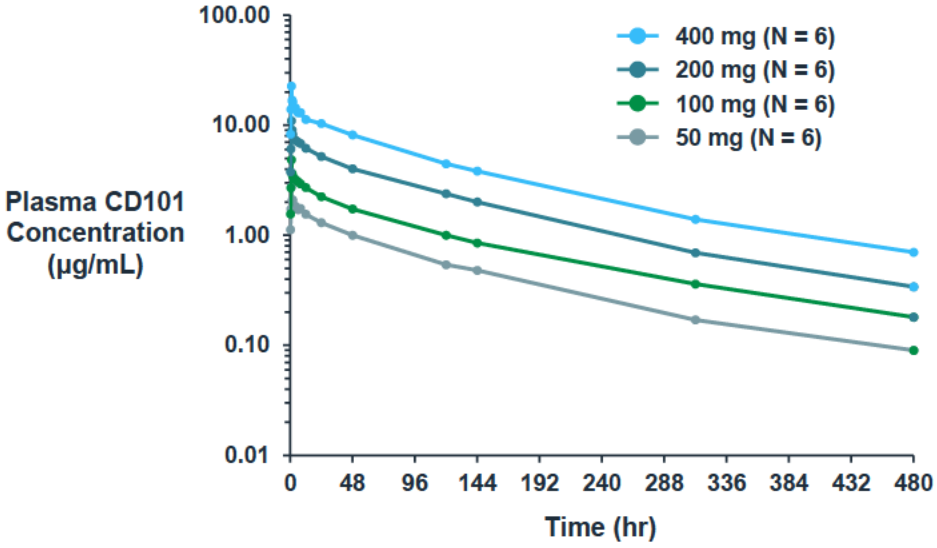
Rezafungin was found not to be a substrate for the following: ABC transporters: BCRP (breast cancer resistance protein), MDR1 (P-glycoprotein; P-gp) and MRP2, or the human solute carrier transporters OATP1B1, OATP1B3, OCT1, OCTN1, or OCTN2. However, rezafungin was determined to be an inhibitor of transporters P-gp, OATP1B1, OATP1B3, OAT1, OCT2, OCT1, MATE1 and MATE2-K, but not BCRP, OAT3, or bile salt export pump. These potential interactions were studied clinically and were found to not be clinically meaningful.

Central to mouse-to-human dose projection is assessing comparative plasma protein binding. Like other echinocandins, protein binding of rezafungin is high across different animal species and humans (> 97%), but higher in mouse (primary animal efficacy model) than in human plasma. The mean/median protein binding in mouse and human plasma are 99.2% and 97.4%, respectively. Corresponding mean/median % free-drug values were 0.8% and 2.6% in mouse and human plasma, respectively. Protein binding assessments in clinical samples were highly variable, but consistent with the in vitro results when similar methodologies were used. The % free rezafungin values in patients was nearly 3-fold higher than in healthy participants on average, likely due to reduced albumin levels common to severe illness.

5.1.2 Pharmacokinetics

Pharmacokinetics from the human single-ascending dose (SAD) study (CD101.IV.1.01) where rezafungin was administered via IV infusion over 1 hour at doses of 50, 100, 200, and 400 mg, showed that elimination of rezafungin appears multiphasic with a long apparent terminal half-life (mean $t_{½}$ ranged from 127 to 146 hours; Figure 9). The area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) increased in a dose-proportional manner, indicating linear kinetics. Mean total body clearance was slow (approximately 0.2 L/h) throughout the dose levels, and mean volume of distribution at steady-state and mean apparent volume of distribution during the terminal phase ranged from 33 to 48 L.

Figure 9: Single-Dose Pharmacokinetics of IV Rezafungin



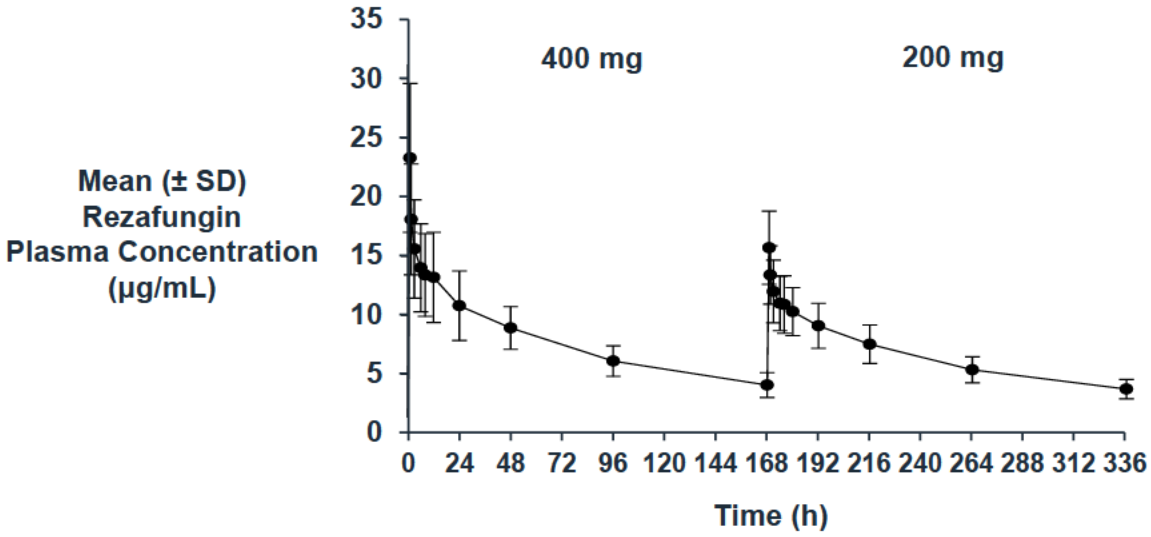
CD101: rezafungin

In the human multiple-dose administration (MAD) study (CD101.IV.1.02), rezafungin was administered at doses of 100 mg × 2 doses, 200 mg × 2 doses, and 400 mg × 3 doses as an IV infusion over 1 hour (± 5 minutes) and doses were separated by 7 days (i.e., once weekly). Exposures following the first dose were comparable to those observed in the SAD study, with AUC and C_{max} generally increasing in a dose-proportional manner. Minor accumulation was observed for the 400 mg dose; 1.74-fold as measured by C_{max} ratio or 1.55-fold as measured by the $AUC_{0\text{-}168}$ ratio of last/first dose after 3 doses.

Fecal excretion was found to be the major route of elimination, accounting for approximately 74.3% of the recovered radioactivity, with 25.7% in urine in a human study using radiolabeled rezafungin. Metabolism was confirmed to be minor for rezafungin as the vast majority of circulating and excreted radioactivity was unchanged rezafungin (Ong 2022).

In the drug-drug interaction study (CD101.IV.1.17), the pharmacokinetics of rezafungin were determined using the Phase 3 dosing regimen of 400 mg followed by 200 mg once-weekly. The mean plasma concentration-time profiles are shown in Figure 10. After the first dose (400 mg), AUC values are maintained with subsequent doses (200 mg).

Figure 10: Pharmacokinetics of Rezafungin 400 mg Dose Followed by 200 mg Dose



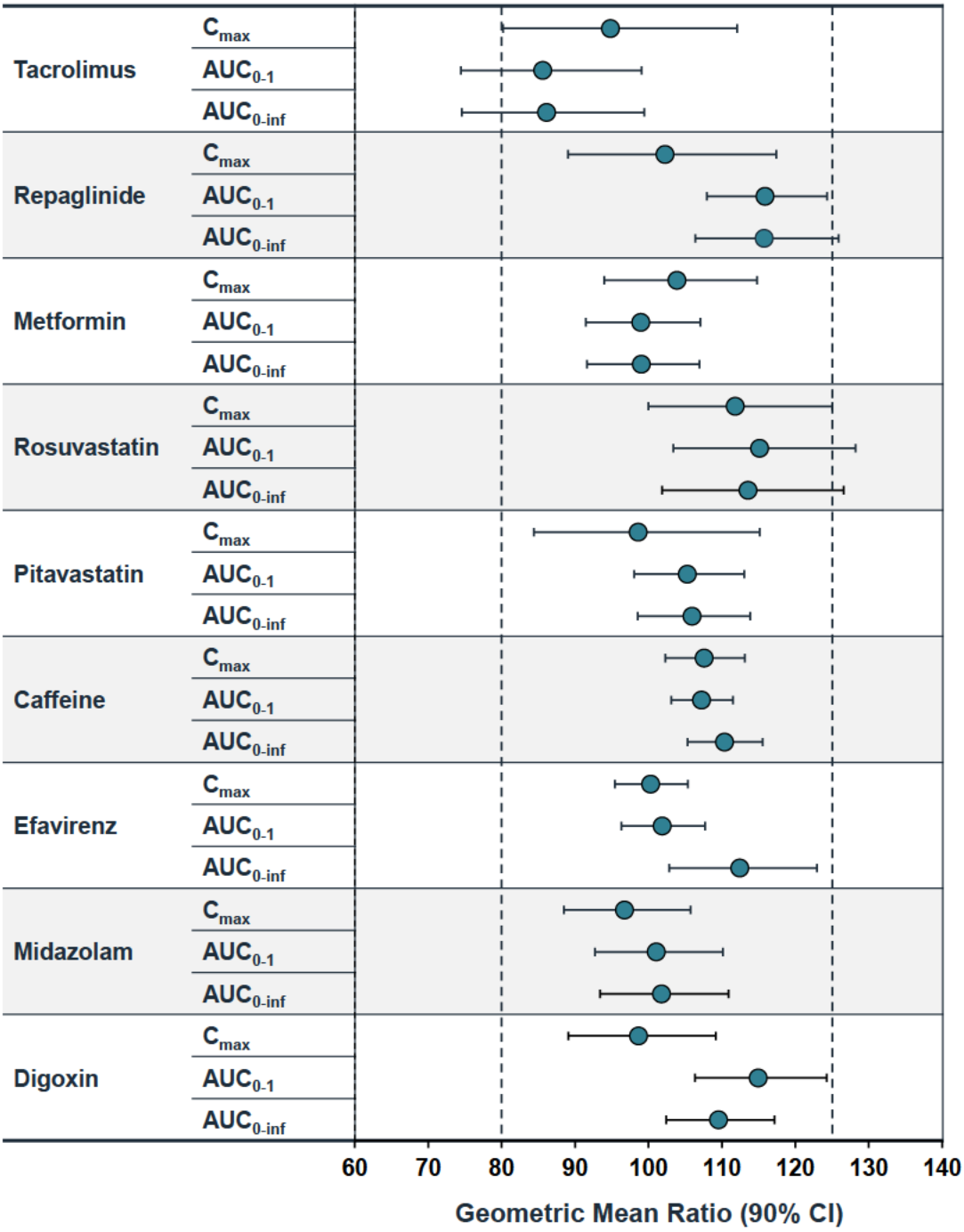
SD: standard deviation

The effect of rezafungin on the QT interval and other electrocardiogram (ECG) intervals has been assessed in healthy adult participants (CD101.IV.1.06). The doses of rezafungin administered were 600 mg and 1,400 mg, selected to achieve relevant therapeutic and supratherapeutic exposures, respectively. Rezafungin, in single doses of up to 1,400 mg did not prolong the QT interval. There were no clinically significant findings in other cardiac parameters, including heart rate, PR interval, and QRS interval, compared to placebo. Echocardiogram results post-dose were normal in all participants, indicating no effect on cardiac contractility or ejection fraction for single doses of rezafungin of up to 1,400 mg.

5.1.2.1 Drug-Drug Interactions

The drug-drug interaction potential of rezafungin with a number of probe substrates of cytochrome P450 enzymes and/or drug transporter proteins was assessed in a study in healthy volunteers (CD101.IV.1.09). Participants were dosed with each of 3 cocktails: tacrolimus (CYP3A and P-gp) and repaglinide (CYP2C8 and OATP); metformin (OCT-1 and OCT-2 and MATE1 and MATE2), rosuvastatin (BCRP and OATP), and pitavastatin (OATP); caffeine (CYP1A2), efavirenz (CYP2B6), midazolam (CYP3A4), and digoxin (P-gp), alone and in combination with rezafungin (600 mg with tacrolimus and repaglinide; 400 mg for the remaining 2 cocktails), in a single-sequence cross-over study. No clinically relevant drug interactions were observed, therefore the need for dose adjustments is considered unlikely for drugs that are substrates for these cytochrome P450 enzymes and drug transporter proteins, when administered with rezafungin (Figure 11). In addition, no clinically relevant drug interaction was observed with tacrolimus, which is also a likely co-medication, therefore no dose adjustment is necessary for tacrolimus when administered with rezafungin.

Figure 11: Geometric Mean Ratio and 90% CI of Probe Drugs when Administered with Rezafungin Relative to Probe Drugs



Cmax: maximum plasma concentration; AUC: area under the concentration-time curve

A second drug-drug interaction study was performed in healthy participants to assess the potential of rezafungin to interact with a number of drugs likely to be co-administered with rezafungin, namely cyclosporine, ibrutinib, mycophenolate mofetil, and venetoclax (CD101.IV.1.17). Participants were dosed with the drugs alone and in combination with rezafungin (400 mg with cyclosporine and 200 mg with the other drugs), in a sequential, cross-over design. No clinically meaningful drug interactions were observed. Therefore, no dose adjustments are necessary for cyclosporine, ibrutinib, mycophenolate mofetil, and venetoclax when administered with rezafungin.

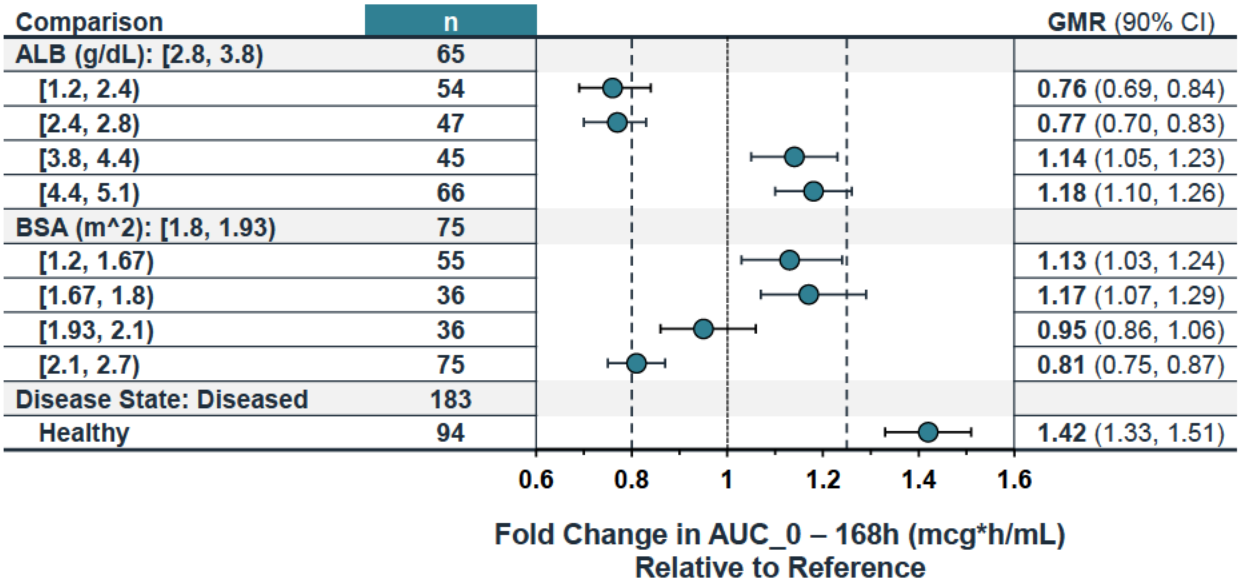
5.1.2.2 Population PK Modeling

Throughout the clinical development of rezafungin, population PK modeling has been utilized to guide dose selection. The initial population PK model was developed using data from the single- and multiple-ascending dose studies in healthy participants (Lakota 2018) and used set doses for Phase 2 based on nonclinical PK/PD data (Bader 2018). The inclusion of data from Phase 2 STRIVE Part A and an additional Phase 1 study was added to update the structural model and evaluate covariate effects (Rubino 2021). The results of these studies were used to inform dose selection for Phase 3, as described in Section 6.2 Dose Selection.

The final PK model was developed based upon data from 5 Phase 1 studies (CD101.IV.1.01, CD101.IV.1.02, CD101.IV.1.06, CD101.IV.1.07, and CD101.IV.1.15), the Phase 2 study (STRIVE), and the Phase 3 study (ReSTORE). The model found to best describe the available data was a 3-compartment model with first-order elimination characterized by the PK parameters clearance, central volume of distribution (V1), shared parameter of peripheral volume of distribution for both peripheral compartments (V23), intercompartmental clearance 1 (Q2), and intercompartmental clearance 2 (Q3). The variability model included interindividual variability in clearance, V1, and V23 and their covariabilities, and a proportional residual variability model.

Albumin concentrations, body surface area, and disease state were found to be statistically significant covariates and included in the final population PK model (Figure 12). Disease state was defined as patients from the Phase 2 and Phase 3 studies (STRIVE and ReSTORE, respectively) and hepatically impaired participants (CD101.IV.1.15). This was primarily to account for confounding albumin concentrations, which were only within normal ranges in healthy individuals and predominantly below normal ranges in patients. Other factors assessed, including sex, race, age, liver function tests, and estimated creatinine clearance did not explain the variability in the PK of rezafungin. Individual rezafungin PK exposure estimates in patients were calculated to further evaluate intrinsic factors, as well as for exposure response analyses. The PK model was also used to generate Monte Carlo simulated exposures for target attainment analyses.

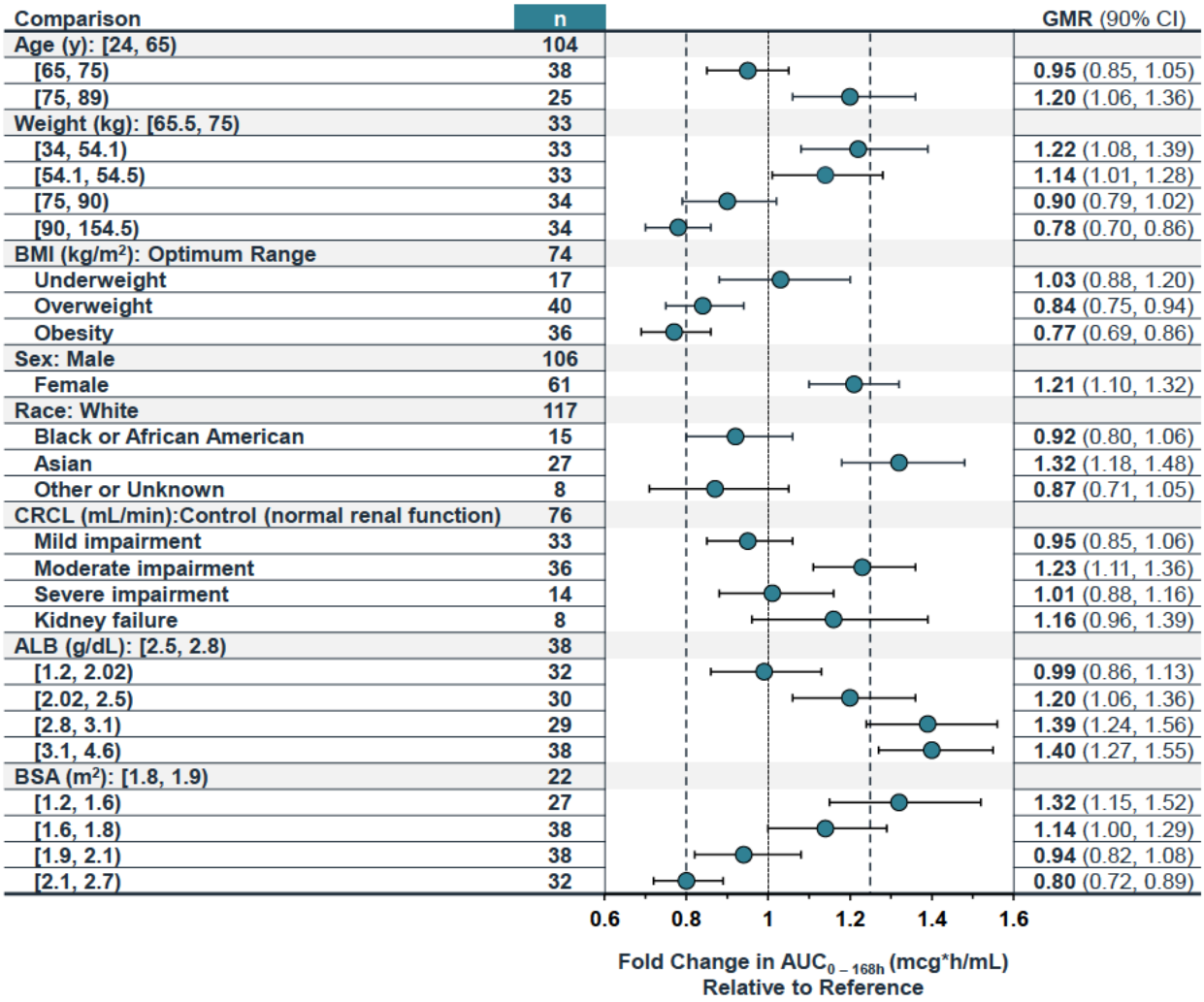
Figure 12: Forest Plots Illustrating the Impact of Covariate Effects in the Final Population Pharmacokinetic Model on Rezafungin Exposure Following a Single 400 mg Dose, All Participants



ALB: albumin; AUC_{0-168h}: area under the concentration-time curve from time 0 to 168 hours or time of next dose if next dose given before 168 hours; BSA: body surface area; n: the number of participants in each group.
Reference values are the middle quintile for continuous variables, or as stated.
[or] indicates respective endpoint is included in the interval.
(or) indicates respective endpoint is not included in the interval.

The overall variability in rezafungin PK exposure across a wide range of patient factors, including those included in the model, did not result in marked differences between predefined categories or relative to the median quintile for continuous variables (Figure 13). Overall geometric mean and 90% CI were within 0.6 to 1.6 for all comparisons, indicating that a single rezafungin dose regimen is appropriate for all adults.

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



ALB: albumin; $AUC_{0–168h}$, area under the concentration-time curve from time 0 to 168 hours or time of next dose if next dose given before 168 hours; BMI: body mass index; BSA: body surface area; n: the number of participants in each group; CRCL: creatinine clearance.
Reference values are the middle quintile for continuous variables, or as stated.
[or] indicates respective endpoint is included in the interval.
(or) indicates respective endpoint is not included in the interval.

5.1.2.3 Patient Populations

Elderly

A population PK analysis, including data from Phase 1, Phase 2, and Phase 3 studies, showed that age was not a significant covariate of rezafungin PK. No dose adjustments are required in elderly patients aged 65 years or more.

Sex

A population PK analysis, including data from Phase 1, Phase 2, and Phase 3 studies, showed that sex was not a significant covariate of rezafungin PK.

Race

A population PK analysis, including data from Phase 1, Phase 2, and Phase 3 studies, showed that race was not a significant covariate of rezafungin PK.

Weight: Obesity or Low Body Weight Patients

A population PK analysis, including data from Phase 1, Phase 2, and Phase 3 studies, showed that body surface area (BSA) was a significant covariate of rezafungin PK. Differences in exposure (AUC_{0-168h}) across the BSA range were not considered clinically meaningful. Though not included in the model, other body size measures (weight or body mass index [BMI]) are highly correlated with BSA and would also correlate to rezafungin exposure. Relative to patients with ideal body weight (BMI 18.5 to < 25 kg/m^2), rezafungin exposure in clinically obese (BMI ≥ 30 kg/m^2) patients from Phase 2 STRIVE and Phase 3 ReSTORE studies was reduced by ~ 23%, which is not considered clinically meaningful (Figure 13). Rezafungin exposure in underweight patients (BMI < 18.5 kg/m^2) was approximately the same as in those with ideal body weight. No dose adjustments are required for obese or low body weight patients.

Individuals with Renal Impairment

A population PK analysis, including data from Phase 1, Phase 2, and Phase 3 studies, showed that measures of renal function, serum creatinine and creatinine clearance, were not significant covariates of rezafungin PK. No dose adjustments are required for patients with renal impairment.

Individuals with Hepatic Impairment

The PK of rezafungin (400 mg) was assessed in participants with moderate (Child-Pugh B, n=8) and severe (Child-Pugh C, n=8) hepatic impairment (CD101.IV.1.15). Mean rezafungin exposure was reduced by approximately 30% in participants with moderate and severe hepatic impairment compared to matched participants with normal hepatic function. Rezafungin PKs were similar in participants with moderate and severe hepatic impairment, did not change with increasing degree of hepatic impairment, and importantly were similar to concentrations achieved in patients with candidemia and invasive candidiasis due to similarities in important PK covariates such as albumin which is an important component in the Child-Pugh score. Hepatic impairment did not have a clinically meaningful effect on rezafungin PK, therefore, a dose adjustment in patients with hepatic impairment is not necessary.

5.2 Microbiology

5.2.1 Spectrum and Potency

During profiling and surveillance studies conducted throughout development, the in vitro activity of rezafungin was consistent with that observed for other currently utilized echinocandins and in particular for anidulafungin from which it was derived.

Surveillance studies that have been performed with rezafungin since 2014 have demonstrated a consistent activity profile for rezafungin, with no apparent difference in MIC distribution over time and with low MIC/$MEC_{50/90}$ (minimum inhibitory and effective concentrations to inhibit 50% and 90% of isolates tested, respectively) values against most *Candida* spp. and *Aspergillus* spp. isolates, characteristic of the echinocandin class (Table 8; Pfaller 2017a; Pfaller 2017b; Pfaller 2020; Carvalhaes 2022a; Carvalhaes 2022c).

Table 8: In Vitro Activity of Rezafungin and Other Echinocandins

***Candida* species (n)**	**$MIC_{50/90}$ (range) (µg/mL)**			
	Rezafungin	**Anidulafungin**	**Caspofungin**	**Micafungin**
C. albicans (2,370)	0.03/0.06 (0.002–0.5)	0.015/0.06 (0.002–1)	0.015/0.03 (0.002–2)	0.015/0.03 (0.002–2)
C. glabrata (1,054)	0.06/0.12 (0.002–4)	0.06/0.12 (0.008–4)	0.03/0.06 (0.004–8)	0.015/0.03 (0.004–4)
C. parapsilosis (897)	1/2 (0.015–4)	2/4 (0.015–8)	0.25/0.5 (0.015–2)	1/1 (0.008–2)
C. tropicalis (557)	0.03/0.06 (0.008–2)	0.03/0.06 (0.004–1)	0.03/0.06 (0.002-> 8)	0.03/0.06 (0.008–2)
C. krusei (172)	0.03/0.06 (0.008–0.12)	0.06/0.12 (0.015–0.25)	0.12/0.25 (0.015–0.5)	0.06/0.12 (0.15–0.25)
C. dubliniensis (179)	0.06/0.12 (0.002–0.25)	0.03/0.12 (0.008–0.12)	0.03/0.06 (0.015–0.25)	0.015/0.03 (0.008–0.12)

MIC: minimum inhibitory concentration

Candida spp. clinical isolates collected in JMI international SENTRY Antifungal Surveillance Program 2014–2021

*CLSI methodology employed for MIC (M27) determination

5.2.2 Development and Mechanism of Resistance

Overall, the potential for development of resistance to rezafungin in vitro as assessed during spontaneous mutation frequency and serial passage assays was low and was consistent with the echinocandin comparators (Locke 2016). Of note, following 20 passages under selection with rezafungin, all *C. albicans*, *C. krusei*, and *C. glabrata* strains evaluated still had rezafungin MIC values ≤ 1 µg/mL.

Mutations in *FKS* genes arising under selective pressure from rezafungin also conferred cross-resistance to approved echinocandins, and vice versa. This susceptibility trend is consistent with rezafungin and comparator echinocandins when tested against clinical *Candida* spp. isolates possessing Fks alterations (Locke 2016; Pfaller 2016).

An in vitro mutant prevention concentration study for rezafungin against *C. albicans* and *C. glabrata* determined this value to be 16 µg/mL, equivalent to that of micafungin (Zhao 2016).

5.2.3 In Vitro Time-Kill Kinetic Assays

In vitro time-kill kinetic assays demonstrated sustained fungicidal activity of rezafungin against wild-type *Candida* spp. isolates at multiples of the MIC consistent with that observed for comparator echinocandins, and this killing was also observed for rezafungin with a subset of *fks* mutant isolates (Hall 2017; data on file). Although fungicidal activity against *C. auris* isolates was not sustainably achieved, rezafungin performed similarly or better than approved echinocandins at physiologically relevant concentrations (Kovacs 2021).

5.2.4 Post-Antifungal Effect

The post-antifungal effect (PAFE) was evaluated in 2 separate studies where *Candida* spp. were exposed to rezafungin and other echinocandins, and re-growth following drug removal was monitored (Carvalhaes 2022b; data on file). In both studies, rezafungin yielded PAFE values consistent with those of the comparator echinocandins and demonstrated prolonged PAFE for some of the evaluated isolates as has been documented for this class (Manavathu 2004; Ernst 2000).

5.2.5 Biofilm Activity

Rezafungin activity against biofilms of *Pneumocystis jirovecii* (formerly *P. carinii*) and *C. albicans* was also evaluated in separate studies to investigate biofilm prevention and disruption. Rezafungin was able to inhibit biofilm formation and was active against established biofilms for both organisms (Cushion 2018; Chandra 2018).

5.2.6 Antimicrobial Interaction Studies

The potential for rezafungin to interact with representatives of all major anti-infective drug classes (antibacterial and antifungal) was evaluated in in vitro checkerboard assays against a variety of clinically relevant genera of fungi (yeasts and molds) and bacteria (Gram-positive and -negative). Rezafungin was tested in combination with 16 antimicrobial drugs (4 antifungal and 12 antibacterial) against 13 strains (11 fungal and 2 bacterial). All drug combinations against all strains using standard echinocandin susceptibility readouts (e.g., MIC, MEC) for rezafungin generated synergistic, additive, or indifferent interactions. The lack of antagonism suggests that there is a low intrinsic potential for rezafungin to negatively impact, or have its activity negatively impacted by, other anti-infective drugs.

5.3 Target Attainment

Rezafungin PK/PD studies of 24 hours to one week across a broad range of exposures showed dose-proportional efficacy for rezafungin that correlated strongly with free-drug C_{max}/MIC and free-drug $AUC_{0–24}$/MIC ratio, as has been observed with other echinocandins. This concentration-/exposure-dependent pattern of fungicidal activity for rezafungin has important implications for dose regimen selection and, in subsequent studies, the free-drug AUC/MIC ratio was chosen as the PK/PD index, as it is more robustly calculated than C_{max}, with less dependence on sampling times.

At partially effective doses in an extended dosing PK/PD study in an established disseminated *C. albicans* candidiasis model, the importance of front-loading was established (Lakota 2017). The simulated concentration-time profiles for 3 different rezafungin fractionated dosing regimens providing the same weekly dose divided once, twice, or seven times a week is shown in Figure 14. Figure 15 shows the change in log_{10} colony-forming units (CFU) in the animals dosed with these regimens. Once-daily dosing was similar to control, and twice-weekly only produced stasis, whereas the once-weekly dosing regimen provided the greatest efficacy.

Figure 14: Simulated Free-Drug Concentration-Time Profiles for the fractionated Rezafungin 2 mg/kg regimens

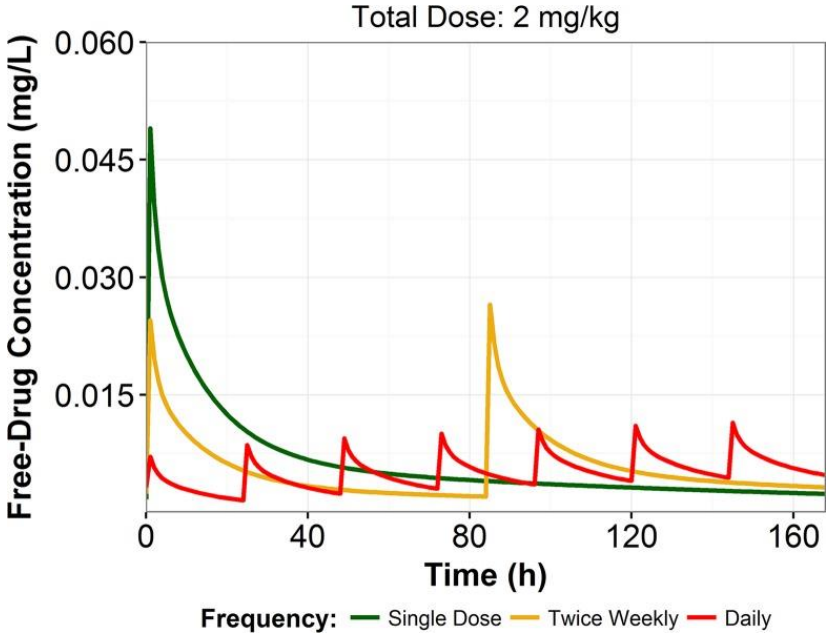


Figure 15: Mean Change and Range of Change in Log_{10} CFU from the Baseline at 168 h after Administration of Rezafungin (2 mg/kg) by Fractionation Schedule

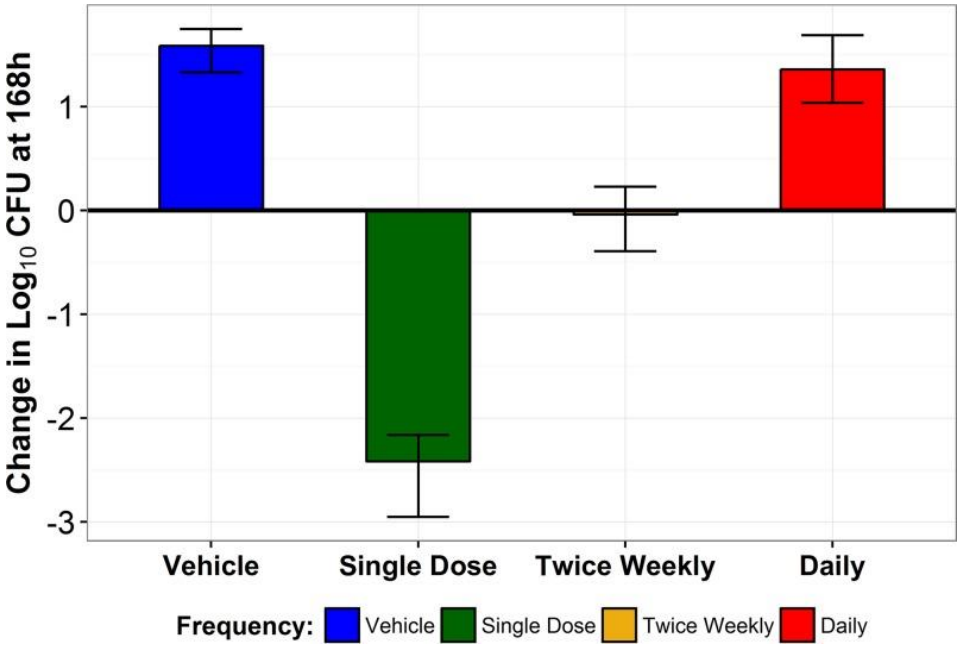


Figure 16 shows the estimated PK/PD target attainment for stasis and 1-log kill in CFU using CLSI broth microdilution methodology to calculate MIC, over the *Candida* species MIC distribution, separately for each species. The bars represent the observed distribution of MIC values from a compilation of data derived in upwards of 12 studies for each species (e.g., 2014-2020 SENTRY surveillance data and 5 additional clinical isolate susceptibility study datasets; Zhao 2016, Pfaller 2016, Boikov 2017, Hall 2017, Pfaller 2017a, Pfaller 2017b, Toth 2019, Pfaller 2020, Carvalhaes 2022a). The grey horizontal line represents the simulated probability of target attainment for the first dose of 400 mg rezafungin from Monte Carlo simulation using the final PopPK model described in Section 5.1.2.2.

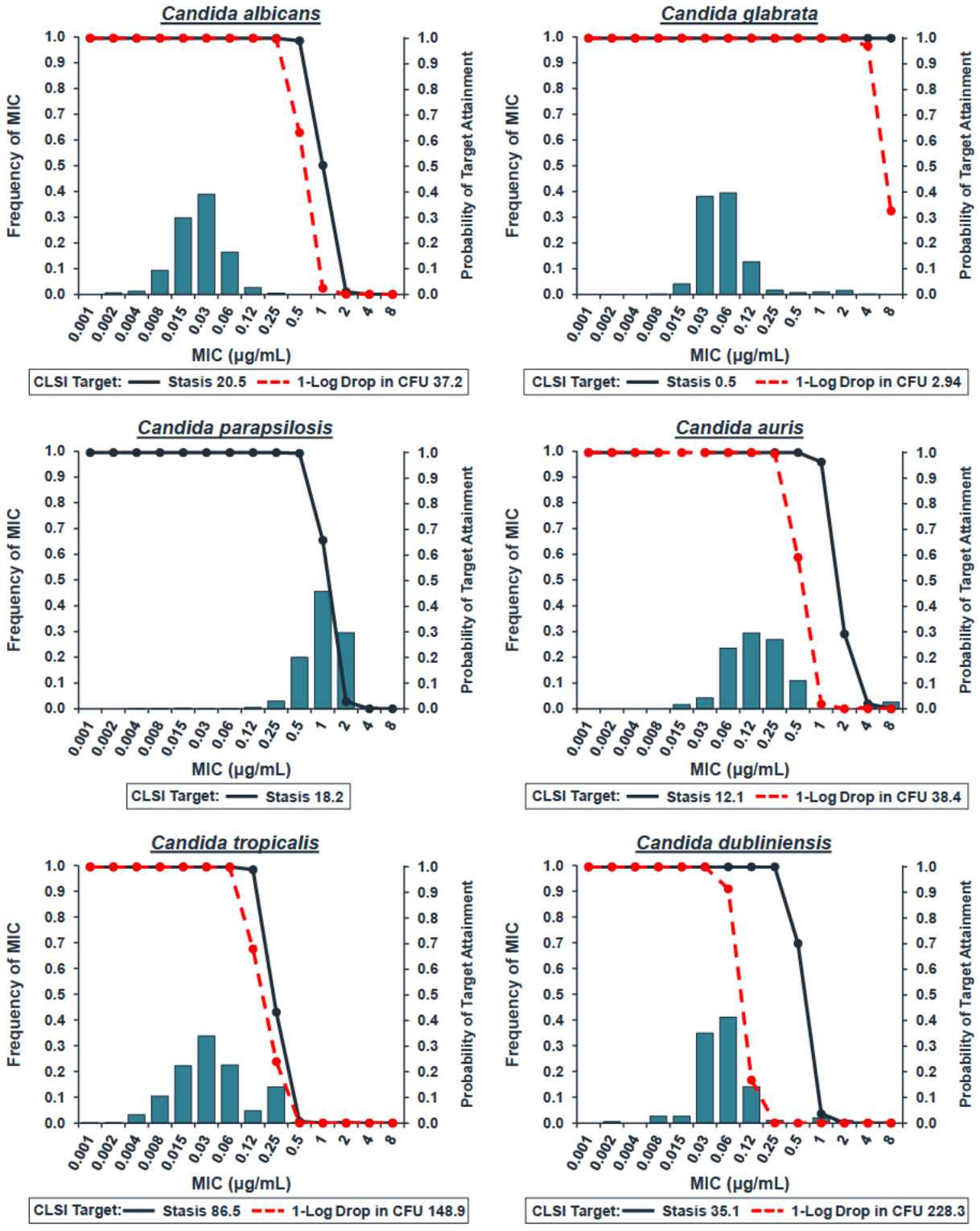
For *C. albicans*, the simulated probabilities of target attainment for both stasis and 1-log kill were ≥ 90% at MIC values ≤ 0.25 µg/mL, while the probability approached zero for MIC values > 0.5 µg/mL for 1-log kill in CFU and > 1 µg/mL for stasis. For *C. glabrata*, the simulated probabilities of target attainment for both targets were ≥ 90% at MIC values of 4 µg/mL. Of note, 2 of the 3 *C. glabrata* target attainment modeling strains possessed Fks alterations (F659V and F659S) and had elevated rezafungin MIC values (1 and 0.5 µg/mL, respectively) (Lepak 2018). For *C. parapsilosis*, the simulated probabilities of target attainment for the stasis target were ≥ 90% at MIC values 0.5 µg/mL, whereas most of the MIC distribution is above this value, as has been observed with other echinocandins. This is believed to be attributed to an artificially high nonclinical target due to the difficulty in establishing infection in mice for this lesser mouse-virulent *Candida* species. As a result, the PK/PD targets may be elevated for this

fit subset of *C. parapsilosis* wild-type strains amenable for use in target attainment modeling studies (Andes 2010). For *C. auris*, the simulated probabilities of target attainment for both targets were ≥ 90% at MIC values ≤ 0.25 µg/mL. For *C. tropicalis*, the simulated probabilities of target attainment for both targets were ≥ 90% at MIC values ≤ 0.06 µg/mL. For *C. dubliniensis*, the simulated probabilities of target attainment for both targets were > 90% at MIC values ≤ 0.06 µg/mL.

In the clinic, all patients in the Phase 2 and 3 studies achieved their *f*AUC/MIC targets for the species which Cidara has characterized except for 3 patients with *C. parapsilosis* infections. It should be noted that all 3 of these were clinical cures at Days 5 and 14, demonstrating the apparent disconnect seen with other echinocandins, where nonclinical efficacy targets are much higher than needed clinically.

In conclusion, rezafungin achieves target attainment for important *Candida* species.

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



AUC: area under the concentration-time curve; CFU: colony-forming units; CLSI: Clinical and Laboratory Standards Institute; *f:* free; MIC: minimum inhibitory concentration; PD: pharmacodynamic; PK: pharmacokinetic.

5.4 Provisional Clinical Susceptible Breakpoints

The CLSI Subcommittee on Antifungal Susceptibility Tests approval of provisional clinical “susceptible” breakpoints for rezafungin for common *Candida* spp. included a breakpoint for *C. glabrata* of ≤ 0.5 µg/mL that exceeds the established susceptible breakpoints for anidulafungin (≤ 0.125 µg/mL), caspofungin (≤ 0.125 µg/mL), and micafungin (≤ 0.06 µg/mL) (CLSI M27M44S Ed3 2022).

Even as the epidemiology of *C. glabrata* shifts towards reduced susceptibility to echinocandins, rezafungin is better positioned to treat infections caused by isolates with higher MICs. In addition, the CLSI granted rezafungin a provisional susceptible breakpoint of ≤ 0.5 µg/mL for *C. auris* which covers the MIC required to inhibit the growth of all wild-type *C. auris* isolates (N=157) evaluated to date, and marks the first CLSI breakpoint for this emerging non-*albicans Candida* spp. threat.

Although *C. auris* was not observed in Phase 2 STRIVE or Phase 3 ReSTORE, nonclinical data support rezafungin as a treatment option for this new threat and unmet medical need.

5.5 Nonclinical Safety

A comprehensive nonclinical safety package to support clinical development of rezafungin has been conducted, including IV toxicology studies in rats and cynomolgus monkeys of up to 6 months duration, and a full battery of genotoxicity, reproductive/developmental, local tolerance, and phototoxicity studies.

In rats, rezafungin induced an acute histamine-release response which was also observed with caspofungin and micafungin in rats, but has not been observed in monkeys, and is considered to be of minimal consequence in the clinic. Minor hematological findings were observed in rats in studies of up to 3 months duration (once every 3-day dosing) at the highest rezafungin dose (45 mg/kg), including signs of hemolysis and regenerative anemia, which were also observed following anidulafungin and micafungin in rats. These changes have not been observed in monkeys or humans with rezafungin, caspofungin, or anidulafungin, but signs of hemolysis have been observed in dogs and humans with micafungin. In addition, minor clinical chemistry changes were observed in rats at the high dose in studies of up to 6 months duration, but were not considered toxicologically significant, as these changes were always without microscopic correlates. In the rat chronic toxicity study (once-weekly dosing), which included detailed neuropathology evaluations (both central and peripheral nervous systems) and longitudinal neurobehavioral test batteries, 6-month results demonstrated only Schwann cell phospholipidosis without any other noteworthy microscopic or neurobehavioral changes. Phospholipidosis was confined to Schwann cells and showed complete or partial reversal after a 26-week recovery period. The AUC plasma levels at the reported no-observed-adverse-effect level (NOAEL) in repeat-dose safety studies in rats at study durations of 1, 3, and 6 months were 6-fold, 7-fold, and 4- to 5-fold, respectively, over the clinical AUC exposure.

In monkeys, similar to rats, minor clinical chemistry changes were observed at 30 mg/kg in studies up to 6 months duration but were not considered toxicologically significant as these changes were always without microscopic correlates. In monkey studies of 3-months duration (once every 3-day dosing), the high dose of 60 mg/kg (> 15-fold over clinical AUC exposure) exceeded the maximum tolerated dose, with animals displaying declining condition and tremors. Generally minor, barely perceptible tremoring that was considered non-adverse was also recorded occasionally for some monkeys administered 30 mg/kg (9-fold over the clinical AUC exposure). A comprehensive neuropathology assessment was conducted, which included whole-body perfusions to maintain cell architecture and detailed exams of the brain, brain stem, spinal cord, and peripheral ganglia/nerves (paraffin and plastic sections), along with special stains and electron microscopy to diagnose light microscopic findings. This evaluation identified phospholipidosis in Schwann cells of ganglia and peripheral nerves as the primary finding, with no meaningful change in nerve conduction, and no qualitative or quantitative changes in axon-myelin ratio of peripheral nerves (i.e., no myelinopathies).

In the 6-month monkey study, because barely perceptible tremors had been previously documented in control animals, and to avoid any potential bias in recording neurobehavioral measures, staff conducting the examinations and recording the in-life data were blinded to the dose administered to individual animals, in contrast to the unblinded 3-month monkey studies. Throughout the 6-month monkey study (once-weekly dosing), daily blinded abbreviated neurobehavioral measures by technical staff and weekly blinded full exams by the veterinary staff found no rezafungin-related effects on tremoring but rather generalized tremor observations were noted in all groups (including controls) that represented a set of minor background findings in the monkeys in the study. Nerve conduction evaluations of both motor and sensory nerves remained within normal functional ranges throughout the dosing period and during recovery. A detailed neuropathology exam was conducted that found Schwann cell phospholipidosis to dramatically reduce by the end of the 52-week recovery period. No nerve/axonal degeneration or demyelination was present at the end of the dosing or recovery periods.

The reported monkey NOAEL was 30 mg/kg in the 1-month and 3-month safety studies when administered every 3 days (9-fold the clinical AUC exposure) and 30 mg/kg after 6 months of once-weekly dosing (6-fold the clinical AUC exposure).

Embryo-fetal development studies in pregnant rats demonstrated an expected transient histamine-release response at rezafungin doses of 15 mg/kg and above but no reproductive nor developmental toxicity at doses of up to 45 mg/kg (5-fold the clinical AUC exposure). In pregnant rabbits, lower mean body weight gains were reported at the high dose of 35 mg/kg (3-fold the clinical AUC exposure) but no effects on reproductive or developmental toxicity were observed. Rezafungin did not affect mating or fertility in male and female rats following IV administration at doses of up to 45 mg/kg. In a pre- and post-natal development study in rats, at doses of up to 45 mg/kg, there were no adverse effects on offspring growth, maturation, or measures of neurobehavioral or reproductive function.

Rezafungin was not genotoxic in a standard battery of in vitro and in vivo assays. Rezafungin did show a minimal phototoxic response after multiple doses in rats. The human formulation of rezafungin (rezafungin for injection) demonstrated no potential for vascular irritation.

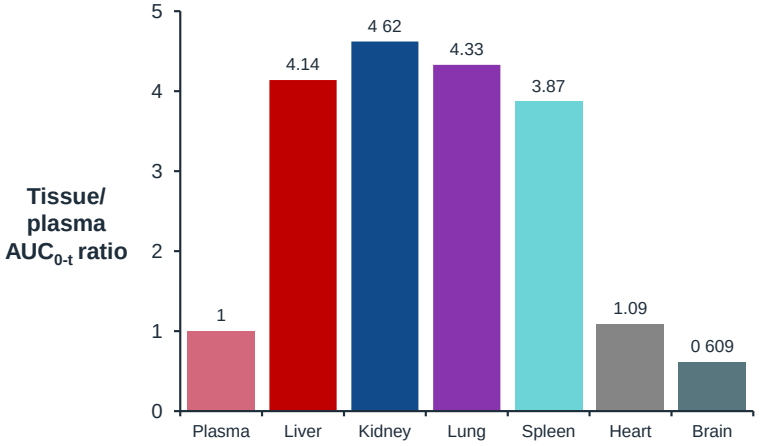
The nonclinical safety results generated support the safety profile and registration of rezafungin in patients at the proposed single 400 mg dose on Day 1, followed by 200 mg dose on Day 8 and once weekly thereafter for up to a 4-week treatment for candidemia and invasive candidiasis

5.6 Distribution

Like other echinocandins, protein binding of rezafungin is high across different animal species and humans (> 97%), but higher in mouse (primary animal efficacy model) than in human plasma. The mean/median protein binding in mouse and human plasma are 99.2% and 97.4%, respectively. Corresponding mean/median % free-drug values were 0.8% and 2.6% in mouse and human plasma, respectively, indicating that there is a higher free-fraction of drug available in humans for pharmacological efficacy.

Tissue distribution was evaluated in rats after IV administration of rezafungin, demonstrating widespread exposure in various organs, with tissue/plasma AUC ratios that were comparable (and approximately 4-fold higher in tissue than plasma) for major organs (kidney, lung, liver, spleen), with exceptions of the heart and brain (Figure 17). Subsequent studies in the rat and monkey with [^{14}C]-radiolabeled rezafungin and quantitative whole-body autoradiography (QWBA) confirmed the widespread tissue distribution with drug-derived radioactivity detectable in nearly all tissues through 865 hours (50 of 54 sampled tissues) following a single IV dose administration.

Figure 17: Distribution of Rezafungin in Major Organs



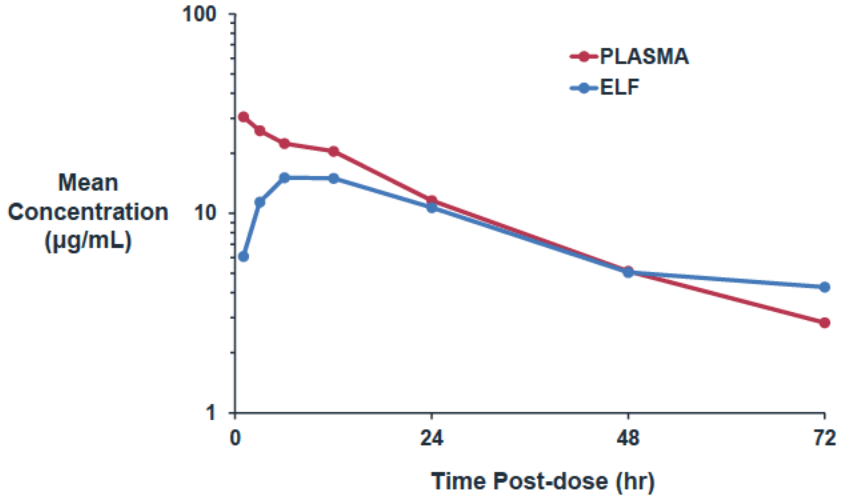
AUC: area under the concentration-time curve
Source: Ong 2017

A study in mice was conducted to determine rezafungin penetration into the respiratory tract epithelial lining fluid (ELF). In the study, rezafungin (20 mg/kg intraperitoneal injection [IP] in the mouse is approximately the human 400 mg equivalent AUC exposure dose) was administered IP to female ICR mice.

The mean concentration-time profiles are shown in Figure 18. Following rezafungin administration, the mean C_{max} measured was 30.5 µg/mL, observed at 1-hour post-dose, the first collection time point. The corresponding mean plasma AUC_{last} and AUC_{inf} were 762 and 848 µg × hr/mL, respectively, with a half-life of 21.1 hours. The mean maximum ELF concentration measured was 15.1 µg/mL, which was reached at 6 hours post-dose. Rezafungin concentrations were comparable between plasma and ELF beyond 24 hours post-dose. Corresponding mean ELF AUC_{last} and AUC_{inf} were 606 and 802 µg×hr/mL, respectively, with a half-life of 31.9 hours. Based on AUC exposure ratios of ELF/plasma, the distribution of rezafungin from plasma into respiratory tract ELF is close to unity (0.80 and 0.95 based AUC_{last} and AUC_{inf}, respectively).

As respiratory tract ELF levels are free-drug concentrations, while plasma concentrations represent total-drug (free plus protein-bound), plasma concentrations were also corrected for mouse plasma protein binding (99.2%, or 0.8% free fraction). For comparison, although the ELF/Plasma AUC_{last} ratio was 0.80 for total-drug exposures, the same ratio was 100 based on free-drug exposures.

Figure 18: Mean Concentration by Time of Respiratory Tract Epithelial Lining Fluid in the Mouse



Conc: concentration; ELF: epithelial lining fluid

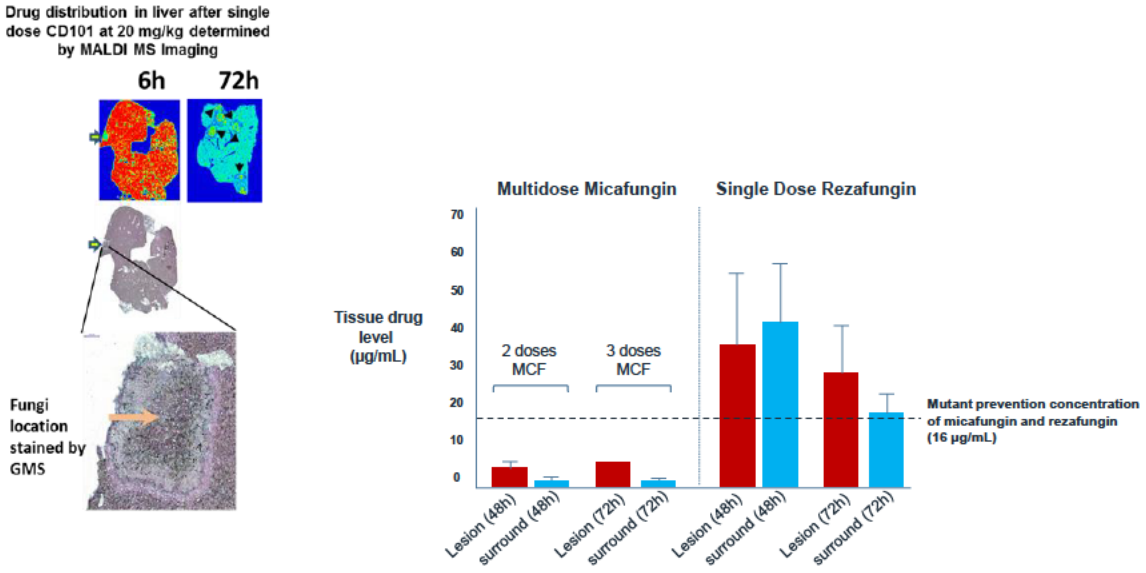
Tissue distribution of rezafungin was also investigated using a novel matrix-assisted laser desorption ionization mass spectrometry imaging (MALDI-MSI) technique in an immunocompetent invasive candidiasis mouse model (Zhao 2017).

C. albicans strain SC5314 was inoculated at 1×10^7 CFU in sterile stools and saline to induce peritonitis and abscess formation. A single dose of IP rezafungin at 20 mg/kg

(equivalent to human 400 AUC exposure) was given on Day 3 post-inoculation and compared with once-daily treatment of micafungin at 5 mg/kg (equivalent to human 150 mg therapeutic exposure) starting on Day 3 post-inoculation, with a total of 3 doses of micafungin administered. Livers and kidneys were collected at up to 72 hours post-first dose of each drug for MALDI imaging as well as drug concentration determination.

It was observed that even as drug levels in the tissue declined, rezafungin was concentrated within the lesion 6 hours post-dose in both liver and kidney tissue. For example, it was noted that rezafungin had an extensive tissue distribution with a drug level of 80.1 µg/mL in the non-lesion part of liver at 6 hours after a single dose treatment at 20 mg/kg (Zhao 2017; Figure 19). Importantly, rezafungin was observed to quickly penetrate into abscesses as early as 3 hours and rapidly reach the necrotic core interacting with the main fungal population at 6 hours, with an average of 31.6 µg/mL drug in lesions (Zhao 2017). Given the long half-life of rezafungin, sustained drug penetration and accumulation within the lesion was continuously observed for all remaining time points included in the study. At the last time point of 72 hours following a single dose of rezafungin, drug levels inside the lesions were still close to 30 µg/mL, about 6-fold higher than that for micafungin at steady state (after 3 doses). Micafungin was found to penetrate more slowly into liver and kidney abscesses and reached detectable levels inside lesions at 6 hours after the first dose. The penetration improved upon multiple doses of treatment, and only at steady state were drug signals observed from the necrotic core, where a large number of fungal cells were found to proliferate. In this in vivo study, rezafungin demonstrated superior penetration and concentration at the site of the abscess versus micafungin, suggesting that rezafungin offers the potential to fill an unmet need in patients with invasive candidiasis. The mutant prevention concentration for rezafungin (16 µg/mL) is equivalent to that of micafungin (Zhao 2016), however only rezafungin was able to achieve and sustain these levels. In addition to the therapeutic benefit of higher tissue and lesion drug concentrations, in turn it could also help eliminate this hidden reservoir for echinocandin resistance development (Shields 2014).

Figure 19: Rezafungin Penetrates and Accumulates at a Higher Level at Site of Liver Infection than Micafungin



CD101: rezafungin; GMS: Gömöri methenamine silver stain; MALDI-MS: matrix-assisted laser desorption ionization mass spectrometry; MCF: micafungin

With low clearance, a long t½, widespread penetration into tissues, lack of significant biotransformation, and extensive excretion as unchanged drug, rezafungin is suitable for once-weekly treatment, providing high drug exposures relative to other echinocandins for candidemia and invasive candidiasis.

Additional distribution study results are provided in Appendix Section 10.1.

6 CLINICAL EFFICACY

Summary

- In the Phase 2 STRIVE study:
  - Overall success at Day 14 was 61% in the rezafungin 400/400 mg group, 76% in the rezafungin 400/200 mg group, and 67% in the caspofungin group.
  - 30-day ACM was 24% in the rezafungin 400/400 mg group, 9% in the rezafungin 400/200 mg group, and 16% in the caspofungin group.
  - The 400 mg dose in Week 1 followed by 200 mg once weekly for a total of 2 to 4 doses was found to be an efficacious regimen, and advanced into the Phase 3 study.
- In the Phase 3 ReSTORE study:
  - The primary efficacy endpoint was met. Rezafungin 400/200 mg was noninferior to caspofungin with regard to 30-day ACM.
  - Secondary endpoints supported the primary findings, demonstrating comparable results between groups, including the key secondary endpoint of Global Cure at Day 14 and additional secondary endpoint of mycological success at Day 5 and Day 14.
- Overall, all pre-specified primary and secondary endpoints in both Phase 2 and 3 studies demonstrated rezafungin 400/200 mg is efficacious for the treatment of patients with candidemia and invasive candidiasis.

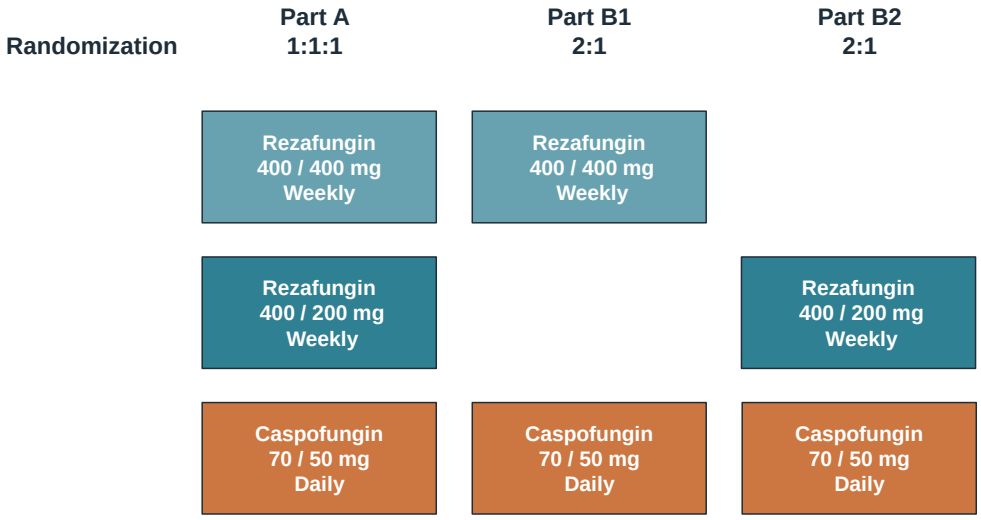
6.1 Phase 2 Study: STRIVE

6.1.1 Study Design Overview

STRIVE was a Phase 2, multicenter, prospective randomized, double-blind 3-part study of rezafungin or caspofungin with optional oral stepdown therapy for treatment of adults with candidemia and/or invasive candidiasis.

The randomization ratios of each study part are illustrated in Figure 20.

Figure 20: STRIVE Study Design: Randomization



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

IV: intravenously

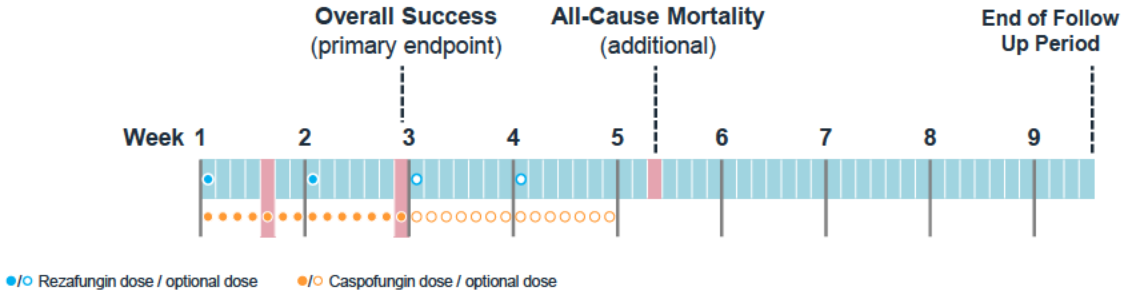
In Part A, patients were randomized 1:1:1 to the following groups:

- Rezafungin 400/400 mg
- Rezafungin 400/200 mg
- Caspofungin 70/50 mg

Part B was conducted to further assess the safety and efficacy of rezafungin and began after 107 patients were enrolled in Part A. Patients enrolled in Part B1 (n=69) were randomized in a 2:1 ratio to rezafungin 400/400 mg or caspofungin, and patients enrolled in Part B2 (n=31) were randomized in a 2:1 ratio to rezafungin 400/200 mg or caspofungin. Since Part B enrollment was enrolling rezafungin 400/400 mg patients while the Part A data were being locked and analyzed, the final dosing decision for Phase 3 (see Section 6.2) also prompted the switch from 400/400 mg (STRIVE B1) to 400/200 mg (STRIVE B2).

Assessments of mycological eradication and clinical response were performed on Day 5 and Day 14; on Day 28, for patients with invasive candidiasis; and at the Follow-up visit (Days 45–52 for patients with candidemia only or Days 52–59 for patients with invasive candidiasis with or without candidemia). Blood cultures were performed daily or every other day until 2 blood cultures drawn ≥ 12 hours apart were negative without an intervening positive culture.

Figure 21: STRIVE Study Design: Dosing Schedule and Endpoints



6.1.2 Treatment Regimen

Patients were randomized to one of the following groups:

- Rezafungin 400/400 mg: rezafungin 400 mg on Day 1 and Day 8; an optional 400 mg dose on Day 15; and for patients with invasive candidiasis (with or without candidemia), an optional 400 mg dose on Day 22.

  Patients received IV saline (placebo for caspofungin) on other study days to maintain the blind.

- Rezafungin 400/200 mg: rezafungin 400 mg on Day 1, 200 mg on Day 8; an optional 200 mg dose on Day 15; and for patients with invasive candidiasis (with or without candidemia), an optional 200 mg dose on Day 22.

  Patients received IV saline (placebo for caspofungin) on other study days to maintain the blind.

- Caspofungin IV: 70 mg loading dose on Day 1 and then 50 mg/day for ≥ 3 days, up to a maximum of 21 days for patients with candidemia only, or up to a maximum of 28 days for patients with invasive candidiasis (with or without candidemia.

In all treatment groups, patients could receive oral stepdown therapy after ≥ 3 days of IV therapy if all of the following criteria were met:

- Able to take oral medication
- ≥ 3 days of IV study drug
- The *Candida* species isolated was susceptible to fluconazole
- The patient's clinical status was considered stable based on Investigator assessment
- If a blood culture is positive at Screening, 2 post-baseline blood cultures drawn ≥ 12 hours apart were negative for *Candida* spp., without an intervening positive

culture, and the first of the 2 cultures was drawn ≥ 48 hours prior to oral study drug initiation

- No evidence of moderate or severe hepatic insufficiency (ALT or AST > 3 × the ULN)
- No history of hypersensitivity or any other contraindications to the use of fluconazole and in the Investigator's opinion, the patient can tolerate oral fluconazole therapy

Patients in the rezafungin groups who switched to stepdown therapy received oral placebo (for fluconazole) and rezafungin IV once weekly. Patients in the caspofungin group could be switched to oral stepdown therapy with fluconazole (800/400 mg). To maintain the blind, patients who had already switched to oral stepdown therapy received both oral fluconazole daily and IV saline placebo (for rezafungin) once weekly.

6.1.3 Enrollment Criteria

Eligible patients were ≥ 18 years of age with ≥ 1 systemic sign attributable to candidemia and/or invasive candidiasis. Diagnosis was based on a recent (≤ 96 hours before randomization) sample and required:

- ≥ 1 blood culture positive for yeast or *Candida*

  OR

- positive test for *Candida* from a rapid in vitro diagnostic or positive Gram stain for yeast

  OR

- positive culture for *Candida* spp. from a specimen obtained from a normally sterile site.

Patients with prosthetic joint septic arthritis, osteomyelitis, endocarditis, myocarditis, meningitis, endophthalmitis, central nervous system infection, neutropenia, extremely elevated liver enzymes, or severe hepatic impairment were not eligible for the study. These criteria were implemented because of poor echinocandin penetration in the central nervous system, prolonged dosing required for treatment, or safety considerations.

Patients who received systemic treatment with an antifungal agent for > 48 hours in the 96 hours before randomization or who had an indwelling vascular catheter/device that could not be removed and was likely to be the source of candidemia were not eligible.

6.1.4 Endpoints

The primary efficacy endpoint was Overall Success at Day 14, defined as mycological success (eradication/presumed eradication) AND resolution of attributable systemic signs of candidemia and/or invasive candidiasis that were present at baseline, and the patient was not lost to follow-up on the day of assessment (Table 9). The possible signs

of infection that might be attributable to candidemia and/or invasive candidiasis at baseline included fever, hypothermia, hypotension, tachycardia, and tachypnea.

Table 9: STRIVE Overall Response Categories

Overall Response	Mycological Response	Clinical Signs
Success	Success (eradication/presumed eradication)	Resolution of attributable systemic signs of candidemia/IC that were present at baseline
Failure	Success (eradication/presumed eradication)	Recurrence or lack of resolution of attributable systemic signs of candidemia/IC
	Failure	Resolution of attributable systemic signs of candidemia/IC that were present at baseline
	Failure	Recurrence or lack of resolution of attributable systemic signs of candidemia/IC
	Failure	Assessment of systemic signs was not completed for any reason (including death)
Indeterminate	Indeterminate	Resolution of attributable systemic signs of candidemia/IC that were present at baseline
	Success (eradication/presumed eradication)	Assessment of systemic signs was not competed for any reason

IC: invasive candidiasis
Note: Presumed eradication was defined only for a culture from a normally sterile site and was not defined for a blood culture.

Secondary efficacy outcome measures included Mycological Success and Investigator assessment of Clinical Cure (see Appendix Section 10.3 for additional endpoint definitions). An additional efficacy outcome measure was Day 30 ACM, defined as a death on or prior to Day 30 or unknown survival status.

6.1.5 Statistical Methods

6.1.5.1 Sample Size

The STRIVE study was not powered for inferential statistical analyses. A sufficient number of patients were randomized to the rezafungin and caspofungin groups in Part A to provide an initial, substantive analysis of safety and tolerability, and estimate efficacy. In Part A, assuming a 73% overall success rate, the sample size of 30 patients in each rezafungin group will yield a 95% CI of 53.8% to 87.5%. With the addition of Part B patients and assuming a 73% overall success rate, a total approximate sample size of 60 patients in the rezafungin treatment group (consisting of both rezafungin treatment groups) will yield a 95% CI of 60.0% to 83.7%, and a total approximate sample size of 110 patients in the rezafungin treatment group (consisting of both rezafungin treatment groups) will yield a 95% CI of 63.7% to 81.0%.

6.1.5.2 Interim Analyses

Three interim analyses were performed: a blinded review of safety data of rezafungin 400/400 mg patients, which determined that stopping criteria were not met; an

unblinded review of selected efficacy and safety data for 70 patients in Part A; and an unblinded review after Part A database lock of all data for the 107 patients. An unblinded statistician performed the analysis on the interim and final unblinded Part A data.

6.1.5.3 Analysis Populations

The primary efficacy population was the mITT Population which included all patients who had documented *Candida* infection based on Central Laboratory evaluation of a blood culture obtained within 96 hours of randomization, or from a specimen obtained from a normally sterile site, and received ≥ 1 dose of study drug. Patients were analyzed based on the treatment group to which they were randomized.

6.1.5.4 Endpoint Analyses

Given that STRIVE is a Phase 2 study providing supportive evidence of efficacy, analyses present data pooled across Parts A and B.

For the primary efficacy outcome of Overall Success at Day 14, the number and percentage of patients programmatically determined to be an overall success (mycological success and resolution of clinical signs of candidemia and/or invasive candidiasis), failure, or with an indeterminate overall response were summarized by treatment group for patients in the mITT Population. Exact 2-sided 95% CIs for the percentage of patients who achieved success in each treatment group were determined using the Clopper-Pearson method.

Descriptive analyses by treatment group were provided for the secondary outcomes in the mITT Population:

- Overall Response at Day 5, Day 28, and Follow-up: the number and percentage of patients with an overall success, failure, and indeterminate response were summarized by treatment group for patients in the mITT Population.
- Mycological response at Day 5 and Day 14: the number and percentage of patients programmatically determined as having mycological success (eradication/presumed eradication), failure, or with an indeterminate mycological response were summarized.
- Investigator’s assessment of clinical response at Day 14 and Follow-up: the number and percentage of patients with a clinical cure, failure and indeterminate response were summarized.

The number and percentage of patients who died on or before Day 30 or with an unknown survival status and who were alive were summarized. Two-sided 95% CIs for the weighted (by part A and B) treatment difference estimate in death rates, rezafungin minus caspofungin, was calculated using the stratified (by part A and B) methodology of Miettinen and Nurminen.

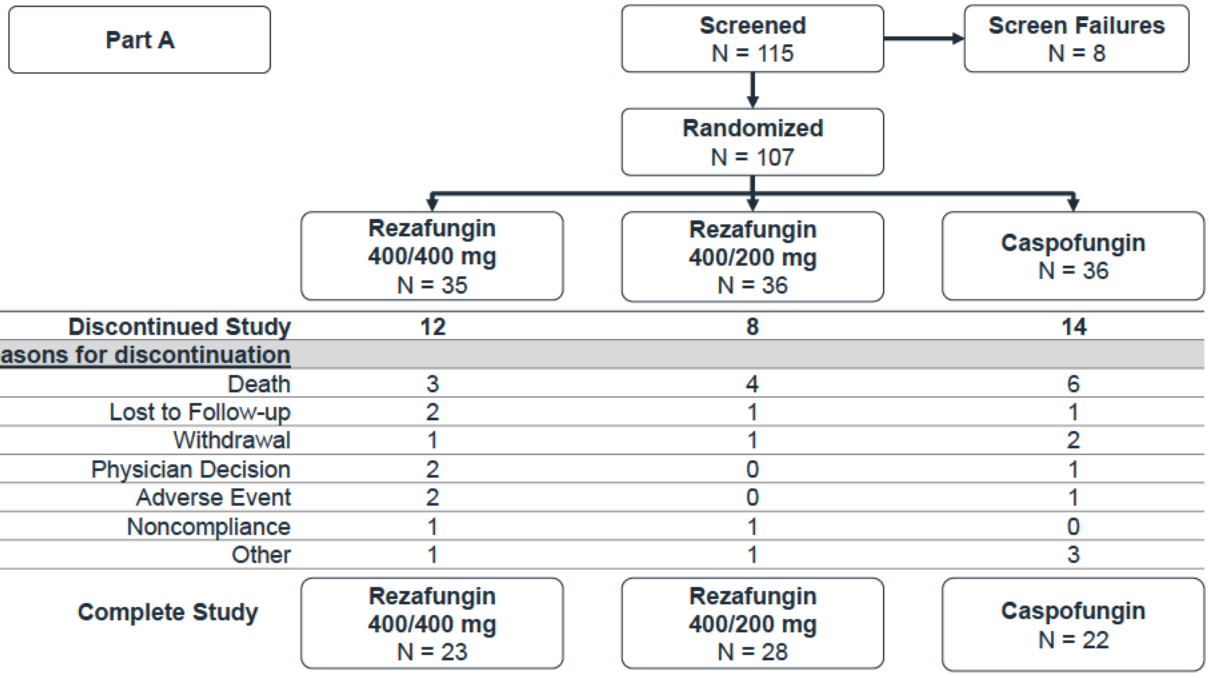
6.1.6 Patient Population

6.1.6.1 Disposition

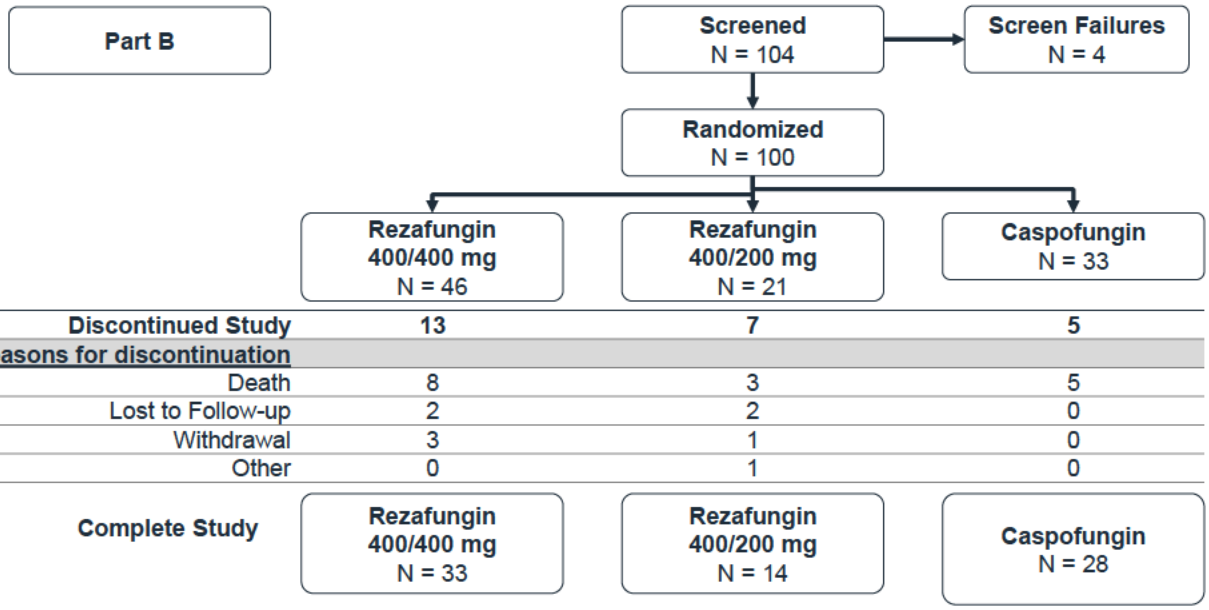
A total of 207 patients were randomized in STRIVE (107 in Part A and 100 in Part B; Figure 22). The ITT Population comprised 81 patients in the rezafungin 400/400 mg group, 57 in the rezafungin 400/200 mg group, and 69 in the caspofungin group.

In the mITT Population, there were 76 patients in the rezafungin 400/400 mg group, 46 patients in the rezafungin 400/200 mg group, and 61 patients in the caspofungin group.

Figure 22: STRIVE Patient Disposition



	Rezafungin 400/400 mg N = 35	Rezafungin 400/200 mg N = 36	Caspofungin N = 36
Discontinued Study	**12**	**8**	**14**
Reasons for discontinuation			
Death	3	4	6
Lost to Follow-up	2	1	1
Withdrawal	1	1	2
Physician Decision	2	0	1
Adverse Event	2	0	1
Noncompliance	1	1	0
Other	1	1	3



	Rezafungin 400/400 mg N = 46	Rezafungin 400/200 mg N = 21	Caspofungin N = 33
Discontinued Study	**13**	**7**	**5**
Reasons for discontinuation			
Death	8	3	5
Lost to Follow-up	2	2	0
Withdrawal	3	1	0
Other	0	1	0

In the rezafungin 400/400 mg group, 33% of patients discontinued the study early, compared to 20% of patients in the rezafungin 400/200 mg and caspofungin groups. The most common reason for study discontinuation was death, followed by lost to follow-up and withdrawal by the patient (Table 10).

Table 10: STRIVE Patient Disposition (mITT Population)

Disposition Reason, n (%)	Rezafungin 400/400 mg (N=76)	Rezafungin 400/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Completed study	51 (67.1)	37 (80.4)	48 (78.7)
Discontinued study early	25 (32.9)	9 (19.6)	13 (21.3)
Adverse event	2 (2.6)	0	0
Death	11 (14.5)	5 (10.9)	10 (16.4)
Lost to follow-up	4 (5.3)	2 (4.3)	1 (1.6)
Non-compliance	1 (1.3)	1 (2.2)	0
Physician's decision	2 (2.6)	0	1 (1.6)
Withdrawal by patient	4 (5.3)	1 (2.2)	1 (1.6)
Other	1 (1.3)	0	0

mITT: microbiological Intent-to-Treat

6.1.6.2 *Demographics*

The STRIVE study population was largely male (57.0%), White (83.1%), and not Hispanic or Latino (86.0%), with a mean age of 59.6 years (Table 11).

Table 11: STRIVE Patient Demographics (mITT Population)

Characteristic, n (%)	Rezafungin 400/400 mg (N=76)	Rezafungin 400/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Age group			
18 to < 65 years	45 (59.2)	27 (58.7)	36 (59.0)
≥ 65 years	31 (40.8)	19 (41.3)	25 (41.0)
≥ 75 years	12 (15.8)	8 (17.4)	8 (13.1)
Age (years)			
Mean (SD)	59.6 (16.12)	60.3 (15.72)	59.2 (15.50)
Sex			
Male	42 (55.3)	28 (60.9)	34 (55.7)
Female	34 (44.7)	18 (39.1)	27 (44.3)
Race			
Asian	0	1 (2.2)	3 (4.9)
Black or African American	6 (7.9)	6 (13.0)	4 (6.6)
White	66 (86.8)	36 (78.3)	51 (83.6)
Other/Not reported	4 (5.3)	3 (6.5)	3 (4.9)
Ethnicity			
Hispanic/Latino	8 (10.5)	7 (15.2)	6 (9.8)
Geographic region			
North/South America	23 (30.3)	17 (37.0)	22 (36.1)
Europe/Israel/Turkey	53 (69.7)	29 (63.0)	39 (63.9)
BMI (kg/m^2)			
n	75	45	61
Median (min, max)	25.60 (13.9, 69.2)	24.97 (14.7, 64.4)	25.91 (15.9, 44.8)
BMI group			
< 25 kg/m^2 (underweight/normal)	35 (46.1)	23 (50.0)	26 (42.6)
25–30 kg/m^2 (overweight)	22 (28.9)	11 (23.9)	22 (36.1)
> 30 kg/m^2 (obese)	18 (23.7)	11 (23.9)	13 (21.3)

BMI: body mass index; min: minimum; mITT: microbiological Intent-to-Treat; max: maximum; SD: standard deviation.

6.1.6.3 Baseline Characteristics

Baseline characteristics were similar across treatment groups (Table 12). Median APACHE II score was 12 (range 1 to 35) with approximately 20% of patients in the rezafungin groups and 15% of patients in the caspofungin group having a modified APACHE II score ≥ 20. Note, all patients had an absolute neutrophil count (ANC) ≥ 500 because a low ANC was an exclusion criterion.

Table 12: STRIVE Baseline Disease Characteristics (mITT Population)

Characteristic, n (%)	Rezafungin 400/400 mg (N=76)	Rezafungin 400/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Diagnosis			
Candidemia only	57 (75.0)	36 (78.3)	48 (78.7)
Invasive candidiasis	19 (25.0)	10 (21.7)	13 (21.3)
Positive *Candida* culture proximal to randomization[a]			
Yes	40 (52.6)	15 (32.6)	25 (41.0)
No	36 (47.4)	31 (67.4)	36 (59.0)
Modified APACHE II score Median (min, max)	12.0 (2, 31)	14.0 (2, 28)	13.0 (1, 35)
Modified APACHE II score	74	45	58
≥ 20	16 (21.1)	9 (19.6)	9 (14.8)
< 20	58 (76.3)	36 (78.3)	49 (80.3)
10–19	35 (46.1)	23 (50.0)	33 (54.1)
< 10	23 (30.3)	13 (28.3)	16 (26.2)
Renal impairment category based on creatinine clearance			
≥ 60 mL/min (Normal/mild)	57 (75.0)	23 (50.0)	36 (59.0)
< 60 mL/min (Moderate/severe)	17 (22.4)	18 (39.1)	23 (37.7)
Child-Pugh score category			
< 7	0	0	1 (1.6)
≥ 7[b]	5 (6.6)	1 (2.2)	3 (4.9)
No history of liver disease/Not calculated	71 (93.4)	45 (97.8)	57 (93.4)

ANC: absolute neutrophil count; APACHE II: Acute Physiology and Chronic Health Evaluation II; Max: maximum; Min: minimum; mITT: microbiological Intent-to-Treat; SD: standard deviation.
Note: Severe neutropenia was excluded in the Phase 2 STRIVE study.
a. 'Yes' was defined as patients with a culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization, OR a culture from another normally sterile site obtained within 48 hours prior to randomization or within 72 hours after randomization.
b. There was one patient with Child-Pugh score > 9 in rezafungin 400/400 mg group from STRIVE.

The majority of patients with invasive candidiasis had intra-abdominal or peritoneal disease (Table 13).

Table 13: STRIVE Site of Infection for Invasive Candidiasis Patients (mITT Population)

Site of Infection	Rezafungin 400/400 mg (N=19)	Rezafungin 400/200 mg (N=10)	Caspofungin 70/50 mg (N=61)
Intra-abdominal/peritoneal	10 (52.5)	4 (40.0)	9 (69.2)
Skin/soft tissue	5 (26.3)	5 (50.0)	2 (15.4)
Pelvic/rectal	2 (10.5)	1 (10.0)	2 (15.4)
Pulmonary	1 (5.3)	0	0
Other	1 (5.3)	0	0

The most common fungal pathogens at baseline were *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* (Table 14).

Table 14: STRIVE Fungal Pathogens at Baseline (mITT Population)

Species	Rezafungin 400 mg/400 mg (N=76)	Rezafungin 400 mg/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Candida albicans	38 (50.0)	19 (41.3)	34 (55.7)
Candida glabrata	13 (17.1)	14 (30.4)	10 (16.4)
Candida parapsilosis	10 (13.2)	7 (15.2)	11 (18.0)
Candida tropicalis	9 (11.8)	7 (15.2)	6 (9.8)
Candida dubliniensis	4 (5.3)	0	1 (1.6)
Candida guilliermondii	2 (2.6)	0	0
Candida krusei	1 (1.3)	3 (6.5)	1 (1.6)
Candida rugosa	1 (1.3)	0	0
Candida utilis	1 (1.3)	0	0
Candida fermentati	0	0	1 (1.6)
Candida intermedia	0	0	1 (1.6)
Candida kefyr	0	0	1 (1.6)
Candida metapsilosis	0	1 (2.2)	0

mITT: microbiological Intent-to-Treat

6.1.7 STRIVE Results

6.1.7.1 Primary Endpoint Results

Success rates for overall response were high in all treatment groups, with rates of 61% and 76% at Day 14 in the rezafungin 400/400 mg and rezafungin 400/200 mg groups and 67% in patients on caspofungin (Table 15).

The rate of indeterminate response in the rezafungin 400/400 mg group (13.2%) was more than double that of the 400/200 mg group (6.5%) or the caspofungin group (4.9%), contributing to the comparatively lower rate of success in rezafungin 400/400 mg (Table 15). In the rezafungin 400/400 mg group, the primary reasons for an indeterminate response were an inadequate number of mycological cultures (7/76 [9.2%]) and the assessment of the systemic signs not being completed (6/76 [7.9%]).

Table 15: STRIVE Day 14 Overall Response (mITT Population)

Outcome, n (%)	Rezafungin 400/400 mg (N=76)	Rezafungin 400/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Success (95% CI)	46 (60.5) (48.6, 71.6)	35 (76.1) (61.2, 87.4)	41 (67.2) (54.0, 78.7)
Failure/indeterminate	30 (39.5)	11 (23.9)	20 (32.8)
Failure	20 (26.3)	8 (17.4)	17 (27.9)
Indeterminate	10 (13.2)	3 (6.5)	3 (4.9)

CI: confidence interval; mITT: microbiological Intent-to-Treat

6.1.7.2 Secondary Endpoint Results

6.1.7.2.1 Mycological Response

The rate of patients with mycological success at Day 5 was 65.8% and 76.1% in the rezafungin 400/400 mg and 400/200 mg groups, respectively, and 62.3% in the caspofungin group (Table 16).

The rate of patients with mycological success at Day 14 study was 65.8% in the rezafungin 400/400 mg group, 76.1% in the rezafungin 400/200 mg group, and 68.9% in the caspofungin group.

Table 16: STRIVE Mycological Response at Day 5 and Day 14 (mITT Population)

Outcome, n (%)	Rezafungin 400/400 mg (N=76)	Rezafungin 400/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Day 5			
Success	50 (65.8)	35 (76.1)	38 (62.3)
Failure/indeterminate	26 (34.2)	11 (23.9)	23 (37.7)
Failure	17 (22.4)	9 (19.6)	21 (34.4)
Indeterminate	9 (11.8)	2 (4.3)	2 (3.3)
Day 14			
Success	50 (65.8)	35 (76.1)	42 (68.9)
Failure/indeterminate	26 (34.2)	11 (23.9)	19 (31.1)
Failure	19 (25.0)	8 (17.4)	17 (27.9)
Indeterminate	7 (9.2)	3 (6.5)	2 (3.3)

mITT: microbiological Intent-to-Treat

6.1.7.2.2 Investigator's Assessment of Clinical Response

Clinical cure rates at Day 14 were 69.7% in rezafungin 400/400 mg, 80.4% in rezafungin 400/200 mg, and 70.5% in caspofungin (Table 17). The most common reasons for clinical failure in all groups were lack of resolution of attributable signs or requirement for new/prolonged therapy.

Table 17: STRIVE Investigator Assessment of Clinical Response at Day 14 and Follow-up (mITT Population)

Outcome, n (%)	Rezafungin 400/400 mg (N=76)	Rezafungin 400/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Day 14			
Clinical Cure	53 (69.7)	37 (80.4)	43 (70.5)
Clinical Failure/indeterminate	23 (30.3)	9 (19.6)	18 (29.5)
Clinical Failure	18 (23.7)	6 (13.0)	17 (27.9)
Indeterminate	5 (6.6)	3 (6.5)	1 (1.6)
Follow-up			
Success	42 (55.3)	32 (69.6)	38 (62.3)
Clinical Failure/indeterminate	34 (44.7)	14 (30.4)	23 (37.7)
Clinical Failure	25 (32.9)	10 (21.7)	21 (34.4)
Indeterminate	9 (11.8)	4 (8.7)	2 (3.3)

CI: confidence interval; mITT: microbiological Intent-to-Treat

6.1.7.3 Efficacy by Pathogen

Rezafungin demonstrated efficacy against the most common clinically relevant *Candida* spp. (Table 18).

Table 18: STRIVE Overall Success at Day 14 by Baseline *Candida* Species (mITT Population)

Candida Species at Baseline, n/N1 (%)	Rezafungin 400/400 mg (N=76)	Rezafungin 400/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Candida albicans	19/38 (50.0)	14/19 (73.7)	25/34 (73.5)
Candida glabrata	12/13 (92.3)	11/14 (78.6)	7/10 (70.0)
Candida parapsilosis	6/10 (60.0)	6/7 (85.7)	4/11 (36.4)
Candida tropicalis	4/9 (44.4)	5/7 (71.4)	5/6 (83.3)
Candida dubliniensis	4/4 (100.0)	0/0	1/1 (100.0)
Candida guilliermondii	2/2 (100.0)	0/0	0/0
Candida utilis	1/1 (100.0)	0/0	0/0
Candida fermentati	0/0	0/0	1/1 (100.0)
Candida intermedia	0/0	0/0	0/1
Candida kefyr	0/0	0/0	1/1 (100.0)
Candida krusei	0/1	2/3 (66.7)	1/1 (100.0)
Candida metapsilosis	0/0	1/1 (100.0)	0/0
Candida rugosa	0/1	0/0	0/0

N: number of patients in the mITT Population; n: number of patients in the specified category; N1: number of patients with the specified *Candida* pathogen

For *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*, mycological success rates in rezafungin 400/200 mg were > 70% (Table 19). For caspofungin, mycological success rates were > 70% for *C. albicans* and *C. tropicalis* and ≤ 70% for *C. glabrata* and *C. parapsilosis.*

Table 19: STRIVE Mycological Success (Eradication) at Day 14 by Baseline *Candida* Species (mITT Population)

***Candida* Species at Baseline, n/N1 (%)**	**Rezafungin 400 mg/400 mg (N=76)**	**Rezafungin 400 mg/200 mg (N=46)**	**Caspofungin 70/50 mg (N=61)**
Candida albicans	21/38 (55.3)	14/19 (73.7)	25/34 (73.5)
Candida glabrata	12/13 (92.3)	11 /14 (78.6)	7/10 (70.0)
Candida parapsilosis	6/10 (60.0)	6/7 (85.7)	5/11 (45.5)
Candida tropicalis	5/9 (55.6)	5/7 (71.4)	5/6 (83.3)
Candida dubliniensis	4/4 (100.0)	0/0	1/1 (100.0)
Candida guilliermondii	2/2 (100.0)	0/0	0/0
Candida rugosa	1/1 (100.0)	0/0	0/0
Candida utilis	1/1 (100.0)	0/0	0/0
Candida fermentati	0/0	0/0	1/1 (100.0)
Candida intermedia	0/0	0/0	0/1
Candida kefyr	0/0	0/0	1/1 (100.0)
Candida krusei	0/1	2/3 (66.7)	1/1 (100.0)
Candida metapsilosis	0/0	1/1 (100.0)	0/0

N: number of patients in the mITT Population; n: number of patients in the specified category; N1: number of patients with the specified *Candida* pathogen

6.1.7.4 All-Cause Mortality

The ACM rate at Day 30 in the mITT Population was 15.8% in rezafungin 400/400 mg, 4.3% in rezafungin 400/200 mg, and 13.1% in the caspofungin group (Table 20).

There were no clear factors identified that explain the higher percentage of deceased patients in the 400/400 mg group.

Table 20: STRIVE All-Cause Mortality at Day 30 (mITT Population)

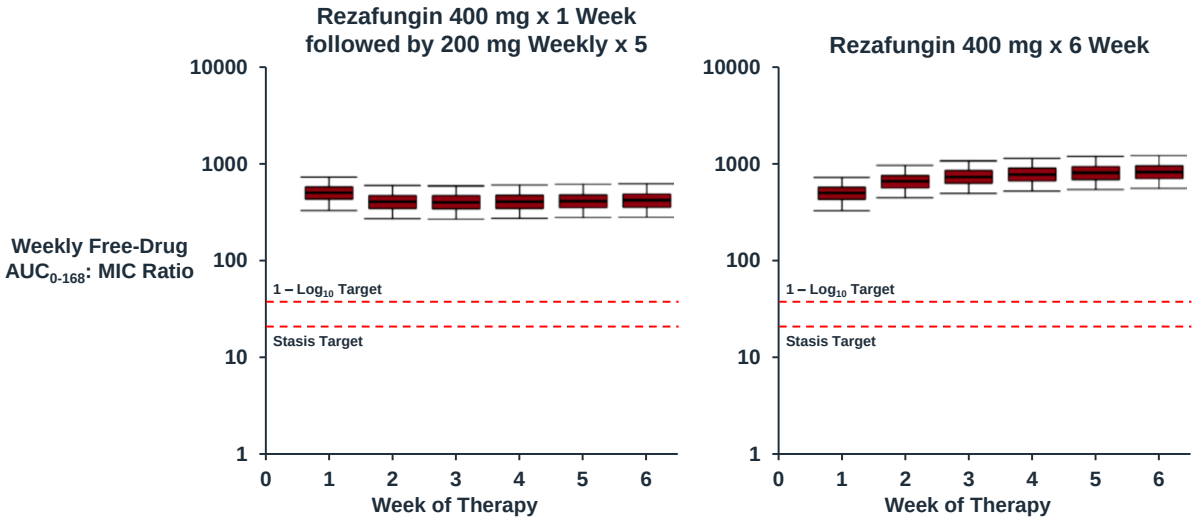
Characteristic, n (%)	Rezafungin 400/400 mg (N=76)	Rezafungin 400/200 mg (N=46)	Caspofungin 70/50 mg (N=61)
Deceased[a]	18 (23.7)	4 (8.7)	10 (16.4)
Known deceased	12 (15.8)	2 (4.3)	8 (13.1)
Unknown survival status	6 (7.9)	2 (4.3)	2 (3.3)
Alive	58 (76.3)	42 (91.3)	51 (83.6)
Difference in death rate (95% CI)[b]	6.7 (-7.1, 20.5)	-7.0 (-21.2, 7.3)	

mITT: modified Intent-to-Treat
a. Patients who died on or before Day 30, or with unknown survival status.
b. Two-sided 95% confidence interval for the weighted (by part A and B) treatment difference estimate in death rates, rezafungin minus caspofungin, was calculated using the stratified (by part A and B) methodology of Miettinen and Nurminen.

6.2 Phase 3 Dose Selection

The lowest effective rezafungin dose of 400 mg followed by 200 mg once-weekly was selected for Phase 3 based on the positive efficacy data from Phase 2 and after confirming that either dose regimen would provide adequate exposures in patients relative to nonclinical PK/PD targets. Data from the initial modeling, shown in Figure 23, of rezafungin PK was key to this decision. The first dose of 400 mg was sufficiently above target, shown here for *C. albicans*, and subsequent doses can be decreased to 200 mg without appreciably reducing the exposure. Given the long half-life of rezafungin, AUC would continue to accumulate for multiple once-weekly doses 400 mg. This increase, which is likely beyond the time where initial early therapeutic benefit had already been realized, does not appreciably change the target attainment obtained with the first dose.

Figure 23: Simulated Distributions of free-drug AUC_{0-168}/MIC Ratios Relative to Targets for *Candida Albicans*



AUC_{0-168}: area under the plasma concentration-time curve from time zero to 168 hours post dose.
Note: Distributions of free-drug AUC_{0-168}/MIC ratios at the MIC90 value for *C. albicans* of 0.06 µg/mL for simulated patients administered the single-dose and weekly rezafungin regimens shown relative to the free-drug AUC_{0-168}/MIC ratio targets associated with net fungal stasis and a 1-log_{10} CFU reduction from baseline
Source: Figure 2 of Bader 2018b

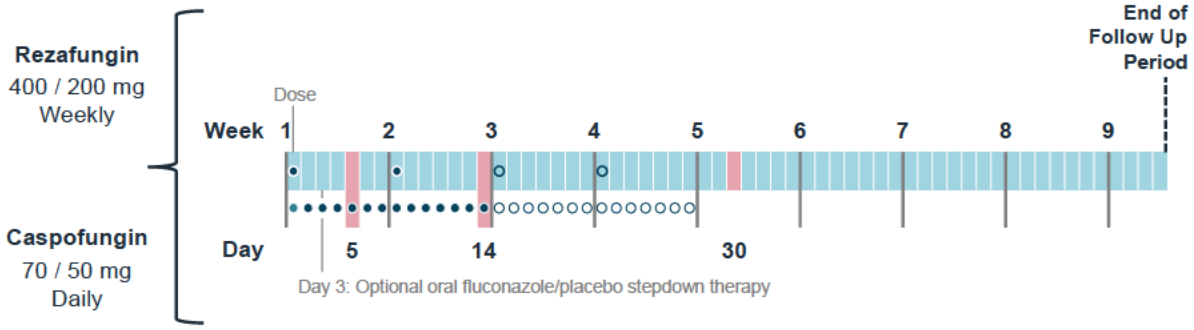
6.3 Phase 3 Study: ReSTORE

6.3.1 Study Design Overview

ReSTORE was a multicenter, prospective, randomized, double-blind, Phase 3 efficacy and safety study of rezafungin for injection IV versus a comparator regimen of caspofungin IV in patients with candidemia and/or invasive candidiasis (Figure 24). Patients were randomly assigned (1:1) to receive either rezafungin 400/200 mg or caspofungin. After ≥ 3 days IV treatment (or the minimum duration of IV therapy advised by the site's national/regional/local guidelines, whichever was greater), patients could be switched to oral stepdown (fluconazole for patients in the caspofungin group or placebo for patients in the rezafungin group) therapy by the Investigator if they met the oral stepdown therapy criteria (see Section 6.3.2.3).

Efficacy assessments for all patients occurred on Day 5, Day 14 (±1 day), Day 30 (minus 2 days), EOT visit (within 2 days of last dose), and the Follow-up visit (Days 52–59). Clinical cure, radiological cure (for qualifying invasive candidiasis patients) and mycological eradication, were assessed on all efficacy assessment days. Survival status was assessed at Day 30 (-2 days) and the Follow-up visit (Days 52–59). Blood cultures were repeated daily (preferred) or every other day until the first negative blood culture result for *Candida* spp. with no subsequent positive culture (in cases when one or more samples were drawn and cultured after the first negative culture was available).

Figure 24: ReSTORE Study Design



Enrollment criteria:
- ≥ 18 years of age
- Established mycological diagnosis of candidemia and/or invasive candidiasis
- ≥ 1 Systemic signs: fever, hypothermia, hypotension, tachycardia, tachypnea, local signs of inflammation

6.3.2 Treatment Regimen

6.3.2.1 Rezafungin Treatment Group

Patients randomized to rezafungin received:

- 400 mg dose in Week 1, followed by 200 mg once weekly, for a total of 2 to 4 doses.

To maintain the blind, patients also received daily saline placebo to match for caspofungin IV or daily oral placebo to match for fluconazole:

- The saline IV was administered on Days 2–7, Days 9–14, and during the optional dosing period on Days 16–21 and Days 23–28.

6.3.2.2 Caspofungin Treatment Group

Patients randomized to caspofungin received:

- A single caspofungin 70 mg IV loading dose on Day 1, followed by caspofungin 50 mg IV once daily for 14 days with the option to continue treatment for up to 28 days.

To maintain the blind, patients in the caspofungin treatment group who switched to oral stepdown therapy received:

- matching IV saline placebo for rezafungin once weekly on the days of scheduled rezafungin for injection doses until study drug was stopped (Day 8; Day 15 [if applicable] and Day 22 [if applicable]).

6.3.2.3 Oral Stepdown Therapy

An oral stepdown therapy was allowed in both treatment groups, provided that the following criteria were met:

- Able to take oral medication
- ≥ 3 days of IV study drug (or the minimum duration of IV therapy advised by the site's national/regional/local guidelines, whichever is greater)
- The *Candida* spp. isolated was susceptible to fluconazole
- All signs and symptoms of candidemia and/or invasive candidiasis that were present at baseline had resolved
- The patient's clinical status was considered stable based on Investigator assessment
- Most recent blood culture was to be drawn following the first dose of study drug AND ≥ 48 hours prior to oral study drug initiation AND must be negative for *Candida* spp.
- No evidence of moderate or severe hepatic injury (ALT or AST > 5 × ULN)
- No history of hypersensitivity to any azole or any other contraindications to the use of fluconazole or its excipients, including concomitant use of the following medications: terfenadine, cisapride, astemizole, erythromycin, pimozide, and quinidine
- No personal or family history of long QT interval on ECG syndrome or a prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) (> 470 msec in males and > 480 msec in females)
- Investigator's opinion, the patient could tolerate oral fluconazole therapy (as described in fluconazole Prescribing Information)
- Patient's weight is ≤ 130 kg

Treatment regimens with caspofungin and fluconazole (the comparator) are consistent with standard of care regimens in approved labeling (Cancidas [caspofungin acetate] Prescribing Information, Diflucan [fluconazole] tablets Prescribing Information).

6.3.3 Enrollment Criteria

Key inclusion criteria included:

- ≥ 18 years of age
- Established mycological diagnosis of candidemia and/or invasive candidiasis from a sample taken ≤ 4 days (96 hours) before randomization defined as:

  a. ≥ 1 blood culture positive for yeast or *Candida*

  OR

  b. Positive test for *Candida* from a Sponsor-approved rapid in vitro diagnostic

  OR

c. Positive Gram stain (or other method of direct microscopy) for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site.

- Presence of one or more systemic signs attributable to candidemia or invasive candidiasis (e.g., fever, hypothermia, hypotension, tachycardia, tachypnea, local signs of inflammation) appearing from ≤ 12 hours prior to the qualifying positive culture through time of randomization.

Key exclusion criteria included:

- Any of the following forms of invasive candidiasis at baseline:

  a. Septic arthritis in a prosthetic joint (septic arthritis in a native joint was allowed)

  b. Osteomyelitis

  c. Endocarditis or myocarditis

  d. Meningitis, endophthalmitis, chorioretinitis, or any central nervous system infection

  e. Chronic disseminated candidiasis

  f. Urinary tract candidiasis due to ascending *Candida* infection secondary to obstruction or surgical instrumentation of the urinary tract

- Received systemic treatment with an antifungal agent at approved doses for treatment of candidemia for > 48 hours (e.g., > 2 doses of a once-daily antifungal agent or > 4 doses of a twice daily antifungal agent) ≤ 4 days (96 hours) before randomization.
- Alanine aminotransferase or aspartate aminotransferase levels > 10-fold the ULN.
- Severe hepatic impairment in patients with a history of chronic cirrhosis (Child-Pugh score > 9).
- Received systemic treatment with an antifungal agent for > 48 hours in the 96 hours before randomization or who had an indwelling vascular catheter/device that could not be removed and was likely to be the source of candidemia

These exclusion criteria were implemented because of poor echinocandin penetration in the central nervous system, prolonged dosing required for treatment, or safety considerations.

6.3.4 Endpoints

The primary efficacy outcome was ACM at Day 30 (-2 days). For patients who discontinued from the study prior to Day 30, all attempts were made to determine survival status post-study discontinuation.

The key secondary efficacy endpoint was global cure at Day 14 (Table 21). Additional secondary endpoints included mycological eradication/presumed eradication, clinical

cure, and radiological cure. Additional endpoint definitions are provided in Appendix Section 10.4.

Table 21: ReSTORE Global Response Categories

Global Response	Mycological Response	Clinical Response, as Assessed by Investigator+	Radiological Response**
Cure	Eradication/presumed eradication*	Cure	Cure
Failure	Eradication/presumed eradication*	Cure	Failure
	Eradication/presumed eradication*	Failure	Cure, failure, or indeterminate
	Eradication/presumed eradication*	Indeterminate	Failure
	Failure	Cure, failure, or indeterminate	Cure, failure, or indeterminate
	Indeterminate	Failure	Cure, failure, or indeterminate
	Indeterminate	Cure	Failure
	Indeterminate	Indeterminate	Failure
Indeterminate	Eradication/presumed eradication*	Cure	Indeterminate
	Eradication/presumed eradication*	Indeterminate	Cure or indeterminate
	Indeterminate	Cure	Cure or indeterminate
	Indeterminate	Indeterminate	Cure or indeterminate

* Presumed eradication is defined only for a culture from a normally sterile site and is not defined for a blood culture.
** For those patients with invasive candidiasis documented by radiologic/imaging evidence at baseline.
+ Confirmed by the Data Review Committee

6.3.5 Data Review Committee

An independent blinded DRC reviewed patient data and confirmed the determination of global response (including mycological response, clinical response as assessed by the Investigator, and radiologic response). The global response as determined by the DRC was used for the analysis of the secondary endpoint. The role of the DRC and procedures for outcome determination were described in the DRC charter.

6.3.6 Statistical Methods

6.3.6.1 Analysis Populations

All efficacy analyses were conducted using the mITT Population, which included all patients who had a documented *Candida* infection based on Central Laboratory evaluation of a blood culture or a culture from a normally sterile site, obtained ≤ 4 days (96 hours) before randomization, and received ≥ 1 dose of study drug. Patients were analyzed based on the treatment group to which they were randomized. Note that this is the same definition as in the STRIVE study for the microbiological mITT Population.

6.3.6.2 Sample Size

For the primary endpoint of ACM, using a 20% NI margin, one-sided alpha of 0.025, an ACM rate of 20% in both treatment groups, 1:1 randomization, and the sample size methodology based on a continuity corrected Z-statistic, a total of 184 patients in the mITT Population provides 90% power to show NI.

6.3.6.3 Noninferiority Margin

A comprehensive literature search was conducted to identify data from clinical studies, or in the absence of, other historical evidence on the effect of placebo, no treatment or inadequate treatment in patients with candidemia and invasive candidiasis. A total of 1,831 articles were identified and 27 articles were selected for detailed full text review. Nearly all studies examined ACM as the efficacy outcome of interest, with only 2 manuscripts utilizing a clinical or therapeutic outcome. Manuscripts that presented only case reports did not provide sufficient data to determine the ACM rates, or included non-adult patients were excluded from the detailed review (11 articles excluded). None of the selected articles were randomized clinical trials that compared antifungal therapy with placebo. In addition, no observational historical studies that examined efficacy outcomes in the time period when antifungals were available and the time period when antifungals were not available were found in the extensive literature review. Thus, the placebo 30-Day ACM rate was estimated from studies where patients received no treatment or inadequate treatment. The active control 30-day ACM rate was derived from 4 contemporary clinical trials of echinocandins.

Random effects weighted analyses yielded a no treatment/inadequate treatment 30-day ACM estimate of 67.1% (95% CI: 58.2% – 75.0%) and for the active control a 30-day ACM rate of 27.9% (95% CI: 24.3% – 31.9%). The treatment effect (M1) is then determined as the lower bound of the 95% CI for the placebo 30-day ACM rate minus the upper bound of the active control 30-day ACM rate, which is 26.3% (58.2% – 31.9%). This approach provides a form of discounting that takes into account uncertainty due to differences in study design and patient comparability.

The NI margin must be no larger than the treatment difference between standard therapy and placebo, and exclusion of a difference greater than the NI margin confirms that at least part of the treatment effect of the standard therapy is preserved for the test drug.

The quantity M2 reflects the clinical judgement about how much of M1 should be preserved. An M2 of 24% was chosen, given the potential efficacy and safety benefits of rezafungin over the available echinocandins.

Rezafungin has excellent activity against multidrug-resistant *C. glabrata,* where the only available therapy is high dose amphotericin, which is associated with renal toxicity. In pre-clinical studies, rezafungin has shown a larger safety margin compared to other echinocandins, with NOAELs of 34- to 47-times the efficacious dose in rats and monkeys. In contrast to other echinocandins, the NOAEL for rezafungin in the 4-week

toxicology studies in rats and monkeys was limited by drug solubility, and target organ toxicity was not observed. Furthermore, a direct comparison of hepatic toxicity in a validated 2-week rat hepatotoxicity model showed that rezafungin caused no elevation in hepatic enzymes and normal histology while anidulafungin administered at the same exposure caused hepatic injury/necrosis as evidence by elevated hepatic enzymes and abnormal histology. Because of the improved safety profile, rezafungin may be administered safely with a high, front-loaded dose, and rezafungin can effectively treat some *Candida* strains not susceptible to the currently approved echinocandins. In Phase 1 and the Phase 2 study in candidemia/invasive candidiasis (ongoing at the time of NI margin determination), rezafungin was shown to be safe and well tolerated at exposures much higher than those observed with approved dosing regimens of the marketed echinocandins. In addition, rezafungin is dosed as weekly 1-hour infusions potentially allowing for patients to be discharged earlier from the hospital as compared with currently available echinocandins.

Finally, preclinical data indicates that rezafungin distributes very well to infected target organ tissues with 6- to 8-fold higher levels of Rezafungin in the tissues 72 hours after a single human equivalent dose in mice compared to 3 daily human equivalent doses of micafungin. Thus, rezafungin has the potential to fill an unmet need in the treatment of patients with invasive candidiasis of the deep tissues.

Utilizing an M2 of 24%, the NI margin is determined to be (1-M2)*M1=20%. A 20% NI margin for 30-day ACM is supported given the unmet need, large benefit of active treatment over placebo, the potential efficacy and safety benefits provided by rezafungin and the feasibility challenges in recruiting a large number of patients in the orphan indication of candidemia and invasive candidiasis.

6.3.6.4 Endpoint Analyses

The number and percentage of patients in each treatment group that were alive and deceased (or with missing data, [i.e., unknown survival status]) at Day 30 (-2 days) were tabulated.

The null and alternative hypotheses were as follows:

$H0$: $p1 - p2 \geq \Delta$, and

$H1$: $p1 - p2 < \Delta$,

where p1 was the ACM rate at Day 30 (-2 days) in the rezafungin treatment group, p2 was the ACM rate at Day 30 (-2 days) rate in the caspofungin treatment group, and Δ was the NI margin of 20%.

To test the null hypothesis, a two-sided 95% CI for the observed difference in primary outcome rates (rezafungin for injection treatment group minus caspofungin treatment group) were calculated for the mITT Population using the unadjusted methodology of Miettinen and Nurminen (Miettinen 1985). If the upper limit of the 95% CI for the

difference in the mITT Population was lower than 20%, then the null hypothesis was rejected and NI of rezafungin versus caspofungin was declared.

The key secondary endpoint was global response (based on DRC assessment) at Day 14 (±1 day). Global response at other time points, Day 5, Day 30 (-2 days), EOT (≤ 2 days of last dose) and Follow-up (Days 52–59), were also determined. The number and percentage of patients with a global response of cure, failure, or indeterminate was presented by treatment group in the mITT Population at each time point.

The additional secondary efficacy endpoints of mycological response and radiological response (for patients with invasive candidiasis documented by radiologic/imaging evidence at baseline) were presented using the number and percentage of patients with a response of cure (eradication for mycological response), failure, or indeterminate, displayed by treatment group in the mITT Population at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤ 2 days of last dose), and Follow-up (Days 52–59).

Two-sided 95% CIs were constructed for the observed differences in the global cure, mycological eradication, radiologic cure, and clinical cure rates at each visit using the method of Miettinen and Nurminen without stratification. The 95% CIs are for descriptive purposes only.

6.3.6.5 Sensitivity Analyses

Sensitivity analyses of the primary outcome included:

- Exclusion of patients whose survival status was not known (these patients were considered deaths in the primary analysis).
- An adjusted (for the randomization stratification factors) 95% CI using the stratified methodology of Miettinen and Nurminen. Cochran Mantel Haenszel weights were used for the stratum weights in the calculation of the CI.
- Multiple imputation for missing data. Missing primary outcome data were imputed with multiple imputation. Fifty data sets were created by treatment group using a logistic regression in which the randomization stratification factors of diagnosis (candidemia only; invasive candidiasis) and APACHE II score/ANC (APACHE II score ≥ 20 OR ANC< 500 cells/μL; APACHE II score < 20 AND ANC ≥ 500 cells/μL) at screening are included as predictive variables.

6.3.7 Patient Population

6.3.7.1 Disposition

Of the 222 patients screened, 199 were randomized (100 patients to rezafungin for injection, and 99 to caspofungin). Ten patients did not have a documented *Candida* infection (6 in rezafungin; 4 in caspofungin) in the 96 hours prior to randomization, and 3 patients did not receive study drug (2 in rezafungin, 1 in caspofungin). Thus, the mITT Population included 93 patients in the rezafungin for injection and 94 in the caspofungin groups (Table 22).

Of the mITT Population, 35 (37.6%) and 37 (39.4%) patients in the rezafungin and caspofungin treatment groups, respectively, discontinued study early, with the primary reason being death (20.4% and 21.3%, respectively).

Discontinuations of study drug before Day 14 occurred in 29 (31.2%) and 26 (27.7%) patients in the rezafungin and caspofungin treatment groups, respectively. The primary reasons for study drug discontinuation prior to Day 14 were death (8.6% and 8.5% for rezafungin and caspofungin patients, respectively) and AEs (7.5% and 6.4%, respectively).

Table 22: ReSTORE Patient Disposition (mITT Population)

Disposition Reason, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)
Completed study	58 (62.4)	57 (60.6)
Discontinued study early	35 (37.6)	37 (39.4)
Adverse event	0	3 (3.2)
Death	19 (20.4)	20 (21.3)
Lost to follow-up	4 (4.3)	5 (5.3)
Withdrawal by patient	6 (6.5)	7 (7.4)
Other	6 (6.5)	2 (2.1)
Completed study drug regimen	64 (68.8)	68 (72.3)
Discontinued study drug regimen prior to study Day 14	29 (31.2)	26 (27.7)
Adverse event	7 (7.5)	6 (6.4)
Diagnosis of other types of Invasive Candidiasis	1 (1.1)	1 (1.1)
Death	8 (8.6)	8 (8.5)
Lack of efficacy	2 (2.2)	3 (3.2)
Lost to follow-up	2 (2.2)	1 (1.1)
Non-compliance	0	1 (1.1)
Physician's decision	0	2 (2.1)
Withdrawal by patient	2 (2.2)	3 (3.2)
Other	7 (7.5)	1 (1.1)

mITT=modified Intent-to-Treat
Percentages are based on the number of patients in the mITT Population.
a. Other reasons for patient disposition were singular in nature and did not have a clear pattern for reason or relationship to treatment assignment.

6.3.7.2 Demographics

In the ReSTORE study, 59.1% and 59.6% of rezafungin and caspofungin patients, respectively, were age 18 to < 65 years old, with a median age across all patients of 59.0 and 62.0 years, respectively (Table 23).

Overall, the majority of patients were White, with Asians making up approximately 30% of the population (due to the geographic region in which the study was conducted, including Asia-Pacific, China, and Taiwan). The percentages of patients in each race were similar between treatment groups. Median BMI (range) was similar between the rezafungin for injection and caspofungin treatment groups (23.6 kg/m^2 and 24.1 kg/m^2, respectively).

Table 23: ReSTORE Patient Demographics (mITT Population)

Characteristic, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)
Age group		
18 to < 65 years	55 (59.1)	56 (59.6)
≥ 65 years	38 (40.9)	38 (40.4)
Age (years)		
Mean (SD)	59.5 (15.82)	61.9 (14.58)
Sex		
Male	62 (66.7)	56 (59.6)
Female	31 (33.3)	38 (40.4)
Race		
American Indian or Alaska Native	1 (1.1)	1 (1.1)
Asian	23 (24.7)	31 (33.0)
Black or African American	5 (5.4)	4 (4.3)
White	59 (63.4)	55 (58.5)
Other/Not Reported	5 (5.4)	3 (3.2)
Ethnicity		
Hispanic/Latino	6 (6.5)	4 (4.3)
Geographic region		
North/South America*	26 (28.0)	24 (25.5)
Europe/Israel/Turkey	38 (40.9)	37 (39.4)
Asia-Pacific/China/Taiwan	29 (31.2)	33 (35.1)
BMI (kg/m^2)		
N	88	83
Median (min, max)	23.63 (13.7, 51.9)	24.11 (12.9, 47.6)
BMI group		
< 25 kg/m^2 (underweight/normal)	52 (55.9)	49 (52.1)
25–30 kg/m^2 (overweight)	17 (18.3)	26 (27.7)
> 30 kg/m^2 (obese)	19 (20.4)	8 (8.5)

BMI: body mass index; Min: minimum; max=maximum; mITT: modified Intent-to-Treat; SD: standard deviation
*Includes only 1 patient enrolled outside of the United States.

6.3.7.3 Baseline Characteristics

The baseline characteristics of these patients in the study were representative of patients with candidemia or invasive candidiasis, and most baseline characteristics were balanced between groups (Table 24). All patients were admitted to the hospital at time of study enrollment. More caspofungin patients were in the intensive care unit (ICU) at the time of dosing or were on mechanical ventilation, 39% and 30%, respectively, compared with rezafungin patients, 31% and 17%, respectively. However,

for the more standardized measure of severity, APACHE II score, 13% and 18% of patients in the rezafungin and caspofungin groups, respectively, had an APACHE II score greater than or equal to 20.

Diagnosis of candidemia and invasive candidiasis was based on blood cultures and tissue/fluid cultures from normally sterile sites as well as radiographic imaging, when relevant.

Table 24: ReSTORE Baseline Disease Characteristics (mITT Population)

Characteristic, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)
Diagnosis[a]		
Candidemia only	64 (68.8)	67 (71.3)
Invasive candidiasis	29 (31.2)	27 (28.7)
Modified APACHE II score, median (min, max)	12.0 (0, 40)	11.5 (0, 37)
Modified APACHE II score, n (%)	92	94
≥ 20	12 (12.9)	17 (18.1)
< 20	80 (86.0)	77 (81.9)
10–19	42 (45.2)	40 (42.6)
< 10	38 (40.9)	37 (39.4)
ANC (µL) at randomization, n (%)	90	94
< 500/µL	7 (7.5)	5 (5.3)
≥ 500/µL	83 (89.2)	89 (94.7)
Modified APACHE II score/ ANC, n (%)[b]	90	94
APACHE II score ≥ 20 or ANC < 500/µL	19 (20.4)	20 (21.3)
APACHE II score < 20 and ANC ≥ 500/µL	71 (76.3)	74 (78.7)
Estimated creatinine clearance (mL/min)		
N	88	83
Median (min, max)	78.43 (9.4, 949.6)	69.22 (8.3, 314.0)
Renal impairment category based on creatinine clearance		
≥ 60 mL/min (Normal/mild)	52 (55.9)	47 (50.0)
< 60 mL/min (Moderate/severe)	36 (38.7)	36 (38.3)
Child-Pugh score ≥ 7	2 (2)	6 (6.4)
ICU at time of dosing	29 (31.2)	37 (39.4)
Mechanical ventilation	16 (17.2)	28 (29.8)

ANC: absolute neutrophil count; APACHE II: Acute Physiology and Chronic Health Evaluation II; Max: maximum; Min: minimum; mITT: modified Intent-to-Treat; SD: standard deviation
a. Final diagnosis of invasive candidiasis was determined based on the radiological and/or tissue/fluid culture assessment through Day 14.
b. Based on laboratory results not randomization strata.

The majority of patients, approximately 70% in both treatment groups, with invasive candidiasis had intra-abdominal or peritoneal disease (Table 25).

Table 25: ReSTORE Site of Infection for Invasive Candidiasis Patients (mITT Population)

Site of Infection	Rezafungin 400/200 mg (N=29)	Caspofungin 70/50 mg (N=27)
Intra-abdominal/peritoneal	20 (69.0)	19 (70.4)
Skin/soft tissue	3 (10.3)	1 (3.7)
Pelvic/rectal	3 (10.3)	5 (18.5)
Other	0	1 (3.7)
Not applicable (diagnosed by radiology only)	3 (10.3)	1 (3.7)

mITT: modified Intent-to-Treat

The most common (in ≥ 20% of either treatment group) fungal pathogen was *C. albicans* in 41.9% and 42.6% of patients in the rezafungin and caspofungin treatment groups, respectively, followed by *C. glabrata* in 25.8% and 26.6% of patients, respectively, and *C. tropicalis* in 21.5% and 18.0% of patients, respectively (Table 25).

There was a single ReSTORE patient treated with rezafungin who had an *fks* mutant baseline isolate (none were identified in STRIVE). This *C. glabrata* isolate possessed a F659V alteration in Fks2 and was caspofungin-intermediate (MIC=0.25 µg/mL), anidulafungin-resistant (MIC=0.5 µg/mL), micafungin-susceptible (MIC=0.06 µg/mL), and rezafungin-susceptible (MIC=0.5 µg/mL; based upon provisional CLSI interpretive criteria; M27M44S Ed3). The patient was a mycological failure at Day 5 but had a successful mycological response at Day 14 and was alive at Day 30.

Table 25: ReSTORE Baseline *Candida* Pathogens from Blood and Sterile Site Cultures (mITT Population)

Candida Species, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)
Candida albicans	39 (41.9)	40 (42.6)
Candida glabrata	24 (25.8)	25 (26.6)
Candida tropicalis	20 (21.5)	17 (18.0)
Candida parapsilosis	8 (8.6)	17 (18.0)
Candida dubliniensis	3 (3.2)	1 (1.1)
Candida guilliermondii	2 (2.2)	0
Candida krusei	2 (2.2)	2 (2.1)
Candida lusitaniae	1 (1.1)	1 (1.1)
Candida metapsilosis	1 (1.1)	0
Candida nivariensis	0	1 (1.1)

mITT: modified Intent-to-Treat
The counts of patients with multiple pathogens at Baseline are as follows:
Rezafungin 1 *C. albicans* and *C. glabrata*, 1 *C. dubliniensis* and *C. glabrata*, 3 *C. glabrata* and *C. tropicalis*, 1 *C. guilliermondii* and *C. tropicalis*,
1 *C. parapsilosis* and *C. tropicalis*.
Caspofungin: 1 *C. albicans* and *C. dubliniensis*, 3 *C. albicans* and *C. glabrata*, 3 *C. albicans* and *C. tropicalis*, 1 *C. glabrata* and *C. krusei*, 2 *C. glabrata* and *C. tropicalis*.

6.3.8 ReSTORE Results

6.3.8.1 Drug Exposure

The majority of patients in the mITT Population in both treatment groups received 14 days of total therapy. Twenty percent of rezafungin patients and 30% of caspofungin patients received 15–28 days of total therapy. In the rezafungin group, 26% received oral placebo, and in the caspofungin group, 36% received oral therapy.

6.3.8.2 Primary Endpoint Results: All-Cause Mortality

Noninferiority of rezafungin was demonstrated in the mITT Population (treatment difference of 2.4 [95% CI: -9.7 to 14.4]), with the upper limit of the 95% CI (14.4) for the difference lower than 20% (Table 26). The rate of patients who were either known to be deceased or with unknown survival status was 23.7% and 21.3% in the rezafungin and caspofungin groups, respectively. The percentage of patients with an unknown survival status was low and the same in both treatment groups (3.2%). No patients on stepdown oral therapy died within 30 days.

Table 26: ReSTORE All-Cause Mortality at Day 30 (-2 days) (mITT Population)

Characteristic, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)
Deceased[a]	22 (23.7)	20 (21.3)
Known deceased	19 (20.4)	17 (18.1)
Unknown survival status	3 (3.2)	3 (3.2)
Alive	71 (76.3)	74 (78.7)
Difference in death rate (95% CI)[b]	2.4 (-9.7, 14.4)	

a. Patients who died on or before Day 30, or with unknown survival status.
b. Two-sided 95% CI for the observed treatment difference in death rates, rezafungin for injection minus caspofungin, was calculated using the unadjusted methodology of Miettinen and Nurminen.

6.3.8.2.1 Sensitivity Analyses

The sensitivity analyses show that the conclusion of NI is consistent and robust to the handling of missing data or method of determination of the CI (Table 27).

Table 27: ReSTORE Sensitivity Analyses of All-Cause Mortality at Day 30 (-2 days) (mITT Population)

Characteristic, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)	Difference (95% CI)
Sensitivity analysis 1: Excluding patients with unknown survival status			
Patients with known survival status, N1[a,b]	90	91	
Deceased	19 (21.1)	17 (18.7)	2.4 (-9.4, 14.2)
Alive	71 (78.9)	74 (81.3)	
Sensitivity analysis 2: Adjusting for randomization strata[d,e]			
Deceased[c]	22 (23.7)	20 (21.3)	2.6 (-9.3, 14.4)
Known deceased	19 (20.4)	17 (18.1)	
Unknown survival status	3 (3.2)	3 (3.2)	
Alive	71 (76.3)	74 (78.7)	
Sensitivity analysis 3: Multiple imputation for missing survival status[d,f]			
Deceased	20 (21.5)	17 (18.1)	2.8 (-8.8, 14.5)
Alive	73 (78.5)	77 (81.9)	

CI: confidence interval; mITT: modified Intent-to-Treat.
Notes: Two-sided 95% CI for the observed difference in death rates (rezafungin for injection treatment group minus caspofungin treatment group) is calculated using methodology of Miettinen and Nurminen.
a. Percentages were calculated using the total number of patients with known survival status in the mITT Population in each treatment group (N1) as the denominator.
b. Method of Miettinen and Nurminen unadjusted for randomization strata.
c. Patients who died on or before Day 30, or with unknown survival status.
d. Percentages are calculated using the total number of patients in the mITT Population in each treatment group as the denominator.
e. Method of Miettinen and Nurminen adjusted for randomization strata.
f. Missing primary outcome data were imputed with multiple imputation using a logistic regression with randomization stratification factors as predictive variables.

6.3.8.3 Secondary Endpoint Results

Analyses of the secondary endpoints provide supportive evidence of the efficacy of rezafungin for injection.

6.3.8.3.1 Day 14 Global Response as Assessed by Data Review Committee

The rate of patients with global cure was 59.1% and 60.6% in the rezafungin and caspofungin groups, respectively (Table 28) (treatment difference of –1.5 [95% CI: -15.4, 12.5]). The failure rate (not including indeterminate responses) was 30.1% and 30.9% in the rezafungin and caspofungin groups, respectively. The indeterminate rate was 10.8% and 8.5%, respectively. The primary reasons for an indeterminate response were lost to follow-up and withdrawal of consent; it is unknown if these were related to Coronavirus Disease 19 (COVID-19).

Table 28: ReSTORE Global Response as Assessed by Data Review Committee at Day 14 (±1 day) (mITT Population)

DRC Global Response, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)	Difference (95% CI)
Cure	55 (59.1)	57 (60.6)	-1.5 (-15.4, 12.5)
Failure or Indeterminate	38 (40.9)	37 (39.4)	
Failure	28 (30.1)	29 (30.9)	
Indeterminate	10 (10.8)	8 (8.5)	

CI: confidence interval; mITT: modified Intent-to-Treat
Notes: Two-sided 95% CI for the observed differences in cure rate (rezafungin for injection treatment group minus caspofungin treatment group) was calculated a using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of patients in the mITT Population in each treatment group as the denominator.

6.3.8.3.2 Day 14 Global Cure as Assessed by Data Review Committee by *Candida* Species

Global Cure as assessed by the DRC at Day 14 (±1 day) by baseline *Candida* species is summarized in Table 29 for the mITT Population. For *C. glabrata*, *C. tropicalis*, and *C. parapsilosis,* the global cure rates in the rezafungin group were 66.7%, 70.0%, and 75.0%, respectively, compared with the caspofungin group, 56.0%, 58.8%, and 64.7%, respectively. The rates of global cure for *C. albicans* were lower than in other species but similar between treatment groups.

Table 29: ReSTORE Global Cure as Assessed by the Data Review Committee at Day 14 (±1 day) by Baseline *Candida* Species (mITT Population)

Candida Species at Baseline, n/N1 (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)
Candida albicans	21/39 (53.8)	23/40 (57.5)
Candida glabrata	16/24 (66.7)	14/25 (56.0)
Candida tropicalis	14/20 (70.0)	10/17 (58.8)
Candida parapsilosis	6/8 (75.0)	11/17 (64.7)
Candida dubliniensis	2/3 (66.7)	1/1 (100.0)
Candida krusei	0/2 (0.0)	2/2 (100.0)
Candida guilliermondii	1/2 (50.0)	0
Candida lusitaniae	1/1 (100.0)	1/1 (100.0)
Candida metapsilosis	1/1 (100.0)	0
Candida nivariensis	0	1/1 (100.0)

DRC: Data Review Committee; N: number of patients in the mITT Population; n: number of patients with DRC global response of Cure at Day 14; N1: number of patients in the mITT Population with the specified *Candida* pathogen at Baseline.

6.3.8.3.3 Global Response as Assessed by Data Review Committee by Visit

Global response as assessed by the DRC was analyzed by visit and summarized in Table 30 for the mITT Population. At each of the secondary endpoint visits, Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (within 2 days of last dose), and Follow-up (Days 52–59), the response rates were similar between treatment groups.

Table 30: ReSTORE Global Response As Assessed by Data Review Committee by Visit (mITT Population)

Visit DRC Global Response, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)	Difference (95% CI)
Day 5			
Cure	52 (55.9)	49 (52.1)	3.8 (-10.5, 17.9)
Failure or indeterminate	41 (44.1)	45 (47.9)	
Failure	32 (34.4)	37 (39.4)	
Indeterminate	9 (9.7)	8 (8.5)	
Day 14 (±1 day)			
Cure	55 (59.1)	57 (60.6)	-1.5 (-15.4, 12.5)
Failure or indeterminate	38 (40.9)	37 (39.4)	
Failure	28 (30.1)	29 (30.9)	
Indeterminate	10 (10.8)	8 (8.5)	
Day 30 (-2 day)			
Cure	46 (49.5)	46 (48.9)	0.5 (-13.7, 14.7)
Failure or indeterminate	47 (50.5)	48 (51.1)	
Failure	31 (33.3)	36 (38.3)	
Indeterminate	16 (17.2)	12 (12.8)	
EOT (within 2 days of last dose)			
Cure	56 (60.2)	59 (62.8)	-2.6 (-16.4, 11.4)
Failure or indeterminate	37 (39.8)	35 (37.2)	
Failure	29 (31.2)	32 (34.0)	
Indeterminate	8 (8.6)	3 (3.2)	
Follow-up (Days 52–59)			
Cure	42 (45.2)	39 (41.5)	3.7 (-10.5, 17.7)
Failure or indeterminate	51 (54.8)	55 (58.5)	
Failure	38 (40.9)	42 (44.7)	
Indeterminate	13 (14.0)	13 (13.8)	

CI: confidence interval; EOT: end of treatment; mITT: modified Intent-to-Treat.
Notes: Two-sided 95% CIs for the observed differences in cure rates (rezafungin for injection treatment group minus caspofungin treatment group) were calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of patients in the mITT Population in each treatment group as the denominator.

6.3.8.3.4 Mycological Response by Visit

Mycological response by visit is summarized in Table 31 for the mITT Population. Eradication rates were similar between treatment groups at the Day 14 (±1 day), Day 30 (-2 days), EOT (within 2 days of last dose), and Follow-up (Days 52–59) visits. At Day 5, eradications rates were 68.8% in the rezafungin for injection group and 61.7% in the caspofungin group (treatment difference of 7.1 [95% CI: -6.6 to 20.6]).

Table 31: ReSTORE Mycological Response by Visit (mITT Population)

Visit Mycological Response, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)	Difference (95% CI)
Day 5			
Eradication	64 (68.8)	58 (61.7)	7.1 (-6.6, 20.6)
Failure or indeterminate	29 (31.2)	36 (38.3)	
Failure	25 (26.9)	27 (28.7)	
Indeterminate	4 (4.3)	9 (9.6)	
Day 14 (±1 day)			
Eradication	63 (67.6)	62 (66.0)	1.8 (-11.7, 15.2)
Failure or indeterminate	30 (32.3)	32 (34.0)	
Failure	26 (28.0)	28 (29.8)	
Indeterminate	4 (4.3)	4 (4.3)	
Day 30 (-2 day)			
Eradication	56 (60.2)	53 (56.4)	3.8 (-10.3, 17.8)
Failure or indeterminate	37 (32.3)	41 (43.6)	
Failure	33 (35.5)	38 (40.4)	
Indeterminate	4 (4.3)	3 (3.2)	
EOT (within days of last dose)			
Eradication	63 (67.7)	63 (67.0)	0.7 (-12.7, 14.1)
Failure or indeterminate	30 (32.3)	31 (33.0)	
Failure	26 (28.0)	29 (30.9)	
Indeterminate	4 (4.3)	2 (2.1)	
Follow-up (Days 52–59)			
Eradication	48 (51.6)	49 (52.1)	-0.5 (-14.7, 13.7)
Failure or indeterminate	45 (48.4)	45 (47.9)	
Failure	41 (44.1)	43 (45.7)	
Indeterminate	4 (4.3)	2 (2.1)	

CI: confidence interval; EOT: end of treatment; mITT: modified Intent-to-Treat
Notes: Eradication includes both documented and presumed eradication. Two-sided 95% CIs for the observed differences in eradication rates (rezafungin for injection treatment group minus caspofungin treatment group) were calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of patients in the mITT Population in each treatment group as the denominator.

6.3.8.3.5 Investigators' Assessment of Day 14 Clinical Response of Cure

Investigators' assessment of clinical response at Day 14 (±1 day) is summarized in Table 32 for the mITT Population. Similar rates of clinical cure were achieved in both treatment groups.

Table 32: ReSTORE Investigators' Assessment of Clinical Response at Day 14 (±1 day) (mITT Population)

Visit Clinical Response, n (%)	Rezafungin 400/200 mg (N=93)	Caspofungin 70/50 mg (N=94)	Difference (95% CI)
Day 14 (±1 day)			
Cure	62 (66.7)	63 (67.0)	-0.4 (-13.8, 13.1)
Failure or indeterminate	31 (33.3)	31 (33.0)	
Failure	26 (28.0)	27 (28.7)	
Indeterminate	5 (5.4)	4 (4.3)	

CI: confidence interval; EOT: end of treatment; mITT: modified Intent-to-Treat
Notes: Two-sided 95% CIs for the observed differences in clinical cure rates (rezafungin treatment group minus caspofungin treatment group) were calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of patients in the mITT Population in each treatment group as the denominator.

For those species with sufficient numbers to enable comparison, the response rates were generally similar (Table 33). The response rate for *C. tropicalis* was higher in the rezafungin for injection group (75.0%) compared to the caspofungin group (52.8%).

Table 33: ReSTORE Mycological Response by *Candida* Species (mITT Population)

Fungal Pathogen	Rezafungin 400/200 mg (N=93) n/N1 (%)	Caspofungin 70/50 mg (N=94) n/N1 (%)
Candida albicans	23/39 (59.0)	24/40 (60.0)
Candida glabrata	20/24 (83.3)	15/25 (60.0)
Candida tropicalis	15/20 (75.0)	10/17 (58.8)
Candida parapsilosis	6/8 (75.0)	14/17 (82.4)
Candida dubliniensis	3/3 (100.0)	1/1 (100.0)
Candida krusei	0/2 (0.0)	2/2 (100.0)
Candida guilliermondii	1/2 (50.0)	0
Candida lusitaniae	1/1 (100.0)	1/1 (100.0)
Candida metapsilosis	1/1 (100.0)	0
Candida nivariensis	0	1/1 (100.0)

6.4 Pooled Efficacy Data

For the pooled data, the treatment difference is weighted by study and Part (for STRIVE). The 95% CIs are calculated with stratification (for study and Part [for STRIVE]) using the methodology of Miettinen and Nurminen (Miettinen and Nurminen, 1985) with inverse variance of the effect size for the stratum weights.

6.4.1 All-Cause Mortality

6.4.1.1 Subgroup Analysis for All-Cause Mortality at Day 30

A forest plot of the difference in ACM at Day 30 is provided in Figure 24. The 95% CIs were overlapping for most of these subgroups, with the exceptions of age group and baseline renal impairment.

Among the pooled groups, the rate of patients with ACM at Day 30 (2 days) in patients aged ≥ 65 years was 14.0% and 31.7% in the rezafungin and caspofungin groups, respectively (weighted treatment difference of 17.6 [95% CI: -32.5 to -2.8], favoring rezafungin for injection; Figure 25); the rate of patients with ACM at Day 30 (-2 days) in patients aged < 65 years was 22.0% and 10.9% in the rezafungin and caspofungin groups, respectively (weighted treatment difference of 10.9 [95% CI: -1.0 to 22.8], favoring caspofungin). Elderly patients are more immunosenescent and cannot clear the infection as well and may therefore benefit more from the higher exposure of rezafungin.

Among the pooled groups, the rate of patients with ACM at Day 30 (-2 days) in patients with moderate/severe renal impairment (creatinine clearance < 60 mL/minute) was 13.0% and 30.5% in the rezafungin and caspofungin groups, respectively (weighted treatment difference of -18.2 [95% CI: -33.1 to -3.2]); the rate of patients with ACM at Day 30 (-2 days) in patients with normal/mild renal impairment (creatinine clearance ≥ 60 mL/minute) was 22.7% and 10.8% in the rezafungin and caspofungin groups, respectively (weighted treatment difference of 11.3 [95% CI: -1.1 to 23.7]). There is no known clinical rationale for a difference in ACM at Day 30 based on renal function.

Figure 25: Subgroup Analysis for All-Cause Mortality (Pooled STRIVE and ReSTORE)

	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)
Sex			
Male	20 / 90 (22%)	17 / 90 (19%)	1.1 (-10.8, 13.1)
Female	6 / 49 (12%)	13 / 65 (20%)	-6.7 (-21.3, 7.9)
BMI			
< 25 kg/m² (underweight/normal)	12 / 75 (16%)	16 / 75 (21%)	-4.1 (-16.9, 8.6)
25 – 30 kg/m² (overweight)	6 / 28 (21%)	8 / 48 (17%)	7.6 (-11.3, 26.4)
> 30 kg/m² (obese)	7 / 30 (23%)	3 / 21 (14%)	3.9 (-19.5, 27.4)
Geographic Region			
North / South America†	6 / 43 (14%)	4 / 46 (9%)	4.1 (-11.5, 19.8)
Europe / Israel / Turkey	10 / 67 (15%)	15 / 76 (20%)	-6.6 (-19.2, 6.1)
Asia-Pacific	8 / 21 (38%)	10 / 27 (37%)	1.4 (-25.7, 28.4)
China / Taiwan	2 / 8 (25%)	1 / 6 (17%)	4.9 (-39.6, 49.5)
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)

ACM: all-cause mortality; APACHE II: Acute Physiology and Chronic Health Evaluation II; CI: confidence interval
* 2-sided 95% CI for the weighted (by study and Part A and Part B) treatment difference in death rates, rezafungin minus caspofungin, is calculated using the stratified (by study and Part A and Part B) methodology of Miettinen and Nurminen.
† Single patient included from South America

6.4.2 Mycological Response

Among the pooled groups, the rate of patients with mycological eradication at Day 5 was 73.4% and 64.5% in the rezafungin and caspofungin groups, respectively (Table 34). At Day 5, the indeterminate rate in the rezafungin group (3.6%) was approximately half that of the caspofungin group (6.5%).

Mycological eradication rates at Day 14 were similar to the results at Day 5.

Table 34: Mycological Response at Days 5 and 14 (Pooled mITT Population)

Visit Mycological Response, n (%)	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)	Difference (95% CI)
Day 5			
Eradication	102 (73.4)	100 (64.5)	10.0 (-0.3, 20.4)
Failure or indeterminate	37 (26.6)	55 (35.5)	
Failure	32 (23.0)	45 (29.0)	
Indeterminate	5 (3.6)	10 (6.5)	
Day 14 (±1 day)			
Eradication	100 (71.9)	106 (68.4)	4.3 (-6.2, 14.7)
Failure or indeterminate	39 (28.1)	49 (31.6)	
Failure	34 (24.5)	45 (29.0)	
Indeterminate	5 (3.6)	4 (2.6)	

CI: confidence interval
2-sided 95% CI for the weighted (by study and Part A and Part B) treatment difference in eradication rates, rezafungin minus caspofungin, is calculated using the stratified (by study and Part A and Part B) methodology of Miettinen and Nurminen.

6.4.3 Time to First Negative Blood Culture –Pooled

Time to first negative blood culture in patients with a positive blood culture before randomization is summarized in Table 35 for the mITT Population. The percentage of patients who achieved a negative blood culture was 90.8% and 82.0% in the rezafungin and caspofungin groups, respectively, with median time to first negative blood culture of 22.3 hours and 26.3 hours, respectively.

At 24 hours, the percentage of patients with negative blood culture was 60.0% and 49.1% in the rezafungin for injection and caspofungin groups, respectively; at 48 hours, the percentage of patients with negative blood culture was 77.7% and 63.5% in the rezafungin and caspofungin groups, respectively.

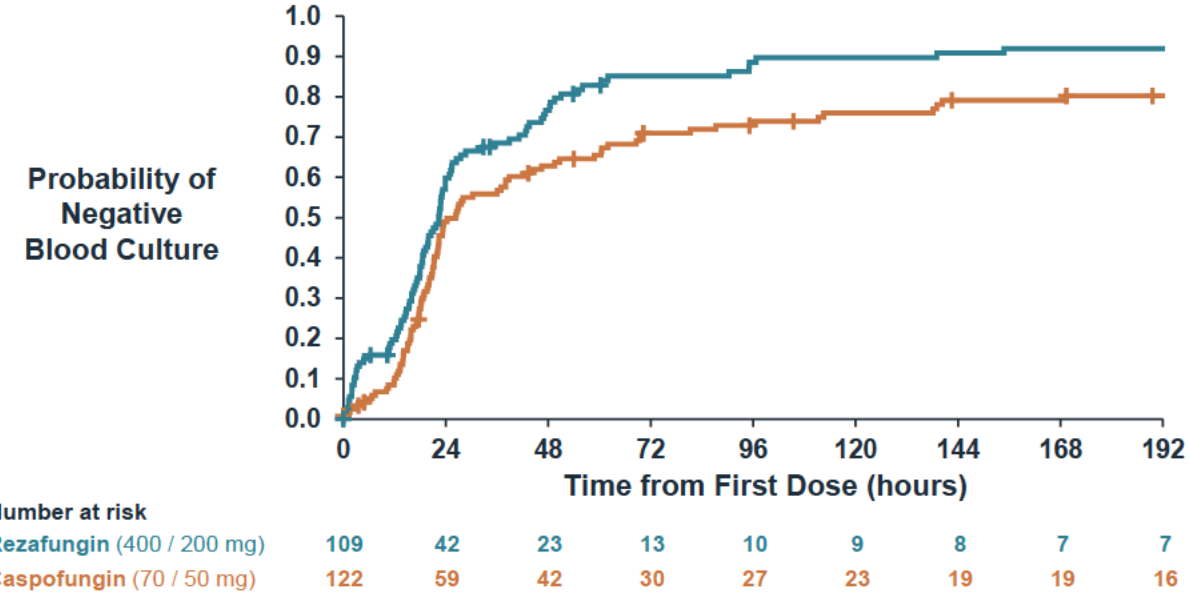
Table 35: Pooled STRIVE and ReSTORE Time to First Negative Blood Culture (Pooled mITT Population)

Characteristic, n (%)	Rezafungin 400/200 mg (N=109)	Caspofungin 70/50 mg (N=122)
Patients with an event (negative blood culture)[a]	99 (90.8)	100 (82.0)
Patients censored[b]	10 (9.2)	22 (18.0)
Time to first negative blood culture (hours)[c]		
Median	22.3	26.3
Patients with negative blood culture[d]		
at 24 hours	63/105 (60.0)	57/116 (49.1)
at 48 hours	80/103 (77.7)	73/115 (63.5)

CI: confidence interval; mITT: modified Intent-to-Treat.
Note: Candidemia patients and IC patients with a positive blood culture prior to randomization.
a. Patients with negative blood culture, without subsequent positive culture from a sample drawn following the first dose of study drug.
b. Patients were censored if they received an alternative antifungal (i.e., other than study drug) for the treatment of their candidemia, died, or were lost to follow-up prior to having a negative blood culture.
c. Time to first negative blood culture and percentages based on Kaplan-Meier estimates.
d. Patients censored prior to 24 and 48 hours are excluded from the denominator for 24 hours and 48 hours, respectively.

A Kaplan-Meier plot of time to first negative blood culture is provided in Figure 26.

Figure 26: Pooled STRIVE and ReSTORE Probability of Negative Blood Culture



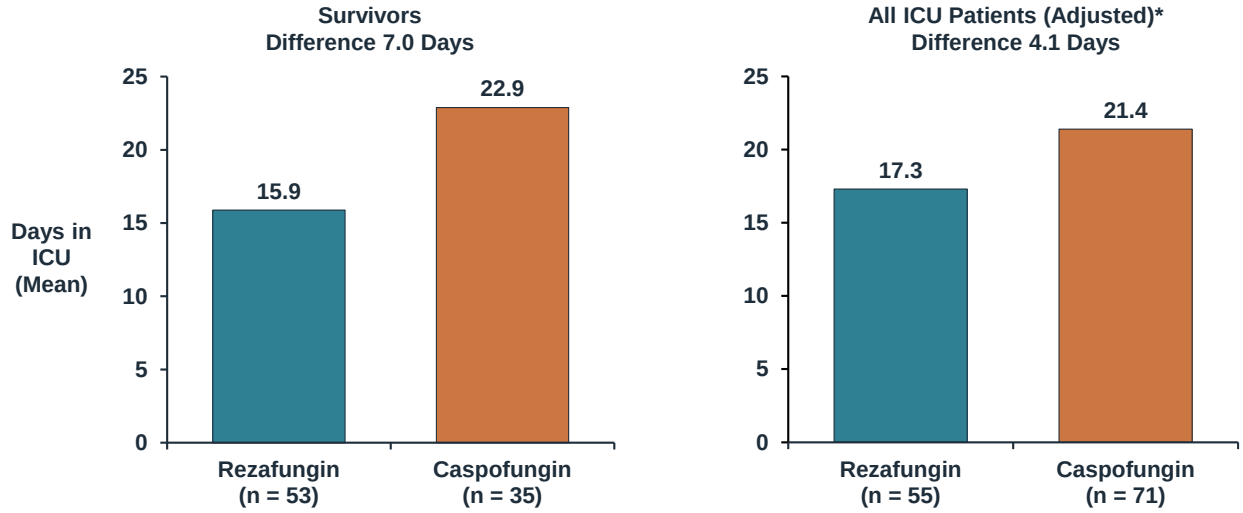
mITT modified Intent-to-Treat
mITT Population with positive blood culture before randomization

6.4.4 Time in Intensive Care Unit

For patients discharged from the ICU, the mean days in the ICU was 15.9 and 22.9 (treatment difference of 7 days) for the rezafungin and caspofungin groups, respectively.

Given the imbalance between treatment groups in mechanical ventilation in ReSTORE, an adjusted analysis was done including an imputation for patients who died. In this analysis, the adjusted mean days in the ICU was 17.3 and 21.4 (treatment difference: 4.1 days) for the rezafungin and caspofungin groups, respectively.

Figure 27: Mean Day in Intensive Care Unit (Pooled STRIVE and ReSTORE)



ICU: intensive care unit
*Adjusted observed baseline imbalance between groups in proportion of patients receiving mechanical ventilation – simulated outcomes for non-survivors.

6.5 Efficacy Conclusions

The totality of data across the clinical program demonstrated that the efficacy of rezafungin in the treatment of candidemia and invasive candidiasis was comparable to caspofungin, which is one of the current first-line standard of care antifungal medications for this disease.

In the Phase 2 study, STRIVE, outcome rates, including overall success at Day 14 and Day 5, were similar or higher for rezafungin compared to caspofungin.

The Phase 3 study, ReSTORE, met its primary efficacy endpoint and demonstrated that rezafungin, administered at a 400 mg dose in Week 1, followed by 200 mg once weekly, for a total of 2 to 4 doses was noninferior to caspofungin for 30-Day ACM. Secondary endpoints, including global cure at Day 14 and mycological response at Days 5 and 14, provided supportive evidence of the efficacy of rezafungin.

7 CLINICAL SAFETY

Summary

- The safety profile of rezafungin is well characterized, with manageable AEs, allowing most patients to remain on therapy.
- Nearly all patients experienced an AE. The incidence of overall AEs, as well as the incidence of SAEs, reflected the severity of the underlying comorbidities in this patient population.
- There was a similar incidence of deaths between the treatment groups, the most common AE leading to death was septic shock.
- Higher levels of liver function test increases were observed for caspofungin.
- There were no events of serious hepatocellular DILI in either rezafungin or caspofungin treatment group.

7.1 Safety Populations

Across the clinical development program, a total of 312 individuals received rezafungin at the proposed dose of 400/200 mg or higher administered for at least 2 weeks.

The design of the Phase 2 STRIVE and Phase 3 ReSTORE studies are nearly identical, allowing an integrated analysis of safety data of the Phase 2 STRIVE rezafungin 400/200 mg group and Phase 3 ReSTORE rezafungin 400/200 mg group (N=151) and caspofungin groups (N=166), referred to as the Pooled Safety Population (Table 36). Patients were followed for safety through the follow-up visit (Day 59); patients who discontinued study drug were to remain on study for safety follow-up.

Phase 1 safety data are presented following the Pooled Safety Population and in Appendix Section 10.5.

Table 36: Summary of Study Drug Exposure

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

7.2 Overall Extent of Exposure

For STRIVE and 3 ReSTORE, the duration of treatment ranged from 1 to 28 days, and the median duration of treatment (IV and oral therapy combined) was 14.0 days (Table 37). Both IV and oral therapy had similar median duration of treatment across the study treatment groups. In the rezafungin group 27.8% of patients received oral therapy compared with 35.5% of caspofungin patients.

Table 37: Study Drug Exposure (Days) (Pooled Safety Population)

Exposure	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
IV and oral therapy combined		
Mean (SD)	12.6 (6.29)	13.8 (6.40)
Median (min, max)	14.0 (1, 28)	14.0 (1, 28)
IV therapy		
Mean (SD)	11.3 (5.81)	12.1 (6.11)
Median (min, max)	14.0 (1, 28)	14.0 (1, 28)
Oral therapy [a]		
n	40	58
Mean (SD)	9.4 (4.95)	9.0 (4.45)
Median (min, max)	10.0 (1, 24)	9.0 (2, 21)
Distribution of study drug exposure duration (days)		
IV and oral therapy combined		
1–7	34 (22.5)	30 (18.1)
8–14	85 (56.3)	86 (51.8)
15–28	32 (21.2)	50 (30.1)
> 28	0	0
IV therapy		
1–7	36 (23.8)	34 (20.5)
8–14	88 (58.3)	87 (52.4)
15–28	27 (17.9)	45 (27.1)
> 28	0	0
Oral therapy [b]	42 (27.8)	59 (35.5)
1–3	5 (11.9)	9 (15.3)
4–7	11 (26.2)	14 (23.7)
8–14	20 (47.6)	27 (45.8)
15–28	4 (9.5)	8 (13.6)
> 28	0	0
Unknown	2 (4.8)	1 (1.7)

IV: intravenous; Max: maximum; Min: minimum; N: number of patients; n: number of patients in the category; SD: standard deviation
Note: Percentages were calculated using the total number of patients in each treatment group (N) as the denominator. Exposure duration calculation included the placebo received to maintain the blind.
a. Oral stepdown therapy was fluconazole for caspofungin group and placebo for rezafungin for injection group
b. Denominator is the number of patients who switched to oral stepdown therapy.

7.3 Overview of Adverse Events

In the Pooled Safety Population, as expected in this seriously ill hospitalized population, nearly all patients experienced at least 1 AE (Table 38). Approximately half of the patients in each treatment group experienced an SAE or a severe AE (defined as an event with a Grade 3 or higher based on Common Terminology Criteria for Adverse Events [CTCAE] criteria). Few patients experienced AEs leading to interruption or discontinuation of study drug.

Table 38: Overview of Adverse Events (Pooled Safety Population)

	STRIVE	Pooled Safety Population	
Number of Patients with ≥ 1:	Rezafungin 400/400 mg (N=81)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Adverse Event	69 (87.2)	138 (91.4)	138 (83.1)
Mild	12 (14.8)	25 (16.6)	23 (13.9)
Moderate	29 (35.8)	39 (25.8)	30 (18.1)
Severe	28 (34.6)	74 (49.0)	85 (51.2)
AE leading to interruption of study drug	0	3 (2.0)	4 (2.4)
AE leading to discontinuation of study drug	6 (7.4)	14 (9.3)	15 (9.0)
AE leading to discontinuation of study	13 (16.0)	24 (15.9)	32 (19.3)
Serious adverse event	35 (43.2)	83 (55.0)	81 (48.8)
Serious adverse event resulting in death	14 (17.3)	35 (23.2)	40 (24.1)

AE: adverse event

7.4 Common Adverse Events

The most common (occurring in ≥ 10% of either pooled treatment group) AEs were hypokalemia, pyrexia, and diarrhea in the rezafungin group and hypokalemia, and diarrhea in the caspofungin group (Table 39). These AEs are expected in this hospitalized patient population.

Table 39: Adverse Events Occurring in ≥ 5% of Patients in Either Pooled Treatment Group (Pooled Safety Population)

Preferred Term, n (%)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Number of patients with ≥ 1 AE	138 (91.4)	138 (83.1)
Hypokalemia	22 (14.6)	17 (10.2)
Pyrexia	18 (11.9)	11 (6.6)
Diarrhea	17 (11.3)	17 (10.2)
Anaemia	15 (9.9)	13 (7.8)
Vomiting	14 (9.3)	7 (4.2)
Nausea	13 (8.6)	8 (4.8)
Hypomagnesaemia	12 (7.9)	5 (3.0)
Pneumonia	12 (7.9)	7 (4.2)
Abdominal pain	11 (7.3)	9 (5.4)
Septic shock	11 (7.3)	12 (7.2)
Sepsis	10 (6.6)	8 (4.8)
Constipation	8 (5.3)	8 (4.8)
Hypophosphataemia	8 (5.3)	5 (3.0)
Hypotension	7 (4.6)	10 (6.0)
Acute kidney injury	6 (4.0)	11 (6.6)
Urinary tract infection	5 (3.3)	9 (5.4)
Hyperkalaemia	3 (2.0)	9 (5.4)
Pleural effusion	3 (2.0)	10 (6.0)

AE: adverse events

7.5 Adverse Events by Severity

Among the pooled groups, the incidence of moderate and severe events was similar between the treatment groups.

The most common severe AEs were septic shock and pneumonia in the rezafungin group and septic shock and sepsis in the caspofungin group (Table 40).

Table 40: Severe Adverse Events (Pooled Safety Population)

Preferred Term, n (%)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Number of patients with ≥ 1 severe AE	74 (49.0)	85 (51.2)
Septic shock	10 (6.6)	12 (7.2)
Pneumonia	7 (4.6)	2 (1.2)
Sepsis	4 (2.6)	6 (3.6)
Urinary tract infection	2 (1.3)	0
Abdominal pain	2 (1.3)	2 (1.2)
Anaemia	2 (1.3)	2 (1.2)
Hypotension	2 (1.3)	1 (0.6)
Acute kidney injury	1 (0.7)	4 (2.4)
Hyperkalaemia	1 (0.7)	2 (1.2)
Hypokalaemia	1 (0.7)	2 (1.2)
Diarrhoea	0	1 (0.6)
Nausea	0	1 (0.6)
Pleural effusion	0	2 (1.2)
Vomiting	0	1 (0.6)

AE: adverse event.

7.6 Adverse Events Leading to Dose Interruption

Among the pooled groups, AEs leading to interruption of study drug (i.e., stopping and then restarting the infusion or missing a dose) occurred in 2.0% of patients in the rezafungin for injection group and 2.4% of patients in the caspofungin group (Table 41). No AE leading to dose interruption occurred in more than 1 patient across the study treatment groups.

Table 41: Adverse Events Leading to Interruption of Study Drug (Pooled Safety Population)

Preferred Term, n (%)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Number of patients with at least one AE leading to interruption of study drug	3 (2.0)	4 (2.4)
Bronchopulmonary aspergillosis	1 (0.7)	0
Infusion-related hypersensitivity reaction	1 (0.7)	0
Nausea	1 (0.7)	0
Vomiting	1 (0.7)	0
Wheezing	1 (0.7)	0
Candida sepsis	0	1 (0.6)
Infusion site extravasation	0	1 (0.6)
Liver function test abnormal	0	1 (0.6)
Renal impairment	0	1 (0.6)
Respiratory tract infection	0	1 (0.6)

AE: adverse event

7.7 Adverse Events Leading to Discontinuation of Study Drug

Among the pooled groups, AEs leading to discontinuation of study drug occurred in 9.3% of patients in the rezafungin group, and 9.0% of patients in the caspofungin group (Table 38). Most AEs leading to discontinuation did not occur in more than 1 patient, with the exception of infusion-related reaction in 2 patients in the rezafungin group, and chorioretinitis and endophthalmitis in 2 patients each in the caspofungin group.

- Infusion-related reaction: 2 (1.3%) versus 0
- Chorioretinitis: 0 versus 2 (1.2%)
- Endophthalmitis: 0 versus 2 (1.2%)

Of note, 4 of the AEs leading to discontinuation of study drug for rezafungin were temporally associated with placebo administration: infusion-related reaction, wheezing, adverse drug reaction, and urticaria in ReSTORE.

7.8 Serious Adverse Events

The most commonly reported SAE in both treatment groups was septic shock (occurring in 6% of patients in both treatment groups of the pooled data). Other preferred terms (PTs) occurred in ≤ 3.6% of patients in either pooled treatment group (Table 42).

There were 3 potentially related SAEs in the rezafungin 400/200 mg group:

- First-degree atrioventricular block (discovered on routine ECG at the EOT; the patient was asymptomatic but required delayed discharge to investigate the diagnosis, with an ECG repeated several days later and found to be normal, followed by patient discharge),
- Infusion-related reaction,
- Urticaria.

The SAEs of atrial flutter and infusion-related reaction were associated with ongoing Day 3 infusions of study drug, which was a saline placebo infusion for those in the rezafungin group.

The SAE of urticaria was deemed by the Investigator to be related to oral study drug (urticaria developed following administration of oral study medication [which is the placebo for patients in the rezafungin group] and resulted in hospitalization being prolonged).

The 5 related SAEs for caspofungin were ventricular tachycardia, rectal hemorrhage (associated with oral fluconazole study drug), hypertransaminaesemia, liver injury, and anaphylactic shock.

Table 42: Serious Adverse Events Occurring in ≥ 2 Patients in Either Pooled Treatment Group (Pooled Safety Population)

Preferred Term, n (%)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Number of patients with at least one SAE	83 (55.0)	81 (48.8)
Septic shock	9 (6.0)	10 (6.0)
Multiple organ dysfunction syndrome	5 (3.3)	4 (2.4)
Bacteraemia	4 (2.6)	2 (1.2)
Pneumonia	4 (2.6)	3 (1.8)
Sepsis	4 (2.6)	6 (3.6)
Cardiac arrest	3 (2.0)	1 (0.6)
Abdominal abscess	2 (1.3)	3 (1.8)
Acute kidney injury	2 (1.3)	3 (1.8)
Gastrointestinal haemorrhage	2 (1.3)	0
Pneumonia aspiration	2 (1.3)	1 (0.6)
Shock	2 (1.3)	0
Staphylococcal bacteraemia	2 (1.3)	0
Upper gastrointestinal haemorrhage	2 (1.3)	0
Acute respiratory failure	1 (0.7)	4 (2.4)
Aspiration	1 (0.7)	3 (1.8)
Respiratory failure	1 (0.7)	5 (3.0)
Ventricular tachycardia	1 (0.7)	2 (1.2)
Bacterial sepsis	0	2 (1.2)
COVID-19 pneumonia	0	2 (1.2)
Klebsiella sepsis	0	3 (1.8)
Hyperkalaemia	0	3 (1.8)
Intra-abdominal haemorrhage	0	2 (1.2)
Pleural effusion	0	2 (1.2)
Pneumothorax	0	2 (1.2)

SAE: serious adverse event

7.9 Deaths

Among the pooled groups in the STRIVE and ReSTORE studies, SAEs resulting in death occurred at similar rates between the rezafungin and caspofungin treatment groups (Table 43). The most common system organ class (SOC) was Infections and Infestations; all other SOCs occurred in ≤ 5.4% of patients in either group.

The most common SAE was septic shock (5.3% and 6.0% patients, respectively); other SAEs occurred in ≤ 3.3% of patients in either pooled treatment group (see Table 58 in Appendix Section 10.6). The mortality rate for these 2 clinical trials is not unusual for

this vulnerable population and is similar to what has been observed in previous clinical trials in this indication.

Table 43: Serious Adverse Events Leading to Death by System Organ Class (Pooled Safety Population)

System Organ Class, n (%)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Number of patients with ≥ 1 serious adverse event resulting in death	35 (23.2)	40 (24.1)
Infections and infestations	14 (9.3)	24 (14.5)
Cardiac disorders	6 (4.0)	4 (2.4)
General disorders and administration site conditions	6 (4.0)	3 (1.8)
Respiratory, thoracic and mediastinal disorders	5 (3.3)	9 (5.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (3.3)	3 (1.8)
Vascular disorders	2 (1.3)	0
Death NOS	1 (0.7)	0
Nervous system disorders	1 (0.7)	0
Gastrointestinal disorders	0	2 (1.2)

NOS: not otherwise specified

7.10 Adverse Events of Special Interest

Infusion-related reactions are associated with echinocandin infusions and related to the rate of infusion. These were noted infrequently in Phase 1 clinical trials at higher doses of rezafungin.

Photosensitivity was noted in nonclinical studies and mild photosensitivity similar to the positive control (ciprofloxacin) was observed in a Phase 1 clinical trial.

In nonclinical 3-month toxicology studies, tremor was observed in some monkeys at high drug exposures. Histopathology in these animals showed reversible Schwann cell hypertrophy and non-adverse phospholipidosis in the sensory ganglia of the peripheral nervous system.

For these reasons, the following were considered AESIs in the clinical trials:

- Infusion-related reactions
- Photosensitivity
- Neurological events (e.g., ataxia, axonal neuropathy, hypoesthesia, paresthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathies, peripheral sensorimotor neuropathy, polyneuropathy, toxic neuropathy, tremors)

AESIs are summarized in Table 44.

Table 44: Adverse Events of Special Interest in Either Pooled Treatment Group (Pooled Safety Population)

System Organ Class Preferred Term, n (%)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Nervous system disorders		
Tremor	4 (2.6)	0
Intensive care unit acquired weakness	1 (0.7)	1 (0.6)
Peroneal nerve palsy	1 (0.7)	0
Polyneuropathy	0	2 (1.2)
Neuropathy peripheral	0	1 (0.6)
Infusion-related reactions		
Infusion-related reaction[a]	3 (2.0)	0
Infusion related hypersensitivity reaction[a, b]	1 (0.7)	0
Anaphylactic shock	0	1 (0.6)
Adverse drug reaction[a, b]	1 (0.7)	0
Photosensitivity	0	0

AESI: adverse event of special interest
a. The infusion-related hypersensitivity reaction, adverse drug reaction, and one patient with infusion-related reactions occurred during administration of saline placebo.
b. The infusion-related hypersensitivity reaction was reported as "rash and significant wheezing during study drug infusion" in a patient receiving saline placebo on Day 3. The adverse drug reaction was a rash that occurred during study drug infusion (saline placebo) in the same patient on Day 4.

7.10.1 Infusion-Related Reactions

Infusion-related reactions occurred in 5 patients in the Pooled Safety Population:

- 4 (2.6%) of whom were in the rezafungin group (2 in patients receiving saline placebo infusion),
- 1 (0.6%) in the caspofungin group (anaphylactic shock during caspofungin infusion on Day 3).

Of the 4 events in the rezafungin group, the AESI of infusion-related hypersensitivity reaction was reported as “rash and significant wheezing during study drug infusion” in a patient receiving saline placebo on Day 3. The AESI of adverse drug reaction was a rash that occurred during saline placebo infusion on Day 4 in the same patient. One additional rezafungin patient with infusion-related reaction experienced the event during a Day 3 placebo infusion.

If only AEs occurring while active study drug is being infused are considered, then in the pooled groups 2 patients in the rezafungin group (1.3%) and 1 patient in the caspofungin group (0.6%) had infusion reactions that can appropriately be attributed to an active study treatment.

7.10.2 Photosensitivity

No events of phototoxicity were reported in the Pooled Safety Population.

7.10.3 Neurological Events

7.10.3.1 Tremor

Of the events reported in the "Nervous system disorders" SOC, only "Tremor" occurred in the rezafungin arms at an incidence higher (4/151) than in the caspofungin arms (0/166).

The causality assessments of these 4 AEs of "Tremor" were assessed by an independent neurologist. The independent neurologist's opinions regarding the causality assessments are excerpted below:

- The AE reported as "tremors of both upper extremities" should have been reported as either "unwitnessed seizure and post-ictal neurological state, attributable to recent cerebral infarction" or "witnessed seizure, attributable to recent cerebral infarction." This AE is definitely not related to rezafungin treatment.
- The AE reported as "fluid shifts with the use of diuretics" is possibly related to treatment of rezafungin, which may have contributed to unreported electrolyte abnormalities, based on class effects of echinocandins.
- The AE of "hypokalemia" is definitely related to rezafungin treatment, based on class effects of echinocandins.
- The AE of "hypocalcemia" is definitely attributable to tumor lysis syndrome, caused by chemotherapy for lymphoma, and definitely not related to rezafungin treatment.

Of these 4 cases, 1 is considered definitely related and 1 is considered possibly related to rezafungin treatment. All 4 AEs were mild in intensity, and were easily treated by correction of serum electrolytes, or resolved without treatment.

Additional details are provided in Appendix Section 10.7.

7.10.3.2 Neuropathy

Incidence of neuropathy (all neuropathy PTs, plus ICU weakness) was lower in the rezafungin treatment group (n=2) than in the caspofungin group (n=4).

7.11 Cardiovascular Safety

In ReSTORE, 7.1% (n=7) of rezafungin patients and 4.1% (n=4) caspofungin patients had an SAE of a cardiac disorder. Based upon Data Safety Monitoring Board feedback due to this imbalance of cardiovascular events, an external cardiology consultant reviewed each of the patients with a cardiac SAE. Notwithstanding the potential shortcomings of the limited cardiac data available and complexity of the patients, the

reviewer concluded that the true rate of cardiac SAEs in the rezafungin for injection group did not differ from that of the caspofungin group.

ECG data were collected at different timepoints in the STRIVE study, prior to first dose and Day 14, and in the ReSTORE Study, prior to first dose and Day 1 after first dose. Thus, data are not pooled for analysis.

In STRIVE, trends in mean values and mean changes from baseline over time for ECG parameters were similar between groups and there were no meaningful changes noted in any group.

In the ReSTORE study, the percentage of patients with a ≥ 500 msec QTcF on Day 1 was 6.0% and 4.8% in the rezafungin and caspofungin groups, respectively. Of these patients with a Day 1 post-infusion elevated QTcF, 3 patients in the rezafungin group and 1 patient in the caspofungin group had a baseline QTcF > 500 msec (i.e., prior to study drug dosing). Those with a ≥ 60 msec Day 1 change from baseline in QTcF were 3.8% and 10.0% for rezafungin and caspofungin, respectively.

Additionally, a Phase 1 Definitive QT Study was performed, and there was no evidence of QT prolongation for rezafungin doses up to 1400 mg (see Appendix Section 10.5).

7.12 Clinical Laboratory Evaluations

While hematology and chemistry values can fluctuate widely in this highly vulnerable population, mean values for the majority of hematology and chemistry parameters were similar between the treatment groups over time, and no meaningful trends were identified.

The laboratory values were graded using the CTCAE version 5.0. If no CTCAE grade was available, Division of Microbiology and Infectious Disease or Division of AIDS grading was used. Among the pooled groups, two-grade increases from baseline in chemistry and hematology laboratory values occurred in the rezafungin and caspofungin groups:

- creatinine increased (13.1% and 19.8% patients, respectively),
- glucose increased (13.8% of patients in both treatment groups),
- potassium decreased (11.0% and 7.5% patients, respectively), and
- leukocytes increased (12.8% and 19.8% patients, respectively).

Two-grade increases in liver enzymes were lower in the rezafungin for injection compared to the caspofungin pooled group with increases in:

- ALT occurring in 2.7% versus 7.5% patients, respectively;
- AST occurring in 4.2% versus 8.8% patients, respectively;
- Bilirubin occurring in 4.1% versus 8.1% patients, respectively; and
- ALP occurring in 5.0% versus 7.4% patients, respectively.

The two-grade increases in remaining laboratory parameters occurred in < 10% of patients in either pooled treatment group. The incidence pattern of two-grade increases in chemistry and hematology laboratory values was similar across the study treatment groups within the individual studies and pooled data

7.12.1 Hepatotoxicity

Liver enzyme abnormalities at any time post-baseline are summarized in Table 45. Across the pooled groups, AST and/or ALT increases (> 3 × ULN, > 5 × ULN, and > 10 × ULN) and total bilirubin increased (> 2 × ULN) occurred in the caspofungin group at a higher rate than in the rezafungin for injection group. The proportion of patients with total bilirubin increased > 2 × ULN and ALP increased > 2 × ULN were similar between the pooled treatment groups. This incidence pattern of liver enzyme abnormalities at any time post-baseline was similar across the study treatment groups within the individual studies.

Table 45: Liver Enzyme Abnormalities at Any Time Post-Baseline (Pooled Safety Population)

Category, n/N1 (%)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
ALT > 3 × ULN	12/149 (8.1)	23/163 (14.1)
ALT > 5 × ULN	2/149 (1.3)	10/163 (6.1)
ALT > 10 × ULN	1/149 (0.7)	3/163 (1.8)
AST > 3 × ULN	18/149 (12.1)	27/163 (16.6)
AST > 5 × ULN	6/149 (4.0)	10/163 (6.1)
AST > 10 × ULN	1/149 (0.7)	5/163 (3.1)
ALT or AST > 3 × ULN	23/149 (15.4)	35/163 (21.5)
ALT or AST > 5 × ULN	7/149 (4.7)	15/163 (9.2)
ALT or AST > 10 × ULN	2/149 (1.3)	5/163 (3.1)
TBL > 2 × ULN	20/149 (13.4)	24/163 (14.7)
ALP > 2 × ULN	46/146 (31.5)	47/160 (29.4)

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; N: number of patients; N1: number of patients having at least one post-baseline measurement of the specified laboratory parameter; n: number of patients who meet the criterion at any time post-baseline; TBL: total bilirubin; ULN: upper limit of normal.
Note: For a combined criterion to be fulfilled, all conditions had to be fulfilled on the same lab measurement.

Table 44 summarizes the combinations of increased AST/ALT and total bilirubin observed in this pooled safety population.

While 6 patients in the rezafungin group were identified as potential severe hepatocellular DILI through the initial screening laboratory criteria, no patients met the definition of Hy's law cases in the rezafungin development program. Three of the 6 patients in the rezafungin group had elevations in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN at baseline before any study drug was

administered. The remaining 3 patients with treatment-emergent elevations in AST or ALT had elevated total bilirubin > 2 × ULN at baseline. Alternative causes other than DILI were identified in all 3 patients. These 3 patients are summarized in Table 47. Narratives are provided in Appendix Section 10.7.

In patients without elevations in total bilirubin prior to initiation of study drug, 1/134 (0.7%) patients developed elevations in AST or ALT and total bilirubin following treatment with rezafungin and 3/148 (2.0%) developed elevations in AST or ALT and total bilirubin following treatment with caspofungin.

No patient with normal total bilirubin at baseline developed elevations in AST or ALT and total bilirubin with ALP < 2 x ULN in either group following treatment.

Table 46: Liver Enzyme Abnormalities by Baseline Bilirubin Status (Pooled Safety Population)

Category	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Overall Safety Population		
ALT or AST > 3 × ULN and TBL > 2 × ULN	9/149 (6.0)	4/163 (2.5)
ALT or AST > 5 × ULN and TBL > 2 × ULN	2/149 (1.3)	2/163 (1.2)
ALT or AST > 10 × ULN and TBL > 2 × ULN	0/149 (0.0)	1/163 (0.6)
ALT or AST > 3 × ULN and TBL > 2.0 × ULN and ALP ≤ 2 × ULN	6/146 (4.1)	0/160 (0.0)
Patients with Baseline TBL ≥ 2 × ULN		
ALT or AST > 3 × ULN and TBL > 2 × ULN	8/15 (53.3)	1/15 (6.7)
ALT or AST > 5 × ULN and TBL > 2 × ULN	1/15 (6.7)	0/15 (0.0)
ALT or AST > 10 × ULN and TBL > 2 × ULN	0/15 (0.0)	0/15 (0.0)
ALT or AST > 3 × ULN and TBL > 2.0 × ULN and ALP ≤ 2 × ULN	6/15 (40.0)	0/15 (0.0)
Patients with Baseline TBL < 2 × ULN	_	
ALT or AST > 3 × ULN and TBL > 2 × ULN	1/134 (0.7)	3/148 (2.0)
ALT or AST > 5 × ULN and TBL > 2 × ULN	1/134 (0.7)	2/148 (1.4)
ALT or AST > 10 × ULN and TBL > 2 × ULN	0/134 (0.0)	1/148 (0.7)
ALT or AST > 3 × ULN and TBL > 2.0 × ULN and ALP ≤ 2 × ULN	0/131 (0.0)	0/145 (0.0)

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; N: number of patients; N1: number of patients having at least one post-baseline measurement of the specified laboratory parameter; n: number of patients who meet the criterion at any time post-baseline; TBL: total bilirubin; ULN: upper limit of normal.

Table 47: Elevation in AST or ALT > 3 × ULN with ALP < 2 × ULN Following Treatment with Rezafungin

Age / Sex	Bili > 2 × ULN at Baseline	ALT or AST > 3 × ULN at Baseline	ALP < 2 x ULN at Baseline	Study Day of ALT or AST > 3× ULN	Alternative Causality
39 / M	Yes	No	Yes	8	Gunshot wound to the liver
27 / F	Yes	No	Yes	8	Sickle cell anemia and intermittent sickle cell crisis
64 / M	Yes	No	Yes	14	Congestive hepatopathy, hemolytic anemia, maxillofacial and mediastinal infections, concomitant medications, MODS and septic shock

ALT: alanine aminotransferase; AST: aspartate aminotransferase; Bili: bilirubin; MODS: multiple organ dysfunction syndrome; ULN: upper limit of normal

Determination of DILI AEs were based on standardized MedDRA queries. The percentage of patients with at least one DILI AE for the rezafungin versus the caspofungin pooled groups were 13.9% and 17.5%, respectively (Table 48).

Table 48: Potential Drug-Induced Liver Injury Adverse Events (Pooled Safety Population)

Standardized MedDRA Query	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Number of patients with at least one drug-induced liver injury adverse event	21 (13.9)	29 (17.5)
Cholestasis and jaundice of hepatic origin	4 (2.6)	4 (2.4)
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	2 (1.3)	6 (3.6)
Liver-related investigations, signs and symptoms	15 (9.9)	21 (12.7)
Liver-related coagulation and bleeding disturbances	0	2 (1.2)

7.13 Phase 1 Safety

No AEs in the rezafungin group were reported at an incidence ≥ 30% in the Phase 1 studies. All AEs for participants receiving rezafungin for injection in the Phase 1 studies were mild or moderate in severity, with one exception:

- In Study CD101.IV.1.17 (DDI-2), one participant experienced an event of severe abdominal pain, considered related to the administration of rezafungin and venetoclax. The event started on Day 16, approximately 1 day after the coadministration of rezafungin and venetoclax on Day 15, and led to the participant's transport to the hospital that day. The participant had ultrasounds

and a computed tomography scan and received ketorolac tromethamine and morphine sulfate IV. The participant was not hospitalized and returned to the clinical research unit later that evening with a diagnosis of “gas in the intestines.” The event was considered resolved approximately 2 days from onset.

There were no SAEs or deaths in the Phase 1 studies.

7.14 Safety Conclusions

The safety profile of rezafungin is well characterized with manageable AEs, allowing most patients to remain on therapy. Nearly all patients experienced an AE, and the incidence of overall AEs as well as the incidence of SAEs reflect the severity of the underlying comorbidities, which is expected in this ill, hospitalized population.

There was a similar incidence of deaths between the treatment groups, which aligns with background rates in this population.

With respect to AESIs in the pooled safety populations, infusion-related reactions occurred in 4 rezafungin-treated patients (2 with reactions during infusions of active drug), and 1 caspofungin-treated patient. Four patients receiving rezafungin experienced tremors. There was a low incidence of neuropathy in both treatment groups.

Lower levels of liver enzyme increases (AST and ALT) were observed for rezafungin than caspofungin, and there were no cases of serious hepatocellular DILI in either treatment group.

8 BENEFIT-RISK CONCLUSIONS

Echinocandins are the current first-line therapy for candidemia and invasive candidiasis, however gaps in the ideal treatment option continue to exist rendering candidemia and invasive candidiasis a high morbidity and mortality condition. Patients with candidemia and invasive candidiasis need new antifungal treatments that can address increasing rates of reduced susceptibility and resistance, dosing and drug interaction challenges, and tissue penetration while being effective and safe.

Rezafungin is an echinocandin with increased molecular stability and earlier concentration-dependent killing associated with more healthcare provider- and patient-friendly once-weekly dosing. Rezafungin also demonstrated a lack of drug-drug interactions, which is important in patients with multiple comorbidities and concomitant medications. No dose adjustment of rezafungin is required, including for those with renal or hepatic dysfunction. Rezafungin demonstrated a consistently favorable benefit-risk profile across the clinical development program and thus can provide patients with a next generation echinocandin treatment option for this rare disease with high mortality.

In both the Phase 2 and Phase 3 trials, rezafungin demonstrated comparable efficacy to a currently used echinocandin. Both STRIVE and ReSTORE trials suggest improvement in early mycological eradication with rezafungin treatment. Given the importance of early appropriate antifungal therapy, rezafungin may shorten the gap between diagnosis and effective exposure via high front-loaded dosing and thus may provide clinical benefit to patients while reducing the risk of resistance development.

Importantly, based on PK/PD target attainment data, rezafungin could treat less susceptible *Candida* pathogens, including *C. glabrata* and *C. auris*, that are not always treatable with approved options. In the clinical program, there were 3 patients (one in the ReSTORE study and 2 in expanded access) who had infections caused by *fks* mutant *C. glabrata* isolates exhibiting reduced in vitro susceptibility to the approved echinocandins and rezafungin, however all had positive outcomes when treated with rezafungin. Although no *C. auris* patients were seen in in the clinical development program, nonclinical and target attainment data support the potential efficacy of rezafungin for *C. auris* infections. Based on these data, rezafungin is currently the only antifungal with a *C. auris* provisional CLSI breakpoint (CLSI M27M44S Ed3 2022).

Additionally, the improved higher exposure of rezafungin allows for treatment of deep tissue infections. In fact, rezafungin has demonstrated substantially improved distribution to infected tissues and organs in a nonclinical invasive candidiasis model, further increasing the likelihood of achieving the required pharmacology at the site of infection compared to other echinocandins. This benefit was observed clinically in an expanded access patient who had multiple abdominal abscesses with *C. krusei* and failed micafungin therapy and was then cured following 12 weeks of rezafungin therapy.

Echinocandins have a well-established safety profile and, in general, are well tolerated. The safety data observed for rezafungin is consistent with that of the currently approved

echinocandins. AEs were mostly mild and transient, resolving while patients remained on treatment. SAEs and AEs leading to death occurred at comparable rates between groups and were types of events expected in this very sick, mostly hospitalized population. Notably, lower levels of liver enzyme increases were observed for rezafungin; and there were no cases of severe hepatocellular DILI.

Based on the totality of the data including an extensive nonclinical program and a clinical development program that included 2 global, double-blind randomized clinical studies, rezafungin is an echinocandin that demonstrates consistent efficacy and safety findings across a variety of clinical endpoints and a favorable benefit-risk profile.

The patient population that is most likely to benefit from rezafungin are adult patients with candidemia or invasive candidiasis, including those who are critically ill, who are symptomatic, and have traditional risk factors for candidemia and/or deep tissue (intra-abdominal and peritoneal) invasive candidiasis. Rezafungin offers patients an echinocandin with once-weekly dosing and front-loaded exposure associated with earlier mycological clearance, that lacks drug-drug interactions, requires no dose adjustment (e.g., for those with renal or hepatic dysfunction), and better enables continuity of care.

9 REFERENCES

Adeel A, Qu MD, Siddiqui E, Levitz SM, Ellison RT 3rd. Expanded Access Use of Rezafungin for Salvage Therapy of Invasive Candida glabrata Infection: A Case Report. Open Forum Infect Dis. 2021 Aug 28;8(11):ofab431.

Alexander BD, Johnson MD, Pfeiffer CD et al. Increasing echinocandin resistance in *Candida glabrata*: clinical failure correlates with presence of *FKS* mutations and elevated minimum inhibitory concentrations. *Clin Infect Dis*. 2013; 56: 1724–1732.

Andes D, Ambrose PG, Hammel JP, Van Wart SA, Iyer V, Reynolds DK, et al. Use of pharmacokinetic-pharmacodynamic analyses to optimize therapy with the systemic antifungal micafungin for invasive candidiasis or candidemia. *Antimicrob Agents Chemother*. 2011; 55(5): 2113–2121.

Andes D, Diekema DJ, Pfaller MA, Bohrmuller J, Marchillo K, Lepak A. In vivo comparison of the pharmacodynamic targets for echinocandin drugs against *Candida* species. Antimicrob Agents Chemother. 2010 Jun;54(6):2497-506.

Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. *Clin Infect Dis*. 2012; 54: 1110–1122.

Arastehfar A, Lass-Florl C, Garcia-Rubio R, Daneshnia F, Ilkit M, Boekhout T, et al. The Quiet and Underappreciated Rise of Drug-Resistant Invasive Fungal Pathogens. *J Fungi*. 2020; 6: 138.

Arendrup MC, Dzajic E, Jensen RH et al. Epidemiological changes with potential implication for antifungal prescription recommendations for fungaemia: data from a nationwide fungaemia surveillance programme. *Clin Microbiol Infect*. 2013; 19: E343–353.

Azie N, Neofytos D, Pfaller M, Meier-Kriesche HU, Quan SP, et al. The PATH (Prospective Antifungal Therapy) Alliance registry and invasive fungal infections: update 2012. *Diagn Microbiol Infect Dis.* 2012; 73: 293–300.

Bader JC, Bhavnani SM, Andes DR, Ambrose PG. We can do better: a fresh look at echinocandin dosing. *J Antimicrob Chemother*. 2018a; 73(Issue suppl_1): i44-i50.

Bader JC, Lakota EA, Flanagan S, Ong V, Sandison T, Rubino CM, et al. Overcoming the Resistance Hurdle: Pharmacokinetic-Pharmacodynamic Target Attainment Analyses for Rezafungin (CD101) against *Candida albicans* and *Candida glabrata*. *Antimicrob Agents Chemother*. 2018b; 62(6): e02614-17.

Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016; 25(7): 1029–1036.

Boikov DA, Locke JB, James KD, Bartizal K, Sobel JD. In vitro activity of the novel echinocandin CD101 at pH 7 and 4 against *Candida* spp. isolates from patients with vulvovaginal candidiasis. *J Antimicrob Chemother*. 2017; 72: 1355-8.

Boonstra JM, van der Elst KC, Veringa A, Jongedijk EM, Brüggemann RJ, Koster RA, et al. Pharmacokinetic Properties of Micafungin in Critically Ill Patients Diagnosed with Invasive Candidiasis. *Antimicrob Agents Chemother.* 2017; 61(12): e01398-17.

Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. *Sci Transl Med*. 2012; 4: 165rv13.

Brüggemann RJ, Verheggen R, Boerrigter E, Stanzani M, Verweij PE, Blijlevens NMA, et al. Management of drug-drug interactions of targeted therapies for haematological malignancies and triazole antifungal drugs. *Lancet Hematol*. 2022; 9(1): e58–e72.

Butts A, Reitler P, Ge W, Fortwendel JR, Palmer GE. Commonly Used Oncology Drugs Decrease Antifungal Effectiveness against *Candida* and *Aspergillus* Species. *Antimicrob Agents Chemother*. 2018; 62(7): e00504-18.

Cancidas (caspofungin acetate) [Prescribing Information]. Whitehouse Station, NJ: 2019 February.

Carvalhaes CG, Klauer AL, Rhomberg PR, Pfaller MA, Castanheira M. Evaluation of Rezafungin Provisional CLSI Clinical Breakpoints and Epidemiological Cutoff Values Tested against a Worldwide Collection of Contemporaneous Invasive Fungal Isolates (2019 to 2020). *J Clin Microbiol*. 2022a; 60:e0244921.

Carvalhaes CG, Rhomberg PR, Pfaller MA et al. Evaluation of the Post-Antifungal Effect of Rezafungin and Micafungin against *Candida albicans*, *Candida parapsilosis* and *Candida glabrata*. *Mycoses*. 2022b; 65: 1040-4.

Carvalhaes CG, Rhomberg PR, Strand GD, Klauer AL, Castanheira M. Rezafungin Activity against *Candida* spp. and *Aspergillus* spp. Isolates Causing Invasive Infections Worldwide in 2021. IDWeek 2022, October 19-23, Washington, D.C. Abstract P1731. 2022c.

Centers for Disease Prevention and Control (CDC). Antibiotic resistance threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/. Accessed April 25, 2018.

Centers for Disease Prevention and Control (CDC). Clinical Alert to United States (US) Healthcare Facilities: Global emergence of invasive infections caused by the multidrug-resistant yeast *Candida auris* 2016. https://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-alert.html. Accessed April 25, 2018.

Centers for Disease Prevention and Control (CDC). Antifungal Susceptibility Testing and Interpretation. May 29, 2020. https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html. Accessed May 26, 2022.

Centers for Disease Prevention and Control (CDC). Fungal Diseases: Statistics. August 24, 2021. https://www.cdc.gov/fungal/diseases/candidiasis/invasive/statistics.html. Accessed Dec 19, 2022.

Chandra J and Ghannoum, MA CD101, A novel echinocandin, possesses potent antibiofilm activity against early and mature *Candida albicans* biofilms. *Antimicrob. Agents Chemother*. 2018, 62.

Chowdhary A, Sharma C, Meis JF. *Candida auris*: A rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. *PLoS Pathogens*. 2017; 13(5): e1006290.

Chowdhary A, Voss A, Meis JF. Multidrug-resistant *Candida auris*: 'new kid on the block' in hospital-associated infections? *J Hosp Infect*. 2016; 94(3): 209–212.

Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antifungal Susceptibility Testing of Yeasts – Third Edition. CLSI document M27M44SEd3 [ISBN 978-1-68440-162-8]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2022.

Comlossy M, Walden J. The silver tsunami: states have a fairly long to-do list to get ready for the health care needs of an aging America. *State Legis*. 2013; 39(10): 14–19.

Cushion MT, Locke JB, Ong V, Bartizal K. 2018. Novel once-weekly echinocandin rezafungin (CD101) prevention and treatment of *Pneumocystis* biofilms, abstr. B127. EBMT, Lisbon, Portugal.

Czyrski A, Resztak M, Świderski P, Brylak J, Główka FK. The Overview on the Pharmacokinetic and Pharmacodynamic Interactions of Triazoles. *Pharmaceutics*. 2021; 13(11): 1961.

Demirci-Duarte, S, Arikan-Akdagli, S, Gülmez, D. Species distribution, azole resistance and related molecular mechanisms in invasive *Candida parapsilosis* complex isolates: Increase in fluconazole resistance in 21 years. Mycoses. 2021; 64: 823– 830.

Diekema DJ, Hsueh P-R, Mendes RE, Pfaller M, Rolston KV, Sader HS, et al. The Microbiology of bloodstream infection: 20-Year trends from the SENTRY antimicrobial surveillance program. *Antimicrob Agents Chemother*. 2019; 63(7): e00355-19.

Escribano P and Guinea J. Fluconazole-resistant *Candida parapsilosis*: A new emerging threat in the fungi arena. Front. Fungal Biol., 24 October 2022.

Eraxis (anidulafungin) [Prescribing Information]. New York, NY; Pfizer Roerig; 2020 May.

Ernst EJ, Klepser ME, Pfaller MA. Postantifungal effects of echinocandin, azole, and polyene antifungal agents against *Candida albicans* and *Cryptococcus neoformans*. *Antimicrob Agents Chemother*. 2000; 44(4):1108-1111.

Executive Office of the President, President's Council of Advisors on Science and Technology. Report to the President on Combating Antibiotic Resistance. September 2014.

Falagas ME, Apostolou KE, Pappas VD. Attributable mortality of candidemia: a systematic review of matched cohort and case-control studies. *Eur J Clin Microbiol Infect Dis.* 2006; 25(7): 419–425.

Fernandez J, Erstad BL, Petty W, Nix DE. Time to positive culture and identification for *Candida* blood stream infections. *Diagn Microbiol Infect Dis*. 2009; 64(4): 402–407.

Garcia-Effron G, Lee S, Park S, Cleary JD, Perlin DS. Effect of *Candida glabrata FKS1* and *FKS2* mutations on echinocandin sensitivity and kinetics of 1,3-beta-D-glucan

synthase: implication for the existing susceptibility breakpoint. *Antimicrob Agents Chemother*. 2009; 53(9): 3690–3699.

Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-imortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis*. 2006: 43(1): 245–231.

Grau S, Luque S, Campillo N, Samsó E, Rodríguez U, García-Bernedo CA, et al. Plasma and peritoneal fluid population pharmacokinetics of micafungin in post-surgical patients with severe peritonitis. *J Antimicrob Chemother*. 2015; 70(10): 2854–2861.

Hall RG 2nd, Swancutt MA, Meek C, Leff R, Gumbo T. Weight drives caspofungin pharmacokinetic variability in overweight and obese people: fractal power signatures beyond two-thirds or three-fourths. *Antimicrob Agents Chemother*. 2013; 57(5): 2259–2264.

Hall RG, Swancutt MA, Gumbo T. Fractal geometry and the pharmacometrics of micafungin in overweight, obese, and extremely obese people. *Antimicrob Agents Chemother*. 2011; 55(11): 5107–5112.

Hall D, Bonifas R, Stapert L, Thwaites M, Shinabarger DL, Pillar CM. In vitro potency and fungicidal activity of CD101, a novel echinocandin, against recent clinical isolates of *Candida* spp. *Diagn Microbiol Infect Dis*. 2017; 89: 205-11.

Hiemenz J, Cagnoni P, Simpson D, Devine S, Chao N, Keirns J, Lau W, Facklam D, Buell D. Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. *Antimicrob Agents Chemother*. 2005 Apr;49(4):1331–1336.

Howard SJ, Livermore J, Sharp A, Goodwin J, Gregson L, Alastruey-Isquierdo A, et al. Pharmacodynamics of echinocandins against *Candida glabrata*: requirement for dosage escalation to achieve maximal antifungal activity in neutropenic hosts. *Antimicrob Agents Chemother*. 2011; 55(10): 4880–4887.

James KD, Laudeman CP, Malkar NB, Krishnan R, Polowy K. Structure-activity relationships of a series of echinocandins and the discovery of CD101, a highly stable and soluble echinocandin with distinctive pharmacokinetic properties. *Antimicrob Agents Chemother*. 2017; 61: e01541-16.

Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to Candida infection: importance of empiric therapy and source control. *Clin Infect Dis*. 2012 Jun;54(12):1739–1746.

Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, et al. Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis*. 2010; 50: 1091–1100.

Kordalewska M, Lee A, Park S, Berrio I, Chowdhary A, Zhao Y, et al. Understanding Echinocandin Resistance in the Emerging Pathogen *Candida auris*. *Antimicrob Agents Chemother*. 2018; 62(6): e00238-18.

Kourtis AP, Hatfield K, Baggs J, Mu Y, See I, Epson E, et al. Vital Signs: Epidemiology and Recent Trends in Methicillin-Resistant and in Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections — United States. *MMWR Morb Mortal Wkly Rep*. 2019; 68: 214–219.

Kovacs R, Toth Z, Locke JB et al. Comparison of In Vitro Killing Activity of Rezafungin, Anidulafungin, Caspofungin, and Micafungin against Four *Candida auris* Clades in RPMI-1640 in the Absence and Presence of Human Serum. *Microorganisms*. 2021; 9.

Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet. 2007 May 5;369(9572):1519-1527.

Kwon YJ, Won EJ, Jeong SH, et al. Dynamics and Predictors of Mortality Due to Candidemia Caused by Different *Candida* Species: Comparison of Intensive Care Unit-Associated Candidemia (ICUAC) and Non-ICUAC. *J Fungi (Basel)*. 2021; 7(8): 597.

Labelle AJ, Micek ST, Roubinian N, Kollef MH. Treatment-related risk factors for hospital mortality in *Candida* bloodstream infections. *Crit Care Med.* 2008; 36(11): 2967–2972.

Lakota EA, Bader JC, Ong V, Bartizal K, Miesel L, Andes DR, Bhavnani SM, Rubino CM, Ambrose PG, Lepak AJ. Pharmacological Basis of CD101 Efficacy: Exposure Shape Matters. *Antimicrob Agents Chemother*. 2017 Oct 24;61(11):e00758-17.

Lakota EA, Ong V, Flanagan S, Rubino CM. Population Pharmacokinetic Analyses for Rezafungin (CD101) Efficacy Using Phase 1 Data. Antimicrob Agents Chemother. 2018 May 25;62(6):e02603-17. doi: 10.1128/AAC.02603-17. Erratum in: Antimicrob Agents Chemother. 2019 Mar 27;63(4).

Lempers VJ, van Rongen A, van Dongen EP, van Ramshorst B, Burger DM, Aarnoutse RE, et al. Does weight impact anidulafungin pharmacokinetics? *Clin Pharmacokinet*. 2016: 55: 1289–1294.

Lepak AJ, Zhao M, VanScoy B, Ambrose PG, Andes DR. Pharmacodynamics of a Long-Acting Echinocandin, CD101, in a Neutropenic Invasive-Candidiasis Murine Model Using an Extended-Interval Dosing Design. *Antimicrob Agents Chemother*. 2018; 62(2): e02154-17.

Locke JB, Almaguer AL, Zuill DE, Bartizal K. Characterization of in vitro resistance development to the novel echinocandin CD101 in *Candida* species. *Antimicrob Agents Chemother*. 2016; 60(10): 6100–6107.

Lockhart SR, Etienne KA, Vallabhaneni S, Farooqi J, Chowdhary A, Govender NP, et al. Simultaneous Emergence of Multidrug-Resistant *Candida auris* on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses. *Clin Infect Dis*. 2017; 64(2): 134–140. [Correction in *Clin Infect Dis*. 2018; 67(6): 987.]

Luque S, Hope W, Campillo N, Muñoz-Bermúdez R, Sorli L, Barceló-Vidal J, et al. Population Pharmacokinetics of Anidulafungin in Critically Ill Patients. *Antimicrob Agents Chemother.* 2019; 63(7): e00378-19.

Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, Lynfield R, Maloney M, McAllister-Hollod L, Nadle J, Ray SM, Thompson DL, Wilson LE, Fridkin SK; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014 Mar 27;370(13):1198–208.

Magill SS, O'Leary E, Janelle SJ, Thompson DL, Dumyati G, Nadle J, et al. Changes in Prevalence of Health Care-Associated Infections in U.S. Hospitals. *N Engl J Med*. 2018;3 79(18): 1732–1744.

Mainas E, Apostolopoulou O, Siopi M, Apostolidi S, Neroutsos E, Mirfendereski H, et al. Comparative pharmacokinetics of the three echinocandins in ICU patients. *J Antimicrob Chemother*. 2020; 75(10): 2969–2976.

Manavathu EK, Ramesh MS, Baskaran I, Ganesan LT, Chandrasekar PH. A comparative study of the post-antifungal effect (PAFE) of amphotericin B, triazoles and echinocandins on *Aspergillus fumigatus* and *Candida albicans*. *J Antimicrob Chemother*. 2004 Feb;53(2):386-9.

Maseda E, Grau S, Luque S, Castillo-Mafla M-P, Suárez-de-la-Rica A, Montero-Feijoo A, et al. Population pharmacokinetics/pharmacodynamics of micafungin against *Candida* species in obese, critically ill, and morbidly obese critically ill patients. *Crit Care*. 2018; 22: 94.

Mazi PB, Olsel MA, Stwalley D, Rauseo AM, Aryres C, Powderly WG, et al. Attributable Mortality of *Candida* Bloodstream Infections in the Modern Era: A Propensity Score Analysis. *Clin Infect Dis*. 2022; ciac004, https://doi.org/10.1093/cid/ciac004.

Menzin J, Meyers JL, Friedman M et al. Mortality, length of hospitalization, and costs associated with invasive fungal infections in high risk patients. *Am J Health Syst Pharm*. 2009; 66: 1711–1717.

Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985 Apr-Jun;4(2):213-26.

Mikulska M, Del Bono V, Ratto S, Viscoli C. Occurrence, presentation and treatment of candidemia. *Expert Rev Clin Immunol*. 2012; 8(8): 755–765.

Mycamine (micafungin sodium) [Prescribing Information]. Northbrook, IL: Astellas Pharma US, Inc.; 2020 July.

Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, Garey KW, Alangaden GJ, et al. T2 Magnetic Resonance Assay for the Rapid Diagnosis of Candidemia in Whole Blood: A Clinical Trial. *Clin Infect Dis*. 2015; 60(6): 892–899.

Ong V, Wills S, Watson D, Sandison T, Flanagan S. Metabolism, Excretion, and Mass Balance of [^{14}C]-Rezafungin in Animals and Humans. *Antimicrob Agents Chemother*. 2022 Jan 18;66(1):e0139021.

Ostrosky-Zeichner L. *Candida glabrata* and *FKS* mutations: witnessing the emergence of the true multidrug-resistant *Candida*. *Clin Infect Dis*. 2013; 56: 1733–1734.

Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifield A, et al. Invasive Fungal Infections among Organ Transplant Recipients: Results of the

Transplant-Associated Infection Surveillance Network (TRANSNET), *Clin Infect Dis*. 2010; 50: 1101–1111.

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016: 64(4): e1-50.

Pechacek J, Yakubu I, Vissichelli NC, Bruno D, Morales MK. Successful expanded access use of rezafungin, a novel echinocandin, to eradicate refractory invasive candidiasis in a liver transplant recipient. *J Antimicrob Chemother*. 2022; 77: 2571-3.

Pfaller MA. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. *Am J Med*. 2012a;125:S3–13.

Pfaller MA, Castanheira M, Lockhart SR, Ahlquist AM, Messer SA, Jones RN. Frequency of decreased susceptibility and resistance to echinocandins among fluconazole-resistant bloodstream isolates of *Candida glabrata*. *J Clin Microbiol*. 2012b;50(4):1199–203.

Pfaller MA, Carvalhaes CG, DeVries S, Huband MD, Castanhiera M. Elderly versus nonelderly patients with invasive fungal infections: species distribution and antifungal resistance, SENTRY antifungal surveillance program 2017–2019. *Diagn Micr Infec Dis*. 2022; 102(4): 115627.

Pfaller MA, Diekema DJ, Turnidge JD, Castanheira M, Jones RN. Twenty Years of the SENTRY Antifungal Surveillance Program: Results for *Candida* Species From 1997-2016. *Open Forum Infect Dis.* 2019: 6: S79-S94,

Pfaller MA, Diekema DJ. Epidemiology of Invasive Candidiasis: a Persistent Public Health Problem. *Clin Microbiol Rev. 2007*; 20(1): 133–163.

Pfaller MA, Diekema DJ. Epidemiology of invasive mycoses in North America. *Crit Rev Microbiol.* 2010; 36: 1–53.

Pfaller MA, Messer SA, Rhomberg PR, Jones RN, Castanheira M. Activity of a long-acting echinocandin, CD101, determined using CLSI and EUCAST reference methods, against *Candida* and *Aspergillus* spp., including echinocandin- and azole-resistant isolates. *J Antimicrob Chemother*. 2016; 71(10): 2868–2873.

Pfaller MA, Messer SA, Rhomberg PR, Castanheira M. Activity of a Long-Acting Echinocandin (CD101) and Seven Comparator Antifungal Agents Tested against a Global Collection of Contemporary Invasive Fungal Isolates in the SENTRY 2014 Antifungal Surveillance Program. *Antimicrob Agents Chemother*. 2017a; 61(3): e02045-16.

Pfaller MA, Messer SA, Rhomberg PR, Castanheira M. CD101, a long-acting echinocandin, and comparator antifungal agents tested against a global collection of invasive fungal isolates in the SENTRY 2015 Antifungal Surveillance Program. *Int J Antimicrob Agents*. 2017b; 50(3): 352–358.

Pfaller MA, Carvalhaes C, Messer SA, Rhomberg PR, Castanheira M. Activity of a long-acting echinocandin, rezafungin, and comparator antifungal agents tested against

contemporary invasive fungal isolates (SENTRY Program, 2016 to 2018). *Antimicrob Agents Chemother*. 2020; 64(4): e00099-20.

Prograf® (tacrolimus) capsules, for oral use [Prescribing Information]. Northbrook, IL: Astellas Pharma US, Inc.; 2021.

Ramos-Martínez A, Vicente-López N, Sánchez-Romero I, Padilla B, Merino-Amador P, Garnacho-Montero J, et al. Epidemiology and prognosis of candidaemia in elderly patients. *Mycoses*. 2017; 60(12): 808–817.

Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, Betts R, Wible M, Goldstein BP, Schranz J, Krause DS, Walsh TJ; Anidulafungin Study Group. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med*. 2007 Jun 14;356(24):2472-82.

Ricotta EE, Lai YL, Babiker A, Strich JR, Kadri SS, Lionakis MS, et al. Invasive Candidiasis Species Distribution and Trends, United States, 2009-2017. *J Infect Dis*. 2021; 223: 1295–1302.

Rubino CM, Flanagan S. Population Pharmacokinetics of Rezafungin in Patients with Fungal Infections. *Antimicrob Agents Chemother*. 2021 Oct 18;65(11):e0084221.

Shields RK, Nguyen MH, Press EG, Kwa AL, Cheng S, Du C, et al. The presence of an *FKS* mutation rather than MIC is an independent risk factor for failure of echinocandin therapy among patients with invasive candidiasis due to *Candida glabrata*. *Antimicrob Agents Chemother*. 2012; 56(9): 4862–4869.

Shields RK, Nguyen MH, Press EG, Clancy CJ. Abdominal candidiasis is a hidden reservoir of echinocandin resistance. *Antimicrob Agents Chemother*. 2014; 58:7601–7605.

Sinnollareddy MG, Roberts JA, Lipman J, Akova M, Bassetti M, De Waele JJ, et al. Pharmacokinetic variability and exposures of fluconazole, anidulafungin, and caspofungin in intensive care unit patients: Data from multinational Defining Antibiotic Levels in Intensive care unit (DALI) patients Study. *Crit Care*. 2015; 19(1): 33.

Sirohi B, Powles RL, Chopra R, Russell N, Byrne JL, Prentice HG, et al. A study to determine the safety profile and maximum tolerated dose of micafungin (FK463) in patients undergoing haematopoietic stem cell transplantation. *Bone Marrow Transpl*. 2006; 38(1): 47–51.

Slavin MA, Sorrell TC, Marriott D, Thursky KA, Nguyen Q, Ellis DH, et al.; Australian Candidemia Study, Australasian Society for Infectious Diseases. Candidaemia in adult cancer patients: risks for fluconazole-resistant isolates and death. *J Antimicrob Chemother.* 2010; 65(5): 1042–1051.

Sucher AJ, Chahine EB, Balcer HE. Echinocandins: the newest class of antifungals. *Ann Pharmacother*. 2009 Oct;43(10):1647–1657.

The White House. National Strategy for Combating Antibiotic Resistant Bacteria. September 2014.

Thompson GR, Soriano A, Skoutelis A, et al. Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and

Invasive Candidiasis: The STRIVE Trial. *Clin Infect Dis*. 2021 Dec 6;73(11):e3647-e3655. Erratum in: *Clin Infect Dis*. 2021 Aug 2;73(3):561-562.

Thompson GR 3rd, Soriano A, Cornely OA et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. *Lancet*. 2022 Nov 25:S0140-6736(22)02324-8.

Tortorano AM, Prigitano A, Morroni G, Brescini L, Barchiesi F. Candidemia: Evolution of Drug Resistance and Novel Therapeutic Approaches. *Infect Drug Resist*. 2021; 14: 5543–5553.

Toth Z, Forgacs L, Locke JB, Kardos G, Nagy F, Kovacs R, Szekely A, Borman AM, Majoros L. In vitro activity of rezafungin against common and rare *Candida* species and *Saccharomyces cerevisiae*. *J Antimicrob Chemother*. 2019; 74: 3505-10.

Tsay SV, Mu Y, Williams S, Epson E, Nadle J, Bamberg WM, et al. Burden of Candidemia in the United States, 2017. *Clin Infect Dis*. 2020;71(9):e449–e453.

Vallabhaneni S, Cleveland AA, Farley MM, Harrison LH, Schaffner W, Beldavs ZG, et al. Epidemiology and Risk Factors for Echinocandin Nonsusceptible *Candida glabrata* Bloodstream Infections: Data From a Large Multisite Population-Based Candidemia Surveillance Program, 2008–2014. *Open Forum Infect Dis*. 2015; doi: 10.1093/ofid/ofv163.

Vallabhaneni S, Kallen A, Tsay S, chow N, Welsh R, Kerins J, et al. Investigation of the First Seven Reported Cases of *Candida auris*, a Globally Emerging Invasive, Multidrug-Resistant Fungus - United States, May 2013-August 2016. *MMWR Morb Mortal Wkly Rep*. 2016; 65(44): 1234–1237.

van der Elst KCM, Veringa A, Zijlstra JG, Beishuizen A, Klont R, Brummelhuis-Visser P, et al. Low Caspofungin Exposure in Patients in Intensive Care Units. *Antimicrob Agents Chemother.* 2017; 61(2): e01582-16.

Vincent JL, Rello J, Marshall J et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009; 302: 2323–2329.

Wang JF, Xue Y, Zhu X-B, Fan H. Efficacy and safety of echinocandins versus triazoles for the prophylaxis and treatment of fungal infections: a meta-analysis of RCTs. *Eur J Clin Microbiol Infect Dis*. 2015; 34: 651-659.

Wang J-L, Chang C-H, Young-Xu Y, Chan KA. Systematic Review and Meta-Analysis of the Tolerability and Hepatotoxicity of Antifungals in Empirical and Definitive Therapy for Invasive Fungal Infection. *Antimicrob Agents Chemother*. 2010; 54(6): 2409–2419.

Welte R, Oberacher H, Gasperetti T, Pfisterer H, Griesmacher A, Santner T, et al. Pharmacokinetics and Antifungal Activity of Echinocandins in Ascites Fluid of Critically Ill Patients. *Antimicrob Agents Chemother*. 2021; 65(7): e0256520

Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, et al. Nococomial bloodstream infections in US hospitals: Analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis.* 2004; 39: 309–317.

Zatta M, Di Bella S, Giacobbe DR, Del Puente F, Merelli M, Assini AM, et al. Clinical Features and Mortality of Nosocomial Candidemia in Very Old Patients: A Multicentre Italian Study. *Gerontology*. 2020; 66(6): 532–541.

Zhao Y, Perez WB, Jimenez-Ortigosa C, Hough G, Locke JB, Ong V, et al. CD101: a novel long-acting echinocandin. *Cell Microbiol.* 2016; 18: 1308–1316.

Zhao Y, Prideaux B, Nagasaki Y, Lee MH, Chen PY, Blanc L, et al. Unraveling drug penetration of echinocandin antifungals at the site of infection in an intra-abdominal abscess model. *Antimicrob Agents Chemother*. 2017; 61(10): pii: AAC.01009-17.

10 APPENDICES

10.1 Additional Distribution Studies

10.1.1 In Vivo Studies of Distribution

10.1.1.1 Study NC-134: Whole Blood/Plasma Pharmacokinetics and Tissue Distribution by Quantitative Whole-Body Autoradiography in Rats Following a Single Intravenous Administration of [^{14}C]CD101

NC-134 was conducted using [^{14}C]-radiolabeled rezafungin to characterize the distribution of total radioactivity (using QWBA) and PK in male SD and Long-Evans (LE) rats and to provide a blood-to-plasma ratio in both male LE and SD rats following administration of a single IV dose of [^{14}C] rezafungin. The study also allowed estimation of human radiation dosimetry after a dose of [^{14}C] rezafungin. This was a combined study, with separate groups of animals used to characterize the rate and extent of excretion (mass balance) of total radioactivity in urine, feces, and bile following a single IV dose of [^{14}C] rezafungin to male SD rats.

For the QWBA and PK portion, all SD male rats (N=3) received a single IV bolus dose of [^{14}C] rezafungin at 15 mg/kg and all LE male rats (N=12) received a single IV bolus dose of [^{14}C] rezafungin at 5 mg/kg due to lower tolerability of LE rats to rezafungin.

Whole blood/plasma pharmacokinetics and partitioning

In SD rats, the mean C_{max} of plasma total radioactivity after a single IV dose of [^{14}C] rezafungin at 15 mg/kg in SD rats was 21.824 µg equiv/mL which occurred at 0.083 hr post-dose (T_{max}). Mean plasma total radioactivity concentrations decreased slowly over time with a $t_{1/2}$ of 53.6 hr. The mean $AUC_{inf\ obs}$ of plasma total radioactivity was 701.595 µg equiv•hr/mL.

In LE rats, the C_{max} of total radioactivity in blood (by liquid-scintillation counting, LSC) after a single IV dose of [^{14}C] rezafungin at 5 mg/kg was 7.369 µg equiv/mL at 1 hr post-dose, which was the earliest time point collected for this group of animals and probably did not reflect the true T_{max}. Blood total radioactivity concentrations decreased slowly over time with a $t_{1/2}$ of 70.6 hr. The $AUC_{inf\ obs}$ of blood total radioactivity (by LSC) was 265.887 µg equiv•hr/mL. The C_{max} of total radioactivity in plasma (by LSC) was 4.483 µg equiv/mL at 1 hr post-dose. The $t_{1/2}$ of total radioactivity in plasma of LE rats was 72.7 hr, which was longer than observed in SD rats most likely due to the inclusion of plasma concentrations at later time points (up to 336 hr) than those available from SD rats (up to 120 hr). The $AUC_{inf\ obs}$ of total radioactivity in plasma from LE rats was 238.730 µg equiv•hr/mL, which was approximately 3-fold lower than that observed in SD rats in Group 3 due to the 3-fold lower dose of rezafungin administered.

Blood-to-plasma radioactivity concentration ratios that were determined from LE rat samples were 1.64 at 1 hr post-dose and declined to 0.80-0.94 at 168-336 hr post-dose,

which indicated that [^{14}C] rezafungin was more associated with whole blood at early time points, but then partitioned into plasma at later time points beyond 24 hours.

Quantitative whole-body autoradiography

Drug-derived radioactivity was widely distributed throughout the body of male LE rats, with quantifiable concentrations (lower limit of quantification [LLOQ]=0.008 µg equiv/g) present in nearly all tissues through 865 hr (50 of 54 sampled tissues). Radioactivity concentrations that were quantifiable in 37 of 54 tissues at the last time point examined (1464 hr post-dose).

In general, concentrations in most tissues of pigmented LE rats were higher than, or similar to those in blood (cardiac). The C_{max} in blood was observed at 1 hr post-dose (10.809 µg equiv/g) and concentrations were quantifiable through 865 hr post-dose (0.012 µg equiv/g). The C_{max} of radioactivity in most tissues (31 of 54 tissues) was observed at 4 hr post-dose (T_{max}). Relatively high tissue concentrations observed at C_{max} (> 20.000 µg equiv/g) were found in the following tissues at 4 hr (unless otherwise noted): kidney medulla (71.125 µg equiv/g at 1 hr), small intestine (35.156 µg equiv/g), salivary gland (29.536 µg equiv/g), spleen (26.595 µg equiv/g), kidney cortex (24.501 µg equiv/g), lymph node (23.758 µg equiv/g), lung (21.937 µg equiv/g at 1 hr), liver (20.973 µg equiv/g at 48 hr), mesenteric lymph node (20.700 µg equiv/g), and thymus medulla (20.466 µg equiv/g). Relatively low tissues concentrations observed at C_{max} (< 5.000 µg equiv/g) were in seminal vesicles (4.188 µg equiv/g), skeletal muscle (3.981 µg equiv/g), testis (3.914 µg equiv/g), white adipose (2.580 µg equiv/g), brain tissues (ranging from 0.556 µg equiv/g in cerebrum to 1.965 µg equiv/g in olfactory bulb), spinal cord (0.865 µg equiv/g), bone (0.788 µg equiv/g), and eye lens (0.168 µg equiv/g). Thirty-seven (37) tissues at 1464 hr were observed to have quantifiable concentrations of radioactivity, and most had concentrations of < 0.500 µg equiv/g. However, the following tissues had higher concentrations (> 0.500 µg equiv/g) at 1464 hr: adrenal gland outer medulla (0.603 µg equiv/g), nasal turbinates (0.706 µg equiv/g), spinal cord (0.725 µg equiv/g), brain medulla (0.915 µg equiv/g), and spinal nerve (2.603 µg equiv/g).

The C_{max} in the contents of the alimentary canal of male LE rats ranged from 5.973 µg equiv/g (stomach contents at 24 hr) to 30.018 µg equiv/g (large intestine contents at 8 hr). The C_{max} in bile and urine were 10.613 (at 1 hr) and 6.850 (at 8 hr) µg equiv/g, respectively.

Tissue concentration versus time profiles for male LE rats showed that elimination/tissue release of radioactivity from all tissues was very slow and $t_{1/2}$ values for most tissues were > 200 hr. Relatively long tissue $t_{1/2}$ values (> 500 hr) were observed in spinal nerve (2255.2 hr), lumbar lymph node (740.2 hr), brain cerebellum grey matter (659.2 hr), eye uvea (585.0 hr), adrenal gland outer medulla (505.8 hr), and brain cerebrum (503.9 hr).

Distribution trends and concentrations of radioactivity observed in the pigmented and non-pigmented skin, and the AUC and estimated elimination $t_{1/2}$ for pigmented and non-pigmented tissues were similar, which suggested that [^{14}C] rezafungin-related radioactivity was not specifically associated with melanin.

Spinal nerve had the overall highest exposure to [^{14}C] rezafungin with an $AUC_{inf\ obs}$ of 13241.128 µg equiv·hr/g, which was ≥ 2 times higher than any other tissue. Other tissues with relatively high $AUC_{inf\ obs}$ values (> 3000 µg equiv•hr/g) included: preputial gland (4852.953 µg equiv•hr/g), adrenal gland outer medulla (4723.628 µg equiv•hr/g), kidney cortex (4316.391 µg equiv•hr/g), adrenal gland (entire) (4127.736 µg equiv•hr/g), adrenal gland cortex (3676.899 µg equiv•hr/g), and lumbar lymph node (3349.448 µg equiv•hr/g). Most remaining tissues had $AUC_{inf\ obs}$ values between 500-2500 µg equiv•hr/g. Tissue with relatively low $AUC_{inf\ obs}$ values (< 500 µg equiv•hr/g) were brown adipose, heart, mammary gland region, cardiac blood, seminal vesicles, brain (cerebellum grey matter and cerebrum), skeletal muscle, and white adipose.

A single IV bolus dose of up to 100 µCi (3.70 MBq) of [^{14}C] rezafungin is not expected to represent a major whole-body radiation exposure risk to human male patients as defined in the FDA guidelines.

10.1.1.2 Study NC-162: Whole Blood/Plasma Pharmacokinetics and Tissue Distribution by Quantitative Whole-Body Autoradiography in Cynomolgus Monkeys Following a Single Intravenous Administration of [^{14}C] CD101

NC-162 was conducted using [^{14}C]-radiolabeled rezafungin to characterize the distribution of total radioactivity by QWBA, blood/plasma PK, as well as blood-to-plasma ratio in cynomolgus monkeys following administration of a single IV dose of [^{14}C] rezafungin. The study also allowed estimation of human radiation dosimetry after a dose of [^{14}C] rezafungin.

The study utilized 2 groups of male cynomolgus monkeys. All monkeys received a single 10 mg/kg (~100 µCi/kg) IV infusion dose of [^{14}C] rezafungin, infused over 20 minutes. Urine, feces, and cage residue specimens were collected for 720 hr (30 days) post-dose from 3 monkeys in Group 1 for evaluation of radioactivity excretion. Blood and plasma samples were collected from 3 of 5 animals in Group 2, for evaluation of blood and plasma total radioactivity, PK, and blood-to-plasma ratio. Carcass specimens were collected from 1 animal in Group 1 (at 720 hr post-dose) and from all 5 animals in Group 2 (at 4 hr, 24 hr, 240 hr [10 days], 480 hr [20 days], and 1440 hr [60 days] post-dose) for QWBA analysis. Blood, plasma, urine, feces, and cage residue specimens were analyzed for total radioactivity by LSC. Carcasses were analyzed by QWBA. Dosimetry was performed based on tissue concentrations determined by QWBA.

Whole blood/plasma pharmacokinetics and partitioning

Blood-to-plasma concentration ratios (and AUC ratios) were approximately 1 across time points, indicating approximately equal distribution of radioactivity in plasma and the cellular fraction of blood. Blood and plasma radioactivity concentrations were

quantifiable through at least 1440 hr and 720 hr post-dose, respectively. Blood and plasma radioactivity profiles indicate very slow elimination following IV administration of [^{14}C] rezafungin in monkeys. Mean blood and plasma $t_{1/2}$ values were 227 hr and 170 hr, respectively.

Quantitative whole-body autoradiography

Drug-derived radioactivity was widely distributed throughout the body of monkeys, with quantifiable concentrations (LLOQ=0.033 µg equiv/g) present in nearly all tissues at 1440 hr.

In general, concentrations in most tissues were higher than, or similar to those in blood. The C_{max} in blood was observed at 4 hr post-dose (20.836 µg equiv/g) and concentrations were quantifiable through 1440 hr post-dose (0.067 µg equiv/g). The C_{max} of radioactivity in most tissues (43 of 53 tissues) was observed either at 4 or 24 hr post-dose (T_{max}). Relatively high tissue concentrations observed at C_{max} (> 55.000 µg equiv/g) were found in the following tissues: spinal nerve (dorsal root ganglia), adrenal gland (outer medulla), adrenal gland (cortex), stomach (gastric mucosa), liver, adrenal gland (entire), and kidney medulla. Relatively low tissues concentrations observed at C_{max} (< 2.000 µg equiv/g) were in brain tissues, spinal cord, bone, eye (lens), and preputial gland (which was BQL at all time points). Fifty-one (51) tissues at 1440 hr were observed to have quantifiable concentrations of radioactivity, with most having concentrations of < 3.000 µg equiv/g, although the following tissues had higher concentrations (> 3.000 µg equiv/g): spinal nerve (dorsal root ganglia), spinal nerve, and liver.

In most central nervous system tissues and spinal cord, radioactive concentrations gradually increased from 4 to 720 hr, indicating slow uptake of radioactivity in these tissues. However, the radioactive concentration in these tissues decreased from 720 to 1440 hr.

Tissue concentration versus time profiles for male cynomolgus monkeys showed that elimination/tissue release of radioactivity from all tissues was very slow and $t_{1/2}$ values for most tissues were > 200 hr. Relatively long tissue $t_{1/2}$ values (> 500 hr) were observed in eye lens (3139.7 hr), brain olfactory bulb (915.5 hr), spinal nerve (873.5 hr), urinary bladder (670.9 hr), and lymph node submandibular (556.8 hr). Comparing overall tissue exposure using AUC_{last} values, the greatest exposure was observed for spinal nerve dorsal root ganglia (44605.172 µg equiv•h/g), liver (39575.654 µg equiv•h/g), adrenal gland cortex (23820.956 µg equiv•h/g), adrenal gland outer medulla (22149.642 µg equiv•h/g), thyroid (18153.132 µg equiv•h/g), and adrenal gland (17934.024 µg equiv•h/g) relative to blood (3184.190 µg equiv•h/g).

Concentrations of total radioactivity in pigmented eye uveal tract and skin were comparable to other tissues, suggesting that [^{14}C] rezafungin-related radioactivity was not specifically associated with melanin.

10.2 Expanded Access Program

Patient 1

The patient is a 49-year-old male with no significant past medical history, who initially presented to the hospital with a traumatic thoracic aortic tear due to a motor vehicle accident in 2000 requiring emergent thoracic aortic graft repair and splenectomy. The patient has history of chronic *C. glabrata* infection of foreign material in the mediastinum since 2017.

In (b) (6), the patient presented to the hospital with fever and chills. Work-up revealed thoracic aortic graft infection with *C. albicans*, *C. glabrata* (Table 49). He underwent resection of the left upper lobe of the lung, explanation of the infected aortic graft, and placement of a new thoracic aortic Dacron graft. The post-operative course was complicated by disruption of the thoracic duct which required embolization with multiple platinum-fibered coils. He was treated with IV micafungin for 6 weeks followed up by suppressive therapy with oral fluconazole 800 mg daily was begun given the concern that the new graft was in a contaminated field. In October 2019, the patient had recurrent fever and chest pain; a repeat chest computed tomography (CT) scan found increased mediastinal fluid, pneumomediastinum, a potential thrombus in the graft, and a suspected aorto-esophageal fistula. Esophageal endoscopy indicated migration of one of the platinum coils from the thoracic duct embolization protruding through the esophageal wall along with purulent secretions. The coil was removed endoscopically and grew *C. glabrata* on culture that demonstrated intermediate susceptibility to caspofungin (Isolate 2, Table 49). Patient was started on intravenous (IV) micafungin which was later changed to IV liposomal amphotericin B after chest CT scan showed increased gas in the mediastinum as well as narrowing and irregularity of the aortic graft. After 6 weeks, IV liposomal amphotericin was changed to oral posaconazole therapy. In February 2020, patient developed mediastinitis while on anti-fungal therapy with oral posaconazole, he underwent a procedure to remove the infected thoracic aortic Dacron graft that was originally placed in (b) (6) however, the remaining thoracic duct platinum coils could not be safely removed. Explanted thoracic graft tissue cultures grew 2 different isolates of *C. glabrata* (Isolate 3, 4, Table 49). The post-operative course was complicated by esophageal perforation requiring change to IV micafungin; however, one of the *C. glabrata* isolates (Isolate 3) had intermediate susceptibility and the other (Isolate 4) had resistance to micafungin, therefore, the antifungal therapy was changed to concurrent IV liposomal amphotericin B plus oral flucytosine. The patient developed renal toxicity after 6 weeks of this regimen and both antifungals were discontinued. During outpatient follow-up in April 2020, several long-term suppressive options were discussed due to the retained platinum coils and concern of ongoing chronic infection with multi drug resistant *C. glabrata*. Antifungal susceptibility testing showed that Isolate 4 from the aortic graft material was had an MIC value that fell within the predicted *C. glabrata* target attainment for rezafungin. Sanger sequencing was performed on PCR-amplified “hot spot” (HS) HS1- and HS2-encoding regions of *FKS1* and *FKS2* genes which showed a D666Y alteration in Fks2 HS1.

Table 49: Minimum Inhibitory Concentration Values and Susceptibility Interpretive Criteria for *Candida glabrata* Isolates Obtained from Expanded Access Patient No 1

C. glabrata isolate	MIC (µg/mL) / CLSI interpretation[a]									
	RZF	ANF	CAS	MCF	FLU	VOR	POS	ITR	AMB	5FC
1			≤ 0.25 / S		4 / SDD	0.25 / NA				
2		≤ 0.12 / S	0.25 / I	0.03 / S	256 / R	4 / NA	1 / NA	1 / NA	≤ 0.12 / NA	≤ 0.06 / NA
3		0.5 / R	0.5 / R	0.12 / I	> 256 / R	> 8 / NA	> 8 / NA	> 16 / NA	1 / NA	≤ 0.06 / NA
4	2 / NS[b]	1 / R	0.5 / R	0.5 / R	64 / R				0.5 / NA	

AMB: amphotericin B; ANF: anidulafungin; CAS: caspofungin; 5FC: 5-flucytosine; FLU: fluconazole; I: intermediate; ITR: itraconazole; MCF: micafungin; MIC: minimum inhibitory concentration; NA: not available; NS: nonsusceptible; POS: posaconazole; R: resistant; RZF: rezafungin; S: susceptible; SDD: susceptible-dose dependent; VOR: voriconazole
Isolate 1: aortic graft explant in 2017; Isolate 2: thoracic duct embolization coil in 2019; Isolate 3: first aortic Dacron graft explant tissue isolate; Isolate 4: second aortic Dacron graft explant tissue isolate in 2020 (48 hr. MIC data are reported due to insufficient growth at 24 hr.; isolate possesses Fks2 D666Y alteration)
[a]CLSI M27M44S Ed3 2022
[b]At the time of MIC testing, rezafungin interpretive criteria were not available. The interpretation provided here applies current M27M44S provisional susceptible-only CLSI breakpoints for rezafungin (intermediate and resistant values have not yet been established).
Source: Adeel 2021

The patient was started on compassionate treatment with rezafungin for injection on 14 May 2020 with a dose of 400 mg, followed by maintenance dosing of 200 mg weekly, that remains ongoing (Day 660, as of 03 March 2022). The patient has not exhibited laboratory abnormalities and has only had a transient rash with no evidence of clinical toxicities related to use of rezafungin. Serial serum β-D-glucan assays have remained negative from May 2020 through February 2022 There were no positive fungal cultures during the rezafungin treatment. A repeat chest CT angiogram in October 2020 did not show any findings suggestive of ongoing infection. The patient continues to receive weekly IV rezafungin.

Patient 2

A 68-year-old female with history of alcoholic cirrhosis and history of orthotopic liver transplant (OLT) in (b) (6), developed sepsis with worsening leukocytosis and tachycardia approximately one month after the OLT. The patient has history of hepato-renal syndrome, hypertension and myopathy and has been diagnosed with refractory intra-abdominal candidiasis prior to the OLT.

Prior to the OLT, the patient developed spontaneous bacterial peritonitis. The peritoneal fluid cultures grew *Candida krusei* prompting initiation of anidulafungin. The peritoneal catheter was removed, and the patient completed a 2-week course of anti-fungal treatment with IV micafungin 100 mg per day. Her renal function improved, and she was deescalated to intermittent hemodialysis and was listed for liver transplantation with a model for end-stage liver disease score of 38. She underwent OLT 2 days later,

where cloudy peritoneal fluid was noted intraoperatively. She did not receive induction immunosuppression but was treated with high dose IV methylprednisolone 500 mg intraoperatively, and was maintained on a combination of tacrolimus, mycophenolate mofetil and a prednisone taper. She was given 14 days of micafungin as antifungal prophylaxis due to her recent *C. krusei* growth. Her post-operative course was further complicated by a biliary stricture necessitating placement of 2 biliary stents, with resulting improvement of her hyperbilirubinemia. She was able to stop intermittent hemodialysis and was discharged to a post-acute care facility briefly before being readmitted for worsening abdominal pain. At that time, CT of the abdomen showed a large abdominal fluid collection (12×22×24 cm) mostly consistent with hematoma. The fluid was drained with cultures again growing *C. krusei* (minimum inhibitory concentration [MIC] to micafungin < 0.25 µg/mL, MIC to voriconazole < 0.12 µg/mL, Table 50). She was re-initiated on IV daily micafungin and had an abdominal washout where she was found to have thick-walled abscesses within the abdomen and pelvis, with intraoperative cultures from the unroofed collections also growing *C. krusei*. A repeat CT scan 4 days following washout showed re-accumulation of fluid collections and progression with several large loculated fluid collections within the abdomen, pelvis, and abdominal wall.

The treating doctor inquired about the use of rezafungin for injection under the expanded access program due to the potential for improved rezafungin tissue distribution based on nonclinical data (Zhao 2017). Given radiographic progression despite attempted source control and treatment with micafungin (MIC now 0.25 µg/mL), the patient was started on compassionate rezafungin for injection treatment after institutional review board (IRB) and patient consent.

The patient tolerated the initial 400 mg IV rezafungin for injection, followed by weekly 200 mg IV rezafungin for injection at the transplant. During her 5th rezafungin dose visit (Day 29 of rezafungin), she complained of abdominal pain with leukocytosis. The CT scan of the abdomen showed improvement and resolution of the prior intra-abdominal and pelvic fluid collections; however, there were signs of colitis and diverticulitis. The patient was admitted to the hospital for IV anti-bacterial treatment of this SAE. She responded to the treatment and was discharged. By Week 7 of rezafungin for injection, the patient had improved clinically with improved appetite and energy level. The abdominal CT scan performed during the Week 10 rezafungin for injection visit showed almost complete resolution of the fluid collections. The patient completed 12 weeks of rezafungin for injection treatment (84 days) without AEs (tremor or ataxia) or abnormal laboratory findings. There were no positive fungal cultures during the rezafungin treatment. A follow-up exam 8 weeks following completion of rezafungin for injection therapy demonstrated an AE of cytomegalovirus viremia but no other AEs or abnormal neurologic signs or symptoms.

Table 50: Minimum Inhibitory Concentration Values and Susceptibility Interpretive Criteria for *Candida krusei* Isolate Obtained from Expanded Access Patient No 2

C. krusei isolate	MIC (µg/mL) / CLSI interpretation[a]					
	RZF	ANF	CAS	MCF	AMB	5FC
1	0.25 / S[b]	0.125 / S	0.25 / S	0.25 / S	0.5 / NA	8 / NA

AMB: amphotericin B; ANF: anidulafungin; CAS: caspofungin; 5FC: 5-flucytosine; MCF: micafungin; MIC: minimum inhibitory concentration; NA: not available; RZF: rezafungin; S: susceptible
[a]CLSI M27M44S Ed3 2022
[b]At the time of MIC testing, rezafungin interpretive criteria were not available. The interpretation provided here applies current M27M44S provisional susceptible-only CLSI breakpoints for rezafungin (intermediate and resistant values have not yet been established).
Source: Pechacek 2022

Patient 3

A 24-year-old previously healthy male with history of gunshot wound with multiple abdominal surgeries in (b) (6) leading to exploratory laparotomy, right hemicolectomy of the ascending colon, right nephrectomy, and ileostomy, complicated by abdominal abscesses that have been drained, now with *Candida glabrata* fungemia and peripherally inserted central catheter (PICC) line infection did not tolerate IV voriconazole (facial rash) and self-discontinued it. Although the patient received 2 doses of liposomal amphotericin B, treatment with amphotericin B was less than optimal due to the history of acute kidney injury and right nephrectomy.

The patient was on total parenteral nutrition dependent pending surgery for fistula repair. He was hospitalized due to fungemia with *Candida glabrata* from the PICC line. The organism was resistant to echinocandins (Table 51). The *FKS* sequence data showed that the *C. glabrata* isolate had a deletion of Phe659 in Fks2 HS1. This is a relatively common mutation (clinical and *in vitro*) that confers a high level of reduced susceptibility. The PICC line was subsequently removed and he was discharged home on IV voriconazole. The patient did not tolerate the IV voriconazole; he developed facial rash and subsequently self-discontinued voriconazole. This patient has received 2 doses of IV liposomal amphotericin B. However, IV liposomal amphotericin B is not optimal in this patient given his acute kidney injury and his medical history of right nephrectomy. He was started on weekly IV rezafungin on 05 March 2021 on a compassionate basis. The patient tolerated the initial 400 mg IV rezafungin for injection, followed by one more dose of 200 mg IV rezafungin. There were no tremors, ataxia or neuropathy, no laboratory abnormalities, or positive fungal cultures during the rezafungin therapy. The patient was considered cured following 2 doses of rezafungin, and there was no recurrence of the infection.

Table 51: Minimum Inhibitory Concentration Values and Susceptibility Interpretive Criteria for *Candida glabrata* Isolates Obtained from Expanded Access Patient No 3

C. glabrata isolate	MIC (µg/mL) / CLSI interpretation[a]						
	RZF	ANF	CAS	MCF	FLU	VOR	AMB
1	1 / NS[b]	2 / R	0.5 / R	0.5 / R	4 / SDD	0.25 / NA	1 / NA
2	1 / NS[b]	2 / R	0.5 / R	0.5 / R	32 / SDD	0.5 / NA	1 / NA

AMB: amphotericin B; ANF: anidulafungin; CAS: caspofungin; FLU: fluconazole; MCF: micafungin; MIC: minimum inhibitory concentration; NA: not available; NS: nonsusceptible; R: resistant; RZF: rezafungin; SDD: susceptible-dose dependent; VOR: voriconazole
[a]CLSI M27M44S Ed3 2022
[b]At the time of MIC testing, rezafungin interpretive criteria were not available. The interpretation provided here applies current M27M44S provisional susceptible-only CLSI breakpoints for rezafungin (intermediate and resistant values have not yet been established).

Patient 4

A 49-year-old male with history of perforated sigmoid diverticulitis complicated with intestinal obstruction, multiple intra-abdominal abscesses requiring partial small bowel resection, subtotal colectomy and ileostomy, cardiac arrest requiring cardiopulmonary resuscitation, subsequent short gut syndrome and enterocutaneous fistula requiring total parenteral nutrition developed *Candida parapsilosis* native aortic valve endocarditis resulting in aortic valve replacement on (b) (6). He was initially treated with daily IV micafungin, followed by IV fluconazole until 18 December 2019. Endocarditis treatment was discontinued due to poor insurance coverage.

On (b) (6), he underwent planned open takedown of the enterocutaneous fistula and revision of end-ileostomy while on peri-operative fluconazole prophylaxis; after the procedure, he became septic and developed recurrent fungemia. He was diagnosed with *C. parapsilosis* prosthetic valve endocarditis with high grade candidemia. He was treated with liposomal amphotericin B and flucytosine. Despite periods of neutropenia, the fungemia cleared on 06 March 2020. The patient was started on prophylaxis with oral itraconazole however he had challenges achieving effective blood levels. The repeat transthoracic echocardiogram on 06 May 2020 showed resolution of the vegetation on the prosthetic aortic valve, but there was a new mild to moderate regurgitation. The patient continued suppressive dose of oral itraconazole.

In early November 2020, the patient experienced recrudescence of *C. parapsilosis* aortic prosthetic valve endocarditis (Table 52). He was started on liposomal amphotericin, micafungin and flucytosine as well as filgrastim for neutropenia. The fungal blood cultures were persistently positive on 03 December 2020. On 07 April 2021, the patient was started on weekly IV rezafungin on a compassionate basis after IRB approval and consenting. He tolerated the initial 400 mg IV rezafungin, followed by IV weekly 200 mg rezafungin. There have been no tremors, ataxia or

neuropathy, no laboratory abnormalities, or positive fungal cultures during the rezafungin therapy. Rezafungin treatment is ongoing.

Table 52: Minimum Inhibitory Concentration Values and Susceptibility Interpretive Criteria for *Candida parapsilosis* Isolate Obtained from Expanded Access Patient No 4

C. parapsilosis isolate	MIC (µg/mL) / CLSI interpretation[a]						
	RZF	ANF	CAS	MCF	FLU	VOR	AMB
1	1 / S[b]	4 / I	0.25 / S	1 / S	64 / R	0.5 / I	1 / NA

AMB: amphotericin B; ANF: anidulafungin; CAS: caspofungin; FLU: fluconazole; I: intermediate; MCF: micafungin; MIC: minimum inhibitory concentration; NA: not available RZF: rezafungin S: susceptible; R: resistant; VOR: voriconazole
[a]CLSI M27M44S Ed3 2022
[b]At the time of MIC testing, rezafungin interpretive criteria were not available. The interpretation provided here applies current M27M44S provisional susceptible-only CLSI breakpoints for rezafungin (intermediate and resistant values have not yet been established).

10.3 Efficacy Measures in STRIVE Phase 2 Study

Table 53: STRIVE Mycological Outcome Categories

Outcome	Definition
Success (eradication/ presumed eradication)	• If positive blood culture at baseline: The last blood culture drawn on or prior to the day of assessment and another blood culture drawn at least 12 hours prior are both negative for *Candida* spp. AND Any intervening blood cultures drawn between the 2 qualifying negative blood cultures are also negative for *Candida* spp. OR • If positive culture from a normally sterile site: *Documented* mycological eradication: most recent culture on or prior to the day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is negative OR *Presumed* mycological eradication: follow-up culture is not available (e.g., normally sterile baseline site of *Candida* infection not accessible) in a patient with a successful clinical outcome (i.e., did not receive rescue antifungal treatment and has resolution of systemic signs of invasive candidiasis that were present at baseline) and resolution or improvement of any baseline radiographic abnormalities due to invasive candidiasis AND • There was no change of antifungal therapy for the treatment of candidemia and/or invasive candidiasis AND • The patient is not lost to follow-up on the day of assessment
Failure	• If positive blood culture at baseline: The last blood culture drawn on or prior to the day of assessment or any blood culture drawn prior to and within 12 hours of the last blood culture is positive for *Candida* spp. OR The most recent blood culture drawn at least 12 hours prior to the last blood culture is positive for *Candida* spp. OR • If positive culture from a normally sterile site: Documented mycological persistence: most recent culture on or prior to the day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is positive OR Presumed mycological persistence: follow-up culture is not available (e.g., normally sterile baseline site of *Candida* infection not accessible) in a patient without a successful clinical outcome or with continued (from baseline) radiographic abnormalities due to invasive candidiasis OR • The patient requires a change of antifungal therapy to treat candidemia OR • The patient dies of any cause prior to or on the day of assessment

Indeterminate	• If positive blood culture at baseline: A blood specimen was not available to culture or the result was not available • If positive culture from a normally sterile site: A sterile site tissue/fluid specimen was not available to culture or the result was not available AND an assessment of signs of invasive candidiasis was not available • Patient is lost to follow-up on the day of assessment

Table 54: STRIVE Clinical Response (Investigator's Assessment)

Clinical Response	Definition
Cure (ALL requirements must be met)	• Resolution of attributable systemic signs and symptoms of candidemia/IC that were present at baseline • No new systemic signs or symptoms attributable to candidemia/IC • No additional systemic antifungal therapy administered for candidemia/IC • The patient is alive
Failure (ANY one requirement is met)	• Progression or recurrence of attributable systemic signs or symptoms of candidemia/IC • Lack of resolution attributable systemic signs or symptoms of candidemia/IC • Requirement for new or prolonged therapy to treat candidemia/IC[a] • An AE requires discontinuation of study drug (IV and IV/oral) on or prior to the day of assessment • The patient died of any cause
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow-up • Withdrawal of consent • Extenuating circumstances that preclude the classification of clinical outcome of candidemia/IC

AE: adverse event; IC: invasive candidiasis; IV: intravenous.
a. Prolonged antifungal therapy is defined as therapy for the treatment of candidemia extending beyond the allowable 21 days of study drug or for the treatment of IC extending beyond the allowable 28 days of study drug. The determination of prolonged therapy will only apply to the follow-up visit clinical response assessment.

10.4 Efficacy Measures in ReSTORE Phase 3 Study

Table 55: ReSTORE Qualifying Parameters for Systemic Signs of Candidemia

Systemic Sign of Candidemia	Qualifying Parameters
Fever	Oral or axillary temperature ≥ 38°C (100.4°F) or a tympanic, temporal, rectal, or core body temperature ≥ 38.3°C (101°F)
Hypothermia	Tympanic, temporal, rectal, or core body temperature ≤ 35°C (95.2°F)
Hypotension	Systolic blood pressure < 90 mmHg or mean arterial pressure < 70 mmHg with a normovolemic or hypervolemic status
Tachycardia	Heart rate > 100 beats per minute with a normovolemic or hypervolemic status
Tachypnea	Respiratory rate > 20 breaths per minute
Local signs of inflammation	Erythema (rubor), edema (tumor), heat (calor), and pain (dolor) at the site of infection

Table 56: ReSTORE Mycological Response Definitions

Mycological Response	Definition
Eradication*	• If positive blood culture at baseline: o The last blood culture drawn on or prior to the day of assessments was negative without a subsequent positive culture from a sample drawn following the first dose of study drug • If positive culture from a normally sterile site at baseline (other than blood): o Documented mycological eradication: most recent culture on or prior to the day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) was negative and culture was obtained after the initiation of study drug, OR o Presumed mycological eradication: follow-up culture from all normally sterile sites of baseline *Candida* infection was not available (e.g., normally sterile baseline site of *Candida* infection not accessible) or the most recent culture from all normally sterile sites of baseline *Candida* infection obtained after the initiation of study drug was positive, in a patient with a successful clinical outcome as assessed by the Investigator (i.e., did not receive rescue antifungal treatment and had resolution of systemic signs and symptoms of invasive candidiasis that were present at baseline) and the patient had a successful radiological outcome (for those with documented evidence of disease from imaging at baseline), AND • There was no change of antifungal therapy for the treatment of candidemia and/or invasive candidiasis, AND • The patient was not lost to follow-up on the day of assessment.
Failure	• If positive blood culture at baseline: o The last blood culture drawn on or prior to the day of assessment was positive for *Candida* spp. from a sample drawn following the first dose of study drug, OR • If positive culture from a normally sterile site at baseline: o Documented mycological persistence: most recent culture on or prior to the day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) was positive and culture was obtained after the initiation of study drug, OR o Presumed mycological persistence: follow-up culture from all normally sterile sites of baseline *Candida* infection was not available (e.g., normally sterile baseline site of *Candida* infection not accessible) OR the most recent culture from all normally sterile sites of baseline *Candida* infection obtained after initiation of study drug was positive in a patient without a successful clinical outcome as assessed by the Investigator or without a successful radiological outcome for those with documented evidence of disease from imaging at baseline, OR

	• The patient required a change of antifungal therapy to treat candidemia and/or invasive candidiasis, OR • The patient died of any cause prior to or on the day of assessment.
Indeterminate	Study data were not available for the evaluation of efficacy for any reason including: • If positive blood culture at baseline: A post-baseline blood specimen was not available to culture or the result was not available. • If positive culture from a normally sterile site at baseline: A sterile site/fluid post-baseline specimen was not available to culture or the result was not available AND an assessment clinical outcome by the Investigator was not available or radiographic assessments are not available. • Patient was lost to follow-up on the day of assessment.

* Presumed eradication is defined only for a culture from a normally sterile site and is not defined for a blood culture.

10.5 Phase 1 Safety

10.5.1 Overall Safety Evaluation Plan

The safety and tolerability of rezafungin has been evaluated in 8 completed Phase 1 studies (Table 57).

Table 57: Phase 1 Studies

Study Number	Dose of Rezafungin for Injection	Sample Size in Rezafungin for Injection Group	Study Population
CD101.IV.1.01 (SAD)	Single dose of: Cohort 1: 50 mg Cohort 2: 100 mg Cohort 3: 200 mg Cohort 4: 400 mg	6 participants per cohort	Healthy adults
CD101.IV.1.02* (MAD)	Cohort 1: 100 mg × 2 weekly doses Cohort 2: 200 mg × 2 weekly doses Cohort 3: 400 mg × 3 weekly doses	6 participants per cohort	Healthy adults
CD101.IV.1.06 (QT)	Single dose of Cohort 1: 600 mg Cohort 2: 1400 mg	12 participants per cohort	Healthy adults
CD101.IV.1.07* (Photosensitivity)	400 mg × 4 weekly doses	12 participants	Healthy adults
CD101.IV.1.09* (DDI)	600 mg on Day 1, 400 mg on Day 10, and 400 mg on Day 15	26 participants	Healthy adults
CD101.IV.1.12 (Metabolism and excretion)	Single dose of 400 mg	9 participants	Healthy male adults
CD101.IV.1.15 (Hepatic impairment)	Single dose of 400 mg	Normal hepatic function: 16 participants Moderate hepatic impairment: 8 participants Severe hepatic impairment: 8 participants	Participants with normal hepatic function, moderate and severe hepatic impairment
CD101.IV.1.17* (DDI-2)	400 mg on Day 1, 200 mg on Day 8, and 200 mg on Day 15	32 participants	Healthy adults

DDI: drug-drug interaction; MAD: multiple-ascending dose; SAD: single-ascending dose.
* Patients in these studies received at least 2 doses of rezafungin commercial dose or higher.

10.5.2 Additional Phase 1 Safety Data

No participants in the Phase 1 studies administered rezafungin experienced AEs at an incidence of ≥ 30%. The most common AEs in the Phase 1 participants who received rezafungin were headache (10.7%), constipation (6.2%), diarrhea and nausea (5.1% each). All AEs for participants receiving rezafungin in the Phase 1 studies were mild or moderate in severity, with a single exception: severe abdominal pain in a participant

administered rezafungin and venetoclax in Study CD101.IV.1.17 (DDI-2), diagnosed as “gas in the intestines.”

There were 7 participants with AESIs in the Phase 1 studies in participants receiving rezafungin, as follows:

In the CD101.IV.1.02 (MAD) study, 4 participants in the rezafungin group experienced mild, transient infusion reactions, characterized by flushing, feeling hot, nausea, and chest discomfort. These infusion reactions were associated primarily with the 400 mg dose cohort and were most common with the third dose. In general, these reactions occurred within minutes of infusion initiation and disappeared within minutes without interruption or discontinuation of the study drug infusion. One participant in the 400 mg dose cohort had an infusion reaction with dose 2 and dose 3. No intervention was required for the symptoms and there were no sequelae.

In the CD101.IV.1.07 (photosensitivity) study, a 51-year-old White male with no relevant medical history, experienced an infusion-related reaction (reported as an allergic reaction) that was nonserious and of mild severity. The Investigator and the Sponsor assessed the AE of mild allergic reaction (preferred term: hypersensitivity) as related to rezafungin. Upon further assessment, the Sponsor determined that the symptoms of shortness of breath and facial flushing during study drug infusion was more consistent with an infusion-related reaction and not hypersensitivity.

In the CD101.IV.1.09 (DDI) study, a 52-year-old White female with no relevant medical history, experienced tremors after receiving the rezafungin, tacrolimus, and repaglinide cocktail on Day 1. On Day 1, the participant received repaglinide 1 mg orally and tacrolimus 5 mg orally. Rezafungin 600 mg IV was also administered on Day 1. During administration of rezafungin, the participant experienced tremors of mild intensity that resolved 1 hour and 5 minutes after onset. In addition to tremors, the participant experienced AEs of mild anxiety, mild sensation of warmth, and mild dizziness in parallel. No action was taken with the rezafungin infusion. All events resolved spontaneously on Day 1 and did not recur thereafter. The Investigator considered the tremor to be related to tacrolimus but not related to rezafungin or repaglinide. Tremor is a known effect of tacrolimus and has been reported in up to 56% of participants in the US (Prograf® (tacrolimus) Prescribing Information).

In Study CD101.IV.1.17 (DDI-2), one participant was withdrawn from the study due to an AE of infusion-related reaction experienced during the rezafungin 400 mg infusion on Day 1 of Period 2 (200 mg doses on Day 8 and Day 15 were not administered). The participant was enrolled in the study and received all 3 coadministered drugs from Day -16 to Day -7. On Day 1, the rezafungin 400 mg infusion was started at 07:55. The participant also received an oral dose of cyclosporine at 07:56. One minute after the start of the infusion, at 07:56, the participant reported feeling hot, a rapid pulse, a dry cough, and abdominal pain. The infusion was consequently stopped at 07:57, and it was not resumed. The AE was nonserious, of moderate intensity, and considered related to rezafungin given the temporal relationship and positive dechallenge.

10.6 Summary of SAEs Leading to Deaths in Pooled Safety Population

Table 58: Serious Adverse Events Leading to Death in Either Pooled Treatment Group (Pooled Safety Population)

Preferred Term, n (%)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Number of patients with ≥ 1 serious adverse event resulting in death	35 (23.2)	40 (24.1)
Septic shock	8 (5.3)	10 (6.0)
Multiple organ dysfunction syndrome	5 (3.3)	3 (1.8)
Sepsis	3 (2.0)	3 (1.8)
Cardiac arrest	3 (2.0)	1 (0.6)
Shock	2 (1.3)	0
COVID-19 pneumonia	0	2 (1.2)
Respiratory failure	1 (0.7)	3 (1.8)
Candida sepsis	1 (0.7)	1 (0.6)
Bronchopulmonary aspergillosis	1 (0.7)	0
Catheter bacteraemia	1 (0.7)	0
Device related sepsis	1 (0.7)	0
Pneumonia	1 (0.7)	0
Pneumonia pseudomonal	1 (0.7)	0
Acinetobacter sepsis	0	1 (0.6)
Bacterial sepsis	0	1 (0.6)
Bronchitis	0	1 (0.6)
COVID-19	0	1 (0.6)
Endocarditis *Candida*	0	1 (0.6)
Klebsiella sepsis	0	1 (0.6)
Pneumonia *Klebsiella*	0	1 (0.6)
Pulmonary sepsis	0	1 (0.6)
Cardio-respiratory arrest	1 (0.7)	1 (0.6)
Ventricular tachycardia	1 (0.7)	1 (0.6)
Cardiopulmonary failure	1 (0.7)	0
Myocarditis	1 (0.7)	0
Cardiac failure	0	1 (0.6)
Death	1 (0.7)	0
Acute respiratory distress syndrome	1 (0.7)	1 (0.6)
Acute respiratory failure	1 (0.7)	1 (0.6)
Hypoxia	1 (0.7)	0
Pneumonia aspiration	1 (0.7)	0
Aspiration	0	1 (0.6)

Preferred Term, n (%)	Rezafungin 400/200 mg (N=151)	Caspofungin 70/50 mg (N=166)
Pleural effusion	0	1 (0.6)
Pneumonia lipoid	0	1 (0.6)
Pneumothorax	0	1 (0.6)
Malignant neoplasm progression	1 (0.7)	1 (0.6)
Neoplasm malignant	1 (0.7)	1 (0.6)
Gastric cancer stage IV	1 (0.7)	0
Lymphoma	1 (0.7)	0
Squamous cell carcinoma of the tongue	1 (0.7)	0
Metastases to central nervous system	0	1 (0.6)
Death NOS	1 (0.7)	0
Neurodegenerative disorder	1 (0.7)	0
Intestinal ischaemia	0	1 (0.6)
Intra-abdominal haemorrhage	0	1 (0.6)

NOS: not otherwise specified; PT: Preferred Term; SOC: System Organ Class.
Note: A patient with multiple adverse events within an SOC or PT was counted only once. SOCs and PTs within SOC were sorted by descending frequency in the pooled rezafungin column. Percentages were calculated using the total number of patients in each treatment group (N) as the denominator.

10.7 Narratives for Tremor Events

10.7.1 ReSTORE

Patient 1

AE Reported/Verbatim Term: Tremor
LLT (MedDRA 23.1): Tremor
PT (MedDRA 23.1): Tremor

Treatment assignment was rezafungin 400 mg dose in Week 1, followed by 200 mg once weekly, for a total of 2 to 4 doses

A 77-year-old female patient with hypertension (since 2003, ongoing), GERD (since 2009, ongoing), hypothyroidism (since 2014, ongoing), bilateral lung nodules (since 2017, ongoing), diverticulitis (since 2016, ongoing), abdominal pain (since 22 Feb 2021, ongoing), diverticular perforation (23 Feb 2021) and nausea (since 23 Feb 2021, ongoing) received her first dose of IV study drug for candidemia on 27 Feb 2021.

Thyroid stimulating hormone (TSH) on 22 Feb 2021 was 1.230 uIU/mL (reference range: 0.358– 3.740 uIU/mL). Concomitant medications included: amlodipine, gabapentin, levothyroxine, losartan, metronidazole, Senna plus (docusate sodium, sennoside A+B), and Pepcid (famotidine).

Study drug treatment was continued for 14 days, and the last dose of study drug was administered on 12 Mar 2021. On 12 Mar 2021, a non-serious AE of hypokalemia (CTCAE Grade 1) was reported. Potassium at the end of treatment visit on the same day was 3.1 mEq/L (reference range: 3.5–5.1 mEq/L).

On 19 Mar 2021, the patient developed a non-serious tremor (CTCAE Grade 1) described as mild tremors of both hands, which interfered with the application of her eye makeup but not with drinking, eating, or writing and did not occur at rest. The Investigator reported this as possibly related to study drug.

There was no weakness, paresthesia or ataxia, and the tremors did not affect her legs.

At the Day 30 visit on 26 Mar 2021, potassium was 2.7 mEq/L (reference range: 3.5–5.1 mEq/L). The neurological exam was noted as abnormal due to mild resting tremor.

The Investigator reported that an electrolyte imbalance was a possible alternate cause for the tremor.

On 29 Mar 2021, spironolactone was started to treat the hypokalemia. No other treatment was given for the tremor, and the event was reported as resolved on 16 Apr 2021. Potassium was 3.9 mEq/L at the follow-up visit on 21 Apr 2021, and the hypokalemia was considered resolved. The neurological exam at the follow-up visit was normal.

Causality Assessment

The Sponsor concurs with the Investigator’s assessment and considers the event possibly related to the study drug. The rationale and confounders for this causality assessment are provided as follows:

The temporal relationship is plausible for the IV study drug as the event occurred 7 days after the last dose of the IV study drug (within 5 half-lives of both rezafungin and caspofungin). and 13 days after the last dose of once-weekly rezafungin if the patient was randomized to the rezafungin group.

However, a non-serious AE of hypokalemia (CTCAE Grade 1) was reported on 12 Mar 2021, resolving on 21 Apr 2021 which was noted as a possible alternate cause for the tremor. Additionally, the patient was elderly (aged 77) and essential tremor is more common in people above the age of 40. She was on levothyroxine for her hypothyroidism at the time of onset of the event. Tremor is a listed adverse reaction for levothyroxine.

The patient was also on amlodipine at the time of onset of the event. Tremor is an uncommon adverse reaction for amlodipine.

Outcome: resolved.

Additional information is not expected.

Neurology Expert Review

Facts: Serum TSH measured before study drug administration was in the normal range. The dose of thyroxine was unchanged during the period of observation.

The AE of hypokalemia had an onset date that matches the last dose of IV study drug. The AE of tremor had an onset 7 days later; a serum potassium on this date is not available. Both AEs were reported as resolved 28 days after the onset of tremor. The intervention for hypokalemia was spironolactone, initiated 19 days before the AEs resolved.

Reasoning: Hyperthyroidism and hypothyroidism may both cause tremor. The serum TSH was in the normal range before the administration of study drug, and the dose of thyroxine was unchanged during the period of observation, so excess or insufficient thyroid hormone administration is unlikely to be the cause of tremor.

Hypokalemia may cause of tremor and was apparently present for 7 days before the onset of tremor. The administration of echinocandin antibiotics is associated with hypokalemia (Lionakis 2008), and hypokalemia was still evident on the last day of IV study drug administration. The AEs of hypokalemia and tremor resolved on the same day.

Both study drugs are echinocandins, and 3 members of this class (caspofungin, anidulafungin, micafungin) have been previously associated with hypokalemia (Lionakis 2008). The temporal sequence of echinocandin administration, onset of hypokalemia, onset of tremor, completion of study drug administration, initiation of spironolactone to treat hypokalemia, then simultaneous resolution of both hypokalemia and tremor is compelling evidence that the direct cause of hypokalemia is likely to be administration of study drug and the direct cause of the AE of tremor is most likely to be hypokalemia.

Conclusion: The direct cause of hypokalemia is likely to be administration of study drug. The direct cause of the adverse event of tremor is most likely to be hypokalemia.

Reference:

Lionakis MS, Samonis G, Kontoyiannis DP. Endocrine and metabolic manifestations of invasive fungal infections and systemic antifungal treatment. Mayo Clin Proc. 2008 Sep;83(9):1046-60. doi: 10.4065/83.9.1046. PMID: 18775205.

Patient 2

AE Reported/Verbatim Term: Spontaneous hand-foot tremor
PTs (MedDRA 23.1): Tremor

Treatment assignment was rezafungin 400 mg dose in Week 1, followed by 200 mg once weekly, for a total of 2 to 4 doses

A 28-year-old female patient with acute B-lymphoblastic leukemia, gestational diabetes mellitus, fistula-in-ano, constipation, whole body numbness related to hypocalcemia and a DILI related to chemotherapy was enrolled in the study on 24 May 2021 for candidemia diagnosed according to blood culture results on 23 May 2021.

The patient had a recent acute B-lymphoblastic leukemia diagnosed on 24 Apr 2021 resulting in electrolyte disturbance (hypocalcemia, 1.31mmol/L) on 27 May 2021, which was continued until 15 Jul 2021. IV study drug was started on 24 May 2021. A spontaneous non-serious Grade 1 tremor of the hands and feet was observed on 04 Jun 2021 (Day 12). One of the patient's family members said the symptom had not appeared before the patient started the study.

Given the Grade 1 severity of the event, IV study drug was continued. On 31 May 2021, calcium was 4.15 mmol/L. Calcium gluconate (20 mL IV once daily) was given from 4–6 Jun 2021.

On 06 Jun 2021, calcium was 1.83 mmol/L and calcium gluconate was increased to 20 mL IV twice daily until 07 Jun 2021. The tremor resolved on 06 Jun 2021 (Day 14), which was also the last day of IV study drug administration. On 22 Jun 2021, calcium was 2.08 mmol/L.

Systemic concomitant medications received within 14 days of event onset are included below (All concomitant medications were since 2021 and all medical history above started from 2021).

1. Dexamethasone sodium phosphate injection for immune regulation
2. Sodium methylprednisolone succinate injection, ibuprofen tablet for fever
3. Imipenem and cilastatin injection, Meropenem Injection, Xuebijing injection, Cefoperazone sodium and sulbactam sodium injection, Terbutaline Sulfate Injection, Budesonide Suspension for Inhalation for anti-infection
4. Vidarabine Monophosphate Injection, Recombinant human granulocyte macrophage stimulating factor injection, Furosemide Injection, Injections of human immunoglobulin for Acute B-lymphoblastic leukemia
5. Potassium Chloride Sustained Release Tablets, calcium gluconate injection for electrolyte disturbance
6. Sodium Glycerophosphate Injection for Phosphorous supplementation

Causality Assessment

The Investigator considered the spontaneous tremor event as not related to study drug but due to hypocalcemia since the symptom resolved with calcium gluconate treatment and not any other specific intervention.

The Sponsor agrees with the Investigator's assessment that the event of "spontaneous hand-foot tremor" is not related to IV study drug.

The rationale and confounders for this causality assessment are provided below:

The temporal association is plausible, as the "spontaneous hand-foot tremor" started 12 days after the first dose of IV study drug was administered. However, the Investigator believed the hypocalcemia (which was caused by the disease of acute B-lymphoblastic leukemia) led to the tremor, which resolved with the electrolyte disturbance treatment of calcium gluconate injection.

The symptom resolved without any other specific intervention, however, study drug treatment was completed on the same day the tremor resolved.

Neurology Expert Review

Facts: The sequence of events was:

1. Tumor diagnosis
2. Chemotherapy
3. Drug-induced liver injury
4. Hypocalcemia
5. Candidemia
6. Treatment with study drug
7. Onset of CTCAE Grade 1 tremor
8. Treatment with IV calcium gluconate for hypocalcemia
9. Improvement in hypocalcemia, resolution of tremor, and administration of the final dose of study drug on the same day

Reasoning: The AE of hypocalcemia was due to "tumor lysis syndrome" (Howard 2011), before study drug was administered. Treatment with echinocandin antifungal agents is associated with hypercalcemia, not hypocalcemia (Lionakis 2008), so the administration of study drug is not like to exacerbate hypocalcemia. The AE of CTCAE Grade 1 tremor resolved on the same day that hypocalcemia was adequately treated with IV calcium gluconate, despite administration another dose of study drug.

Conclusion: Administration of study medication is unrelated to CTCAE Grade 1 tremor.

References:

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011 May 12; 364(19): 1844–54. doi: 10.1056/NEJMra0904569. Erratum in: N Engl J Med. 2018 Sep 13; 379(11): 1094. PMID: 21561350; PMCID: PMC3437249.

Lionakis MS, Samonis G, Kontoyiannis DP. Endocrine and metabolic manifestations of invasive fungal infections and systemic antifungal treatment. Mayo Clin Proc. 2008 Sep; 83(9): 1046– 1060. doi: 10.4065/83.9.1046. PMID: 18775205.

10.7.2 STRIVE

Patient 1

A report was received regarding an 84-year-old female patient who experienced nonserious mild tremor 3 days after the last dose of IV study and on the third day of oral study drug treatment. The patient was enrolled in Treatment Group 2 (rezafungin 400/200 mg).

Medical history included sleep apnea, arterial hypertension, dyslipidemia, chronic dizziness, hearing loss, peripheral vascular insufficiency, hyperglycemia, anemia, resection of an infected colonic tumor, Hartmann surgery, and pleural effusion.

Concomitant medications included enalapril, bemiparin, sodium chloride, parenteral nutrition, metoclopramide, metamizole, paracetamol, meropenem, levofloxacin, insulin, iron, furosemide, ceftazidime, ipratropium, codeine, acetylcysteine, pantoprazole, omeprazole, simvastatin, sulpiride/diazepam, torasemide, triflusal, Novasource GI Control, metamizole, nitrofurantoin, and cefuroxime.

IV study drug was initiated 11-Sep-2017 and continued until 18-Sep-2017. The patient was switched to oral study drug 19-Sep-2017 and continued until 08-Oct-2017.

On 21-Sep-2017 (Day 11) the patient developed mild rest and intention tremors in the upper extremities without paresthesia. The patient was discharged from the hospital (b) (6) (b) (6). No action was taken with the study drug and no treatment was provided. On 2-Nov-2017 the tremors had resolved completely. There was no neurological consultation and no neurological tests were performed.

The investigator considered the mild tremor to be related to study drug given that the patient did not have any prior neurological disease and the AE started during the administration of the study drug. The Cidara Medical Monitor agreed that given the patient's history and the temporal relationship that the possible relationship to study drug cannot be ruled out. However, following evaluation by a neurology consultant, the most likely cause of mild tremor was determined to be due to fluid shifts with the use of diuretics in an elderly, chronically ill woman.

Neurology Expert Review:

I agree with the medical monitor.

Patient 2

A report was received regarding a 67-year-old male patient who experienced tremors of both upper extremities. The patient was enrolled in Treatment Group 2 (rezafungin 400/200 mg).

Medical history in August 2018 included Parkinson's disease, acute ischemic stroke of the right cerebral hemisphere with left hemiparesis, ataxia, dysphagia and dysarthria, hemorrhage within the superior right frontal lobe and infarcts in the right temporal lobe, right occipital lobe, right brainstem and right cerebellum, hydrocephalus requiring suboccipital decompressive craniectomy and right frontal external ventricular drain placement, hypothalamic infarct with cerebral edema, aphasia.

IV study treatment was initiated 23-Aug-2018. On (b) (6) the patient was admitted for an unknown reason. On (b) (6) left eye deviation, facial and left eyelid twitching, and tremors of both upper extremities were noted. The tremors of both upper extremities were mild and nonserious and resolved 12-Sep-2018.

Neurology Expert Review:

I agree with the investigator and the medical monitor that the patient's adverse events are unrelated to study medication. I disagree with the choice of AE reported terms and the encoding to AE PTs by the investigator and the medical monitor, as indicated in the paragraphs below.

During the period of 11 August 2018 to 13 August 2018 the patient had a single episode or a series of episodes of brain infarctions, attributable to cardiac emboli from atrial flutter/fibrillation. The brain imaging studies indicated infarction of the right hemisphere, right brainstem, and right cerebellum. Some of these infarctions were hemorrhagic. Local edema from the cerebellar infarction obstructed CSF outflow from the 4th ventricle, causing obstructive hydrocephalus. Obstructive hydrocephalus was treated by insertion of an extra-ventricular drain into the left lateral ventricle followed by surgical decompression of the posterior fossa, probably by removal of the ischemic/necrotic right cerebellar hemisphere.

Presumably, candidemia was diagnosed and attributed to immunosuppression for the renal allograft. Study drug was initiated on 23 September 2018 and discontinued on 05 September 2018. The AE narrative indicates that an AE occurred on 24 September 2018, but the event is unspecified in the narrative; instead, an imaging report is provided that does not indicate any unexpected change from earlier brain imaging studies. I suspect that the investigator was unaware of the earlier imaging results and recorded a treatment-emergent AE based on a radiology report. This is clearly a mistake. The events should have been considered part of the past medical history, rather than as a treatment-emergent AE.

On 28 August 2018, the brain imaging report indicated moderate hydrocephalus. I expect that the extra-ventricular drain had already been removed, and that brain imaging was requested by the attending neurosurgeon to determine the need for a permanent ventriculoperitoneal shunt. The narrative is silent about the removal of the extra-ventricular drain and placement of a permanent ventriculoperitoneal shunt, although later in the narrative a ventriculoperitoneal shunt is seen in on a chest x-ray.

Study medication was discontinued on (b) (6) and the patient was discharged from the hospital on the same day. On (b) (6) the patient was re-admitted to the hospital (reason not specified). On (b) (6) left eye deviation, facial and left eyelid twitching, and tremors of both upper extremities were noted. The patient was intubated, received levetiracetam , and transferred to a second hospital. The event of worsening of neurological symptoms was reported as an SAE with a start date of (b) (6), 6 days after the last dose of IV study drug. The patient was admitted to the Neuro ICU. Two hours later, he became hypotensive, with a systolic BP of 36 mmHg and a diastolic BP of 23 mmHg. Vasopressor support was administered with response within 30 minutes. Bacterial pneumonia and acute respiratory failure were diagnosed. MRI showed subacute infarcts of the right parieto-occipital region, medial temporal lobe, and right cerebellum with prominent areas of enhancement. Small ventricles were noted, as were new bilateral hygromas. The tremors of both upper extremities (considered an AE of special interest) were mild and non-serious and resolved (b) (6). On (b) (6) the patient was discharged to a skilled nursing facility for rehabilitation.

On (b) (6), the patient was found face down and unconscious. The patient was re-hospitalized, and this event was reported as the second serious AE. CT of the brain without contrast showed no acute intracranial process. The right cerebellar and right parietaloccipital infarcts were stable in appearance. The shunted ventricles and bifrontal hygromas were also stable in appearance. On 28-Sep-2018 CT chest showed nodular and airspace consolidations in the left upper and lower lobes, suggestive of multilobar pneumonia. Treatment included moxifloxacin IV from 28 September 2018 until 07 October 2018 for pneumonia.

On (b) (6) the AE of “fall” was considered resolved and the patient was discharged back to the nursing facility. On 08 October 2018 the worsening of neurological symptoms was considered resolved, as the patient was more alert and interactive, was able to state his name, say a few words and follow commands.

For the (b) (6) hospitalization, the serious AE leading to hospitalization should have been described as “neurological deterioration due to pneumonia and sepsis, unrelated to study treatment” then properly coded. The AE reported on (b) (6) (b) (6) of “bilateral arm shaking” or “tremor” is should have been described as either “unwitnessed seizure and post-ictal neurological state, attributable to recent cerebral infarction, unrelated to study treatment” or “witnessed seizure attributable to recent cerebral infarction, unrelated to study treatment.” The attending physician was clearly aware of these possibilities and prescribed the anticonvulsant levetiracetam. The AE of “bilateral hygromas” is clearly due to the ventriculoperitoneal shunt, which had “deflated” the lateral ventricles, and expanded the CSF space between the brain and the dura mater over the cerebral hemispheres.

For the (b) (6) hospitalization, the serious AE leading to hospitalization should have been described as “neurological deterioration due to pneumonia, unrelated

to study treatment" then properly coded. The patient had been found face down on a soft mat in the nursing facility; the patient may have fallen due to weakness from pneumonia, or tripped and fallen due to residual neurological deficits, or a may have had an unwitnessed seizure. The investigator seems unaware of these possibilities. It is unclear whether anticonvulsant treatment with levetiracetam treatment had been continued upon transfer to the skilled nursing facility.

In conclusion, the brain infarctions cannot be treatment-emergent AEs because they preceded study treatment. In addition, both serious AEs (re-hospitalizations) should be described as either "neurological deterioration due to pneumonia and sepsis" or "neurological deterioration due to pneumonia" (if criteria for the diagnosis of sepsis is not fulfilled). These serious AEs should be considered unrelated to study medication.

10.8 Narratives for Potential DILI

Seven patients in the rezafungin \ treatment group met the laboratory criteria of ALT or AST > 3 × ULN and total bilirubin > 2 × ULN and ALP ≤ 2 × ULN at the same visit; no patient on caspofungin met the laboratory criteria for Hy's Law:

A 24-year-old in Group 1 of the Phase 2 STRIVE study had elevation of AST and T. bilirubin at screening and on Day 2. ALT was never elevated above the ULN. The patient was in a motorcycle accident 12 days prior to the Screening visit which resulted in multiple injuries, including an open abdominal wound and subsequent complications including rhabdomyolysis and intra-abdominal infection. Elevated levels of both AST and T. bilirubin were present at screening prior to rezafungin administration and likely related to the severe accident-associated trauma. A slight increase in ALP was noted after the first dose of rezafungin was given, however ALT levels remained within normal limits, and AST and total bilirubin improved during the period of study drug administration through EOT, while ALP remained slightly elevated. The Investigator did not report an AE related to the increased liver function tests (LFTs). Rhabdomyolysis is the most likely explanation for the elevation in AST. There was not a reasonable possibility to suspect a DILI in this patient.

Laboratory test	Screening	Day 2	Day 4	Day 8	End of Therapy	Follow-up
ALT	Grade 0	Grade 0	Grade 0	Grade 0	Grade 0	Grade 0
ALP	Grade 0	Grade 1	Grade 1	Grade 1	Grade 1	Grade 1
AST	Grade 3	Grade 3	Grade 3	Grade 1	Grade 0	Grade 0
Bilirubin	Grade 2	Grade 2	Grade 1	Grade 0	Grade 0	Grade 0

A 27-year-old in the Phase 3 ReSTORE study had elevations in T. bilirubin (10 × ULN) and ALT (2.1 × ULN) at the time of screening. The patient had a history of sickle cell anemia and was in sickle cell crisis with elevated LFTs at the Screening visit. On Day 8 prior to receiving the second dose of rezafungin, ALT was increased to 3.3 × ULN but T. bilirubin was lower (4.0 × ULN) than at the time of screening. When the sickle cell crisis resolved, the patient's LFTs returned to below the enrollment baseline. Sickle cell crisis can result in AST and ALT levels with

significant increases in bilirubin levels due to hemolysis. Bilirubin was significantly elevated (Grade 4) at Screening. Although AST and ALT were elevated on Day 8 prior to rezafungin dosing the values normalized after the second dose. The Investigator did not report an AE related to the increased LFTs. Given these confounding factors, there was not a reasonable possibility to suspect a DILI in this patient. Sickle cell crisis is a more likely reason for elevations in AST, ALT and total bilirubin in this patient.

Laboratory test	Screening	Day 1	Day 2	Day 4	Day 8	End of Therapy	Follow-up
ALT	Grade 1	Grade 1	Grade 1	Grade 0	Grade 2	Grade 0	Grade 0
ALP	Grade 0	Grade 0	Grade 0	Grade 0	Grade 1	Grade 0	Grade 0
AST	Grade 1	Grade 1	Grade 1	Grade 1	Grade 2	Grade 0	Grade 0
Bilirubin	Grade 4	Grade 3	Grade 3	Grade 3	Grade 3	Grade 3	Grade 3

A 39-year-old in the Phase 3 ReSTORE study had elevation in T. bilirubin (3.0 × ULN) and AST (1.8 × ULN) at time of screening. The patient had a through and through left lobe liver gunshot wound injury. On Day 8 prior to receiving the second dose of rezafungin, the ALT was slightly elevated (1.6 × ULN) and AST increased to 3.5 × ULN although the total bilirubin was unchanged. Although ALT and AST increased after the first dose of rezafungin was given, the penetrating traumatic liver injury had led to an increase in AST and bilirubin that was present before receiving rezafungin. Traumatic liver injury can lead to increased LFTs at any time during the course of recovery. LFTs and bilirubin improved following the second dose of rezafungin and were within normal limits at the EOT and follow-up visit; the Investigator did not report an AE related to the increased LFTs. Given these confounding factors and the improvement in liver enzymes and bilirubin with subsequent doses of rezafungin, there was not a reasonable possibility to suspect a DILI in this patient. Penetrating trauma to the liver from gunshot caused elevations in AST and bilirubin before initiation of rezafungin.

Laboratory test	Screening	Day 2	Day 4	Day 8	Day 14	End of Therapy	Day 30	Follow-up
ALT	Grade 0	Grade 0	Grade 0	Grade 1	Grade 1	Grade 0	Grade 1	Grade 0
ALP	Grade 0	Grade 0	Grade 0	Grade 0	Grade 1	Grade 0	Grade 1	Grade 0
AST	Grade 1	Grade 1	Grade 1	Grade 2	Grade 1	Grade 0	Grade 0	Grade 0
Bilirubin	Grade 3	Grade 3	Grade 3	Grade 2	Grade 0	Grade 0	Grade 0	Grade 0

A 58-year-old in the Phase 3 ReSTORE study had elevations in total bilirubin, AST and ALT at the Screening visit. The patient had a history of ischemic and cholestatic hepatitis. Although the AST increased from 1.7 to 3.3 × ULN and the bilirubin increased from 434 to 746 µmol/L by Day 8 after the first dose of rezafungin was given, the ALT decreased from 3.1 × ULN to normal during the same period of time. In addition to underlying liver disease, the patient was in multi-organ failure with

extensive comorbidities and infections at the time of enrollment and died on Day 13 due to bacterial septic shock; the Investigator did not report an AE related to the increased LFTs. Given these confounding factors, there was not a reasonable possibility to suspect a DILI in this patient. The presence of severe liver disease and multiorgan failure syndrome before initiation of rezafungin makes the underlying problem a more likely reason for the elevations between Day 1 and Day 8.

Laboratory test	Screening	Day 1	Day 2	Day 4	Day 8
ALT	Grade 2	Grade 2	Grade 1	Grade 0	Grade 1
ALP	Grade 0	Grade 0	Grade 0	Grade 0	Grade 0
AST	Grade 1	Grade 1	Grade 1	Grade 1	Grade 2
Bilirubin	Grade 4	Grade 4	Grade 4	Grade 4	Grade 4

A 48-year-old in the Phase 3 ReSTORE study had elevation in T. bilirubin, AST and ALT Child-Pugh Class B cirrhosis at the Screening visit. Although the bilirubin increased minimally after the first dose of rezafungin was given, AST and ALT both improved. The patient had underlying liver disease and was critically ill with multiple infections at time enrollment and died on Day 4 from uncontrolled sepsis due to catheter-related bloodstream infection (device-related sepsis); the Investigator did not report an AE related to the increased LFTs. Given these confounding factors, there was not a reasonable possibility to suspect a DILI in this patient. The presence of underlying cirrhosis is a more likely explanation for the minimal increase in bilirubin in this patient.

Laboratory test	Screening	Day 1	Day 2
ALT	Grade 1	Grade 1	Grade 1
ALP	Grade 1	Grade 1	Grade 1
AST	Grade 2	Grade 2	Grade 2
Bilirubin	Grade 4	Grade 4	Grade 4

A 79-year-old in the Phase 3 ReSTORE study had elevations in AST, ALT and T. bilirubin at the Screening visit. The patient had a history of congestive hepatopathy and was hospitalized for severe autoimmune hemolytic anemia and multiple infections at enrollment. Although the bilirubin slightly increased after the first dose of rezafungin was given, ALT improved during this same period of time. On Day 8 before the second dose of rezafungin, AST, ALT and bilirubin were all lower than on the day of screening. After septic shock was diagnosed on Day 2; the patient's overall condition deteriorated, and he died on Day 17 due to acute respiratory distress syndrome, pneumonia, bronchopulmonary aspergillosis, ventricular tachycardia, and septic shock; the Investigator did not report an AE related to the increased LFTs. There was not a reasonable possibility to suspect a DILI in this patient. The most likely reason for elevations in both T. bilirubin and AST at time of screening was the underlying autoimmune hemolytic anemia and congestive hepatopathy.

Laboratory test	Screening	Day 1	Day 2	Day 4	Day 8	End of Therapy
ALT	Grade 1	Grade 1	Grade 1	Grade 0	Grade 1	Grade 1
ALP	Grade 1	Grade 1	Grade 1	Grade 1	Grade 1	Grade 1
AST	Grade 2	Grade 2	Grade 2	Grade 1	Grade 1	Grade 2
Bilirubin	Grade 4	Grade 4	Grade 4	Grade 4	Grade 4	Grade 4

A 64-year-old in the Phase 3 ReSTORE study had elevation in bilirubin at Screening, likely due to underlying cardiorespiratory failure and multiorgan dysfunction syndrome (MODS) due to septic shock at enrollment. Although AST increased from 37 (normal) to 156 (3.5 × ULN) and bilirubin increased from 66 to 157 umol/L after the first 2 doses of rezafungin were given, the ALT increased only slightly from normal to 1.4 × ULN. Prior to dosing, the patient was critically ill with heart failure, respiratory failure, maxillofacial and mediastinal infections and died due to MODS and septic shock on Day 18 due to *Bacteroides* and *Pseudomonas* infections that were diagnosed after initiation of the study. The Investigator did not report an AE related to the increased LFTs. Given these confounding factors, there was not a reasonable possibility to suspect a DILI in this patient. The patient had elevation in bilirubin due to MODS at time of enrollment. The elevations in ALT, AST and Alk phos were more likely related to MODS and “cholestasis of sepsis” in light of the documented infections with Bacteroides and Pseudomonas during the patient’s course.

Laboratory test	Screening	Day 1	Day 2	Day 4	Day 8	Day 14
ALT	Grade 0	Grade 0	Grade 0	Grade 0	Grade 0	Grade 1
ALP	Grade 0	Grade 0	Grade 0	Grade 0	Grade 0	Grade 1
AST	Grade 0	Grade 0	Grade 0	Grade 0	Grade 0	Grade 2
Bilirubin	Grade 2	Grade 2	Grade 3	Grade 2	Grade 3	Grade 3