FDA Briefing Document

NDA #217417

Drug name: Rezafungin for injection

Applicant: Cidara Therapeutics, Inc.

Antimicrobial Drugs Advisory Committee Meeting

1/24/23

Division of Anti-infectives/Office of Infectious Diseases

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee (AC). The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this new drug application to this AC in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the AC The FDA will not issue a final determination on the issues at hand until input from the AC has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the AC meeting.

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Glossary

AC	Advisory Committee
ACM	all-cause mortality
AE	adverse event
AESI	adverse event of special interest
AUC	area under the concentration-time curve
CI	confidence interval
CYP	cytochrome P450
DDI	drug-drug interaction
FDA	Food and Drug Administration
IC	invasive candidiasis
ICU	intensive care unit
ISS	Integrated Summary of Safety
ITT	intent-to-treat
IV	intravenous
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
NDA	new drug application
NI	noninferiority
PD	pharmacodynamics
PK	pharmacokinetics
PTA	probability of target attainment
SAE	serious adverse event
TEAE	treatment-emergent adverse event

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss whether the data contained in the new drug application (NDA) for rezafungin (proposed trade name Rezzayo) support a favorable benefit-risk assessment for the treatment of candidemia and invasive candidiasis (IC) in adults and to discuss the patient population(s) with candidemia and IC that would be appropriate for treatment with rezafungin given that the submission is supported by a single phase 3 noninferiority (NI) study and a limited safety database.

1.2 Context for Issues to Be Discussed at the AC

Candidemia/IC are serious infections caused by the invasion of *Candida* spp. yeast into the blood and/or deep tissues. Treatment of candidemia/IC requires systemic antifungal therapy in combination with control of the infection source, if possible. Rezafungin is a member of the echinocandin class of antifungals, currently considered first-line initial therapy for candidemia/IC except for central nervous system, eye, or urinary tract infections. There are three FDA-approved echinocandins, all of which are available only as intravenous (IV) formulations dosed once daily. Antifungal therapy is usually continued for 2 weeks after documented clearance of *Candida* spp. from the blood in the case of candidemia or following adequate source control and clinical response in IC. However, in clinical practice, most patients are transitioned to oral antifungal therapy once clinically stable. The only available oral therapies for candidemia/IC belong to the azole class of antifungals. While the azoles have been widely used for this indication, some patients are unable to be transitioned to oral azole stepdown therapy and must continue on IV therapy because they require other medications that have unfavorable drug-drug interactions (DDIs) with azoles, are infected with an azole-resistant isolate of *Candida* spp., or are intolerant of azole therapy.

1.3 Brief Description of Issues for Discussion at the AC

On July 22, 2022, Cidara Therapeutics (Applicant) submitted NDA 217417 for rezafungin for injection. The Applicant's proposed indication is treatment of candidemia and IC in patients ≥18 years of age.

The NDA contains a single adequate and well-controlled phase 3 NI study (RESTORE) in adult subjects with candidemia/IC comparing IV rezafungin to IV caspofungin (with optional stepdown to oral fluconazole in the caspofungin arm). Rezafungin was administered as a 400 mg IV loading dose followed by weekly 200 mg IV doses for up to 4 weeks. The primary endpoint was Day 30 all-cause mortality (ACM) and the study was designed with a 20% NI margin. The study met its primary endpoint, with a Day 30 ACM rate of 23.7% in the rezafungin arm and 21.3% in the caspofungin arm in the modified intent-to-treat (mITT) population, a treatment difference of 2.4% (95% confidence interval [CI] -9.7%, 14.4%).

The NDA also contains data from an exploratory dose-finding phase 2 study enrolling a similar population of adult subjects with candidemia/IC. Patients were randomized to receive caspofungin (with optional stepdown to oral fluconazole), rezafungin 400 mg administered weekly, or rezafungin administered as a 400 mg loading dose followed by 200 mg weekly (the proposed clinical dose). The primary endpoint was overall response at Day 14. The phase 2 study was not powered for inferential statistical analysis and no prespecified inferential statistical analyses were conducted.

In the NDA submission, the Applicant proposes pooling data from the phase 3 study with data from the subset of subjects receiving the proposed rezafungin clinical dose or comparator in the phase 2 exploratory study. The Applicant's pooled efficacy analysis yields a narrower NI margin.

During the development of rezafungin, a neurotoxicity safety signal was identified in 13-week nonhuman primate studies. In these studies, animals developed tremors (resting and intention) and neurologic histopathological findings after 3 weeks of rezafungin dosing three times per week at nine-fold the planned clinical exposure. A subsequent 26-week nonhuman primate study using weekly rezafungin dosing (six-fold the planned clinical exposure) also showed a drug-related increase in tremors in rezafungin-treated monkeys compared to control animals.

The Integrated Summary of Safety (ISS) dataset for rezafungin consists of 151 subjects with candidemia or IC exposed to the proposed clinical dose (400 mg loading dose followed by 200 mg weekly) for up to 4 weeks in the phase 2 and phase 3 studies. A further 81 subjects were exposed to a higher rezafungin dose (400 mg weekly) in the phase 2 study. While tremor is reported as an uncommon adverse reaction (<5% of subjects in clinical trials) in the labeling of other echinocandins (Pfizer 2020; Merck 2021), there was an imbalance in the occurrence of tremor in the rezafungin-treated patients compared to caspofungin-treated patients in the ISS comparative safety database. Tremor was observed in four (2.6%) subjects receiving the proposed rezafungin dosage (400 mg loading dose followed by 200 mg weekly) in the ISS dataset and in none of the patients receiving the caspofungin comparator. The safety findings from these clinical studies were otherwise consistent overall with the safety profile of the approved echinocandins.

Rezafungin has an extended half-life that supports once-weekly IV dosing, in contrast to the FDA-approved echinocandins, which require daily IV dosing. It is the Applicant's position that rezafungin may also have antimicrobial and pharmacologic properties that differentiate it from FDA-approved echinocandins, such as improved in vitro activity against isolates with reduced susceptibility to some echinocandins, higher probability of target attainment (PTA), and improved tissue penetration. The Applicant also notes that rezafungin has a lower pharmacokinetic (PK) DDI potential than the azole antifungals and potentially a better DDI profile than the echinocandin caspofungin.

The FDA review team finds that the phase 3 study demonstrates the NI of rezafungin to the caspofungin comparator within a 20% margin but does not agree with the Applicant's proposal in the NDA submission to pool the efficacy data from the phase 2 and phase 3 studies to support the proposed indication. In addition, a neurotoxicity signal was identified in nonclinical studies of rezafungin in nonhuman primates. While the phase 2/3 data from subjects with candidemia/IC exposed to the proposed rezafungin dose show a similar safety profile to the FDA-approved echinocandins, the size of the dataset limits the ability to identify rare adverse reactions that may be unique to rezafungin. At this point in the review, the review team's assessment is that the Applicant has not provided sufficient data to support the position that rezafungin provides improved activity against *Candida* spp. with reduced susceptibility to FDA-approved echinocandins or provides improved tissue penetration. Overall, the review team finds that rezafungin is primarily distinguished from FDA-approved echinocandins by its extended half-life but welcomes the committee's input on whether rezafungin may have additional benefits that would extend treatment options for patients with candidemia/IC to address an unmet need.

1.4 Draft Points for Consideration

- Is the overall benefit-risk assessment favorable for the use of rezafungin for the treatment of candidemia/IC in adult patients with limited or no alternative treatment options?
  - If not, what additional information would be needed for the benefit-risk assessment to be favorable for the use of rezafungin in this/these population(s)?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

IC and candidemia are serious conditions often affecting immunosuppressed individuals and those with significant comorbidities. Based on review of published literature, a conservative estimate of the Day 30 ACM in patients with candidemia/IC receiving no treatment or inadequate treatment is approximately 70%.

Four classes of systemic antifungals have demonstrated clinical effectiveness for the treatment of candidemia/IC: echinocandins, azoles, polyenes (amphotericin B formulations), and a single member of the antimetabolite class (flucytosine). The echinocandins are recommended as first-line therapy by the Infectious Diseases Society of America for the treatment of candidemia/IC, except when affecting the central nervous system, the eyes, or the urinary tract. Echinocandins are only available as IV formulations; transition to oral azole antifungals is recommended in patients with azole-susceptible isolates once they are clinically stable. Amphotericin B is considered a reasonable alternative for patients who have drug intolerances or are infected with drug-resistant pathogens, but its use as a first-line therapy is limited due to nephrotoxicity. Flucytosine is usually only used in combination antifungal therapy due to a low barrier to resistance and may be a useful adjunctive therapy for refractory cases (Pappas et al. 2016).

There are three echinocandin antifungal agents approved by FDA to treat candidemia/IC: caspofungin, anidulafungin, and micafungin. Each of the approved echinocandins was evaluated in a single randomized comparator-controlled NI study in subjects with candidemia/IC in combination with data from other non-comparative or dose-ranging studies. At the time of NDA submission for a proposed candidemia/IC indication, all three drugs had prior FDA approval for treatment indications in other fungal infections or had data submitted concurrently from at least one other randomized, controlled study evaluating another antifungal treatment indication. These data were used to support the risk-benefit assessment for the candidemia/IC treatment indication.

The FDA-approved echinocandins have similar clinical safety profiles. Each includes warnings for hypersensitivity reactions and hepatic adverse reactions in the Warnings and Precautions section of the labeling. The micafungin labeling also includes warnings for hematologic effects, renal effects, and infusion and injection site reactions, and anidulafungin has warnings related to risks associated with two of the inactive ingredients in its formulation. None of the echinocandins have warning statements related to neurotoxicity, and the only nervous system adverse reaction reported in >5% of patients in clinical trials was headache. Tremor was reported as an adverse reaction occurring in <5% of patients participating in an open-label noncomparative clinical trial of anidulafungin in pediatric patients (n=68) and in the pooled safety experience from 34 studies of caspofungin in adult and pediatric patients or volunteers (n=1951) reported in the labeling. The caspofungin and anidulafungin labeling report

hepatotoxicity findings in studies of nonhuman primates dosed for 5 weeks and 3 months, respectively, but do not report neurotoxicity findings of these studies.

2.2 Pertinent Drug Development and Regulatory History

Rezafungin was granted orphan drug designation for the treatment of candidemia and IC caused by susceptible *Candida* species in 2016. Qualified Infectious Disease Product and Fast Track designations were granted for these indications on June 27, 2017. The Applicant is also developing rezafungin for the indication of prevention of invasive fungal infections in adults undergoing allogenic hematopoietic stem cell transplantation. Qualified Infectious Disease Product and Fast Track designations were granted for these indications on September 10, 2018.

For antibacterial drugs with the potential to treat serious infections in patients who have few or no available treatments, FDA may consider a more flexible development program to facilitate development, providing there are adequate data to demonstrate that the drug is safe and effective and the statutory standards for approval are met (FDA 2022). We believe it may be appropriate to utilize a flexible development program for antifungal drugs with the potential to treat serious infections in patients who have few or no available treatments, and in particular for this drug, but we seek the committee's input. If the flexible development program involves smaller, shorter, or fewer clinical trials, there may be less clinical safety data and nonclinical studies may play a greater role in the safety evaluations. In addition, flexible drug development programs may include clinical trials with smaller sample sizes and greater uncertainty, leading to greater reliance on nonclinical information (e.g., activity at therapeutically relevant drug exposures evaluated in vitro and in appropriate animal models of infection). For anti-infective drugs developed under a more flexible program, the drug labeling should include the known risks and benefits of the drug as well as a description of the limitations of the data available to support approval. In addition, the labeled indication should identify the approved patient population for which FDA has determined the benefits of the drug outweigh the risks so that the healthcare community is informed of how to use the drug appropriately. For example, the indication may state that the drug is approved for treatment of a particular infection type in patients who have limited or no alternative treatment options and that approval of the indication is based on limited clinical safety and efficacy data (Cipla 2018; Merck 2020). In further discussions below, we will refer to this as a "limited use statement/indication".

The Applicant had multiple discussions with FDA regarding possible pathways to support approval of rezafungin to meet an unmet need within a flexible development program. FDA noted that a treatment indication could be supported by a single phase 2 and a single phase 3 study and encouraged the Applicant to enroll subjects with both IC and candidemia in these studies. The single phase 3 NI study to evaluate rezafungin for the treatment of IC and candidemia was designed with a 20% NI margin for the primary endpoint of Day-30 ACM, which allowed for a fixed timepoint to assess efficacy after the completion of study treatment for either IC or candidemia. The Applicant submitted an NI margin justification that used data from the published literature to estimate Day-30 ACM rates from patients with candidemia/IC receiving no treatment or inadequate treatment and data from published studies forming the basis of approval for other echinocandins to estimate an echinocandin treatment effect on Day-30 ACM. Based on these data, a conservative estimate of the echinocandin treatment effect (M1) on Day-30 ACM was ≥31%. FDA determined that an NI margin of 10%, which preserves at least two-thirds of the treatment effect for the proposed mortality endpoint, would be recommended to obtain an

indication for treatment of candidemia/IC without a limited use statement. However, a phase 3 study with an NI margin of 20% could be used to support a limited use indication.

In April 2018, prior to the initiation of the phase 3 candidemia/IC study, the Applicant informed FDA of neurological adverse events (AEs) observed in a 13-week repeat dose study of rezafungin in cynomolgus monkeys not previously seen in shorter duration animal studies. The Applicant reported that unexpected neurologic events had not been observed to date in rezafungin-treated subjects with candidemia/IC in the ongoing phase 2 study and presented plans to perform additional repeat-dose nonclinical safety studies in rats and monkeys to further evaluate the neurotoxicity signal. At a meeting in May 2018, the Applicant agreed to FDA's recommendation to add the following safety measures to mitigate the risk of neurotoxicity in the planned phase 3 candidemia/IC study with up to 4 weeks of rezafungin dosing: exclusion of subjects with a history of neuropathy, history of tremors, or receiving neurotoxic medication; addition of safety assessments for neuropathy, ataxia, and tremor; and review of safety information by the data safety monitoring board. Given that the neurologic AEs in the monkey study were observed with longer periods of dosing, FDA expressed concerns regarding the 13-week treatment duration in a planned phase 3 study intended to evaluate rezafungin as a fungal prophylactic therapy in subjects undergoing allogeneic blood and marrow transplantation. The clinical development program evaluating up to 4 weeks of rezafungin dosing was allowed to proceed with the planned mitigation measures, while the Applicant was informed that studies using longer rezafungin dosing regimens in their prophylaxis development program could not be initiated under the investigational new drug application until additional nonclinical data were available for review.

In May 2021, the Applicant submitted a summary of the interim findings of a 26-week repeat-dose toxicology study in nonhuman primates and a summary of neurologic AEs from the ongoing phase 3 candidemia/IC study. Upon review of the data, FDA agreed with initiation of the planned phase 3 prophylaxis study concurrent with the recovery phase of the 26-week nonhuman primate study. The final report of this nonhuman primate study was submitted to the NDA in September 2022.

In June 2021, the Applicant requested to discuss the clinical data to support an NDA for treatment of candidemia/IC. FDA recommended increasing the size of the safety database to include at least 300 subjects with candidemia/IC administered rezafungin at the proposed dose and duration to aid in the evaluation of the neurotoxicity safety signal. The Applicant reported significant difficulties enrolling subjects with candidemia/IC, with the phase 3 enrollment rate only half of the phase 2 enrollment rate, which was further decreased by coronavirus disease 2019 pandemic-related operational challenges. At subsequent meetings with FDA, additional options for increasing the size of the safety database were discussed; these included delaying submission of the NDA until data from both the candidemia/IC phase 3 study and the phase 3 fungal prophylaxis study were available. After unblinding of the candidemia/IC phase 3 study results, the Applicant elected to proceed using the existing safety database to support an NDA for the candidemia/IC treatment indication alone.

3 Summary of Issues for the AC

3.1 Efficacy Issues

- Evaluation of efficacy data supporting the NI assessment of rezafungin versus caspofungin comparator for the primary endpoint of Day-30 ACM.

- Additional considerations for efficacy assessment:
  - Assessment of rezafungin's antimicrobial activity relative to FDA-approved echinocandins.
  - Assessment of rezafungin's tissue penetration relative to FDA-approved echinocandins.

3.1.1 Sources of Data for Efficacy

Data for efficacy were from a phase 3 pivotal study and one exploratory dose-ranging phase 2 study, conducted by the Applicant. There were no external controls or real-world data for efficacy assessment.

3.1.1.1 Phase 3 Study

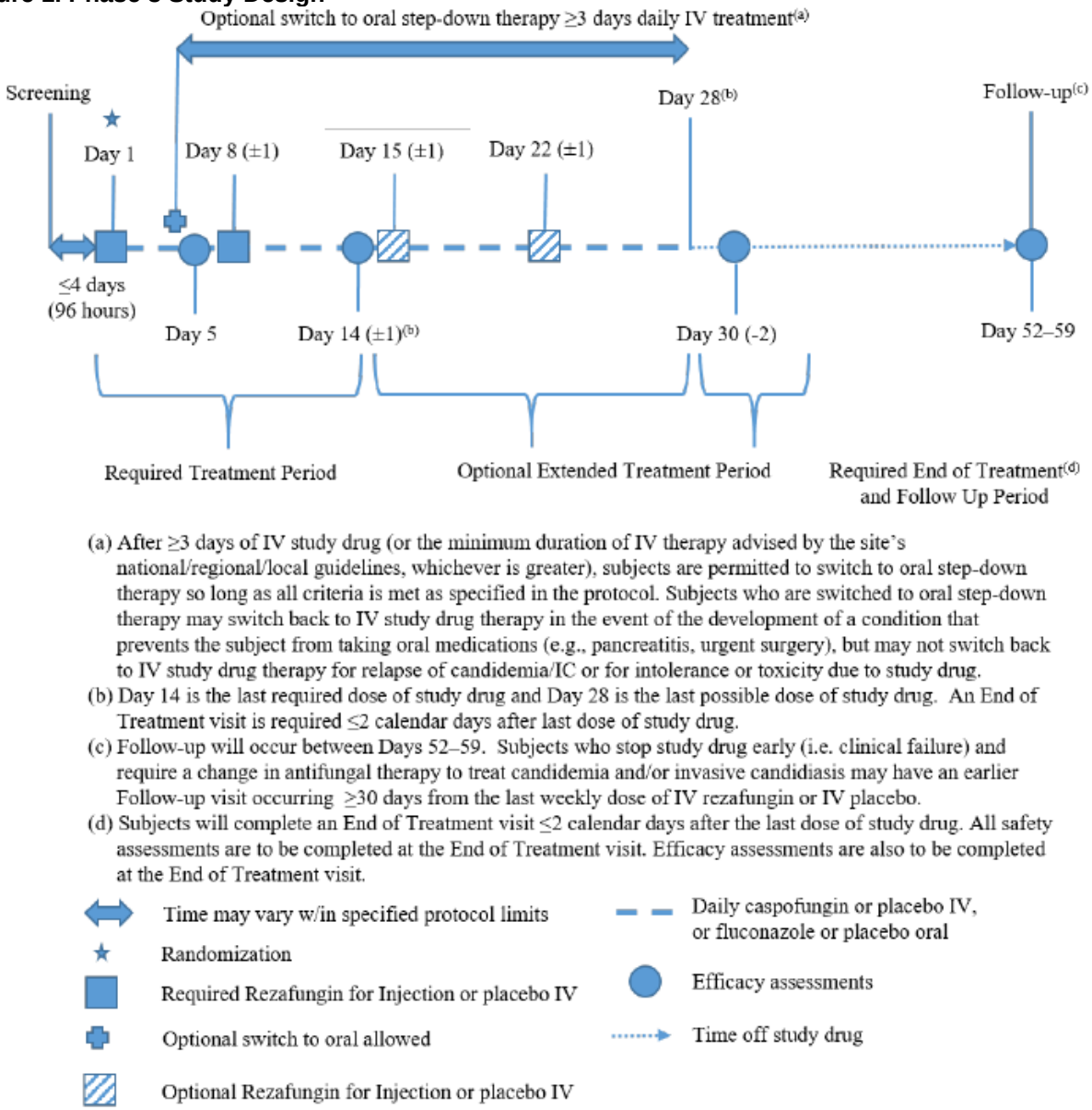
3.1.1.1.1 Phase 3 Study Design

The phase 3 study (Section 6.2.1) was an international, multicenter, randomized, double-blind, double-dummy study to compare the efficacy, safety, and tolerability of rezafungin with caspofungin for the treatment of candidemia and IC in adult subjects.

Subjects were randomly assigned (1:1 ratio) to receive either rezafungin or caspofungin. Randomization was stratified based on diagnosis (candidemia only; IC) and by Acute Physiology and Chronic Health Evaluation II score/absolute neutrophil count at screening.

Subjects in the rezafungin arm were to receive a single 400 mg loading dose on Day 1 of Week 1, followed by 200 mg once weekly, for a total of two to four doses. Subjects in the caspofungin arm were to receive treatment for a total of ≥14 days, beginning with a single 70 mg IV loading dose on Day 1 followed by caspofungin 50 mg IV once daily with the option to continue treatment for up to 28 days. After ≥3 days (or the minimum duration of IV therapy according to the site's national/regional/local guidelines, whichever was greater) of caspofungin treatment, subjects who met the stepdown therapy eligibility criteria could be switched to oral fluconazole at a dose of 6 mg/kg administered once daily (rounded to the nearest 200 mg increment) with a maximum daily dose of 800 mg. The total IV plus oral treatment duration was 14 to 28 days (Figure 1).

Figure 1. Phase 3 Study Design



(a) After ≥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), subjects are permitted to switch to oral step-down therapy so long as all criteria is met as specified in the protocol. Subjects who are switched to oral step-down therapy may switch back to IV study drug therapy in the event of the development of a condition that prevents the subject from taking oral medications (e.g., pancreatitis, urgent surgery), but may not switch back to IV study drug therapy for relapse of candidemia/IC or for intolerance or toxicity due to study drug.
(b) Day 14 is the last required dose of study drug and Day 28 is the last possible dose of study drug. An End of Treatment visit is required ≤2 calendar days after last dose of study drug.
(c) Follow-up will occur between Days 52–59. Subjects who stop study drug early (i.e. clinical failure) and require a change in antifungal therapy to treat candidemia and/or invasive candidiasis may have an earlier Follow-up visit occurring ≥30 days from the last weekly dose of IV rezafungin or IV placebo.
(d) Subjects will complete an End of Treatment visit ≤2 calendar days after the last dose of study drug. All safety assessments are to be completed at the End of Treatment visit. Efficacy assessments are also to be completed at the End of Treatment visit.

Source: Applicant Clinical Study Report CD101.IV.3.05, Figure 1, p. 38.
Abbreviation: IV, intravenous

Efficacy Endpoints

Primary Efficacy Endpoint

- **ACM at Day 30 (-2 days)**: Survival status was determined at Day 30. If survival status was unknown, the subject was considered deceased for the primary efficacy outcome.

Secondary Efficacy Endpoints

- **Global response at Day 14:** A cure was defined as clinical cure as assessed by the Investigator, radiological cure (for qualifying invasive candidiasis subjects), and mycological eradication/presumed eradication confirmed by an independent Data Review Committee at Day 14 (±1 day). This was the primary efficacy endpoint for the EMA, but was a secondary endpoint for the FDA.
- **Mycological response:** Mycological response included eradication, failure, and indeterminate.
- **Investigators' assessment of clinical response**.
- **Radiological response** (for subjects with IC documented by radiologic/imaging evidence at baseline).

Detailed definitions of secondary efficacy endpoints are provided in the Appendix (Section 6.2.1).

Efficacy Analysis

Unless otherwise stated, all efficacy analyses were conducted using the mITT population, defined in Section 6.2.1.

For the primary efficacy endpoint for the FDA (Day-30 ACM [-2 days]), NI was based on the upper limit of the two-sided 95% CI, using the unadjusted Miettinen and Nurminen method and a 20% NI margin.

Treatment differences in secondary efficacy endpoints were assessed using 95% CIs calculated using the same method for the primary efficacy endpoint, for descriptive purposes only.

3.1.1.1.2 Phase 3 Efficacy Results

Subject Disposition

A total of 222 subjects was screened for enrollment (Table 1). Twenty-three subjects (10%) were screening failures. Totals of 199 (100 in the rezafungin arm and 99 in the control arm) and 187 subjects were included in the intent-to-treat (ITT) and mITT populations, respectively (Table 2). The most common reason for exclusion from the mITT population was not having documented *Candida* infection within 96 hours prior to randomization. Approximately 60% of subjects completed the study. The main reasons for discontinuation from the study were death and withdrawal by subject. Approximately 69% of subjects completed study treatment. The main reasons for discontinuation of treatment were death and AEs. More subjects discontinued treatment due to "other" reasons in the rezafungin arm than in the caspofungin arm.

Table 1. Subject Screening and Enrollment, Phase 3 Study

Disposition	N
Subjects screened	222
Screening failures	23 (10.4%)
Inclusion/exclusion criteria not met	23 (10.4%)
Subjects enrolled	199 (89.6%)
Subjects randomized	199 (89.6%)

Source: Figure 5 of the Study Report and the Statistics Reviewer's analysis.

Table 2. Disposition of Subjects, ITT Population, Phase 3 Study

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
ITT population, n (%)	100 (100.0)	99 (100.0)	199 (100.0)
mITT population, n (%)	93 (93.0)	94 (94.9)	187 (94.0)
Reasons for exclusion from mITT, n (%)	7 (7.0)	5 (5.1)	12 (6.0)
Did not have documented *Candida* infection within 96 hours prior to randomization	5 (5.0)	4 (4.0)	9 (4.5)
Did not receive ≥1 dose of study drug	1 (1.0)	1 (1.0)	2 (1.0)
Did not receive ≥1 dose of study drug and did not have documented *Candida* infection within 96 hours prior to randomization	1 (1.0)	0	1 (<1)
Discontinuation from study, n (%)	41 (41.0)	40 (40.4)	81 (40.7)
Adverse event	0	3 (3.0)	3 (1.5)
Death	22 (22.0)	21 (21.2)	43 (21.6)
Lost to follow-up	4 (4.0)	5 (5.1)	9 (4.5)
Other	8 (8.0)	3 (3.0)	11 (5.5)
Withdrawal by subject	7 (7.0)	8 (8.1)	15 (7.5)
Discontinuation of treatment, n (%)	34 (34.0)	28 (28.3)	62 (31.2)
Adverse event	8 (8.0)	7 (7.1)	15 (7.5)
Death	8 (8.0)	8 (8.1)	16 (8.0)
Diagnosis of other type of invasive candidiasis	1 (1.0)	1 (1.0)	2 (1.0)
Lack of efficacy	2 (2.0)	3 (3.0)	5 (2.5)
Lost to follow-up	2 (2.0)	1 (1.0)	3 (1.5)
Noncompliance	0	1 (1.0)	1 (<1)
Other	9 (9.0)	1 (1.0)	10 (5.0)
Physician's decision	1 (1.0)	2 (2.0)	3 (1.5)
Withdrawal by subject	3 (3.0)	4 (4.0)	7 (3.5)

Source: Statistics Reviewer's analysis.
Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

Baseline Demographic and Clinical Characteristics

Overall, the demographic and baseline clinical characteristics were reasonably balanced between the two treatment arms (Section 6.2.1). The mean age was 61 years. About 41% of subjects were 65 years of age or older. Most of the subjects were male. There were more male subjects in the rezafungin arm (67%) versus the caspofungin arm (56.6%). However, the difference was not statistically significant (chi-squared p=0.17).

Primary and Secondary Efficacy Results

Primary Endpoint

The primary efficacy results for Day-30 ACM demonstrated NI using a 20% NI margin (Table 3). The upper limit of the 95% CI for the difference in mortality rates met a margin of 14.4%. It is noted that the study did not meet a 10% NI margin.

Table 3. All-Cause Mortality at Day 30 (-2 Days), mITT Population, Phase 3 Study

Characteristic, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
Deceased	22 (23.7)	20 (21.3)	2.4 (-9.7, 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)	

Source: Table 32 of the Study Report and Statistics Reviewer's analysis.
The FDA reviewer's analysis showed a similar 95% CI (-9.6, 14.3), using the same method as the Applicant.
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat

Secondary Endpoints

Global Response as Assessed by the Data Review Committee at Day 14 (±1 Day)

The proportions of subjects with response assessed as cure were 59.1% and 60.6% in the rezafungin and caspofungin arms, respectively. The weighted treatment difference was -1.1% (95% CI -14.9% to 12.7%), with the lower limit of the 95% CI for the difference in the mITT population exceeding -20% (Table 4).

Table 4. Global Response Assessed by DRC at Day 14 (±1 Day), Phase 3 Study

DRC Global Response, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
Cure	55 (59.1)	57 (60.6)	-1.1 (-14.9, 12.7)
Failure or indeterminate	38 (40.9)	37 (39.4)	
Failure	28 (30.1)	29 (30.9)	
Indeterminate	10 (10.8)	8 (8.5)	

Source: Table 36 of the Study Report and Statistics Reviewer's analysis.
Difference (rezafungin−caspofungin) and 95% CI adjusted for randomization strata (diagnosis and APACHE II score/ANC) using the methodology of Miettinen and Nurminen. The Reviewer's analysis using the Mantel-Haenszel method with adjustment for randomization strata yielded a similar result: -0.7 (-16.0, 14.5).
Abbreviations: ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation II, CI, confidence interval, DRC, Data Review Committee; mITT, modified intent-to-treat

The main reasons for failures in both mycological response and clinical response categories were death and new or prolonged antifungal therapy. For the indeterminate outcome, the numbers between the two treatment arms were comparable.

Global Response by Visit

Global response by visit as assessed by the Data Review Committee is presented in Table 5. At Day 5, the proportions of subjects with response assessed as cure were 55.9% and 52.1% for the rezafungin and caspofungin arms, respectively; at Day 14, they increased to 59.1% and 60.6%, respectively; and at Day 30, they decreased to 49.5% and 48.9%, respectively. At the follow-up visit (Days 52 to 59), the proportions were 45.2% and 41.5%, respectively. At each visit, as indicated by the 95% CIs, there was no statistically significant difference between the two treatment arms.

Table 5. Global Response as Assessed by Data Review Committee by Visit, mITT Population, Phase 3 Study

Visit	DRC Global Response, n (%)	Rezafungin 400/200 mg N=93	Caspofungin (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 days)	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 (≤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)	

Source: Table 41 of the Study Report and Statistics Reviewer's analysis.
Difference and 95% CI calculated using the unadjusted methodology of Miettinen and Nurminen.
Abbreviations: CI, confidence interval; DRC, Data Review Committee; EOT, end of treatment; mITT, modified intent-to-treat; N, number of subjects; n, number of subjects in the category

Mycological Response by Visit

Mycological response by visit in the mITT population is summarized in Table 6. There was no difference between the two treatment arms at each visit.

Table 6. Mycological Response by Visit, mITT Population, Phase 3 Study

Visit	Mycological Response n (%)	Rezafungin 400/200 mg N=93	Caspofungin 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 (67.7)	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 days)	Eradication	56 (60.2)	53 (56.4)	3.8 (-10.3, 17.8)
	Failure or indeterminate	37 (39.8)	41 (43.6)	
	Failure	33 (35.5)	38 (40.4)	
	Indeterminate	4 (4.3)	3 (3.2)	
EOT (≤2 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)	

Source: Table 42 of the Study Report and Statistics Reviewer's analysis.
Eradication includes both documented and presumed eradication.
Abbreviations: CI, confidence interval; DRC, Data Review Committee; EOT, end of treatment; mITT, modified intent-to-treat; N, number of subjects; n, number of subjects in the category

Investigators' Assessment of Clinical Response by Visit

At Day 5, the proportion of subjects with a response assessed as cure was 63.4% in the rezafungin arm, numerically lower than in the caspofungin arm (74.5%). At Day 14, the cure proportion in both arms was circa 67%. The cure proportion decreased to 55% at Day 30, and to about 48% at the follow--up visit (Table 7).

Table 7. Investigators' Assessment of Clinical Response by Visit, mITT Population, Phase 3 Study

Visit	Clinical Response, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
Day 5	Cure	59 (63.4)	70 (74.5)	-11.0 (-24.0, 2.3)
	Failure or indeterminate	34 (36.6)	24 (25.5)	
	Failure	31 (33.3)	22 (23.4)	
	Indeterminate	3 (3.2)	2 (2.1)	
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)	
Day 30 (-2 days)	Cure	51 (54.8)	52 (55.3)	-0.5 (-14.6, 13.7)
	Failure or indeterminate	42 (45.2)	42 (44.7)	
	Failure	32 (34.4)	34 (36.2)	
	Indeterminate	10 (10.8)	8 (8.5)	

Visit	Clinical Response, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
EOT (≤2 Days of last dose)	Cure	65 (69.9)	64 (68.1)	1.8 (-11.5, 15.0)
	Failure or indeterminate	28 (30.1)	30 (31.9)	
	Failure	22 (23.7)	26 (27.7)	
	Indeterminate	6 (6.5)	4 (4.3)	
Follow-up (Days 52-59)	Cure	46 (49.5)	44 (46.8)	2.7 (-11.6, 16.8)
	Failure or indeterminate	47 (50.5)	50 (53.2)	
	Failure	38 (40.9)	40 (42.6)	
	Indeterminate	9 (9.7)	10 (10.6)	

Source: Table 43 and Statistics Reviewer's analysis.
Exploratory Efficacy Outcome Measures.
Abbreviations: CI, confidence interval; EOT, end of treatment; mITT, modified intent to-treat

Investigator's Assessment of Radiological Response by Visit

Radiological response assessed by the Investigator by visit is presented in Table 8. Since there was a limited number of subjects with IC in each arm, it is not possible to reach a reliable conclusion.

Table 8. Radiological Response by the Investigator by Visit for Subjects With Invasive Candidiasis Documented by Radiologic/Imaging Evidence at Baseline, mITT Population, Phase 3 Study

Visit	Radiological Response, n (%)	Rezafungin 400/200 mg N=17	Caspofungin N=17
Day 5	Cure	4 (23.5)	6 (35.3)
	Failure	2 (11.8)	2 (11.8)
	Indeterminate	9 (52.9)	9 (52.9)
	Missing	2 (11.8)	0
Day 14	Cure	11 (64.7)	10 (58.8)
	Failure	2 (11.8)	6 (35.3)
	Indeterminate	4 (23.5)	1 (5.9)
Day 30	Cure	10 (58.8)	11 (64.7)
	Failure	4 (23.5)	6 (35.3)
	Missing	3 (17.6)	0

Source: Table 14.2.5.1 of the Study Report and Statistics Reviewer's analysis.
Abbreviation: mITT, modified intent-to-treat

Subgroup Analyses of the Primary Efficacy Endpoint

Subgroup analyses were conducted to assess potential differences in treatment effect among demographic subgroups. The results of subgroup analyses by age, race, and country in the mITT population are shown in Table 9.

In the <65-year-old subgroup, rezafungin was numerically worse than the control, and in the ≥65-year-old subgroup, rezafungin was numerically better than the control; there was no statistically significant difference in treatment effect between the two treatment arms in each age subgroup. However, a Breslow-Day test for homogeneity of odds ratio by age subgroup was statistically significant (p=0.0347), indicating different treatment effects of rezafungin compared to caspofungin between age subgroups.

In addition, the treatment effect of rezafungin compared to caspofungin appeared consistent across subgroups of sex, race, ethnicity, Acute Physiology and Chronic Health Evaluation II score and absolute neutrophil count, and geographic region. Of note, the sample sizes for some subgroups were small,

which limits the ability to identify trends with certainty. In addition, conducting multiple subgroup analyses without multiplicity adjustment could result in spurious findings due to chance.

Table 9. Subgroup Analyses of All-Cause Mortality at Day 30, mITT Population, Phase 3 Study

Variable	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
Age (years)			
<65	15/55 (27.3)	8/56 (14.3)	13 (-2.2, 28.1)
≥65	7/38 (18.4)	12/38 (31.6)	-13.2 (-32. 3, 6.6)
Sex			
Male	18/62 (29.0)	11/56 (19.6)	9.4 (-6.4, 24.6)
Female	4/31 (12.9)	9/38 (23.7)	-10.8 (-28.9, 8.6)
Region			
United States/South America	3/26 (11.5)	2/24 (8.3)	3.2 (-16.4, 22.4)
Europe/Israel/Turkey	9/38 (23.7)	7/37 (18.9)	4.8 (-14.3, 23.6)
Asia-Pacific (excluding China/Taiwan)	8/21 (38.1)	10/27 (37.0)	1.1 (-25.7, 28.4)
China/Taiwan	2/8 (25.0)	1/6 (16.7)	8.3 (-39.6, 49.5)
Race			
American Indian or Alaska Native	0/1 (0)	0/1 (0)	
Asian	8/23 (34.8)	10/31 (32.3)	2.5 (-22.2, 28.0)
Black or African American	1/5 (20.0)	0/4 (0)	
Not reported	1/4 (25.0)	0/1 (0)	
Other	0/1 (0)	0/2 (0)	
White	12/59 (20.3)	10/55 (18.2)	2.2 (-12.8, 16.8)
Final diagnosis at baseline			
Candidemia only	18/64 (28.1)	17/67 (25.4)	2.8 (-12.5, 18.0)
Invasive candidiasis	4/29 (13.8)	3/27 (11.1)	2.7 (-16.7, 21.7)
APACHE II and ANC			
APACHE II score ≥20 OR ANC <500 cells/μL	9/19 (47.4)	7/20 (35.0)	12.4 (-18.4, 41.1)
APACHE II score <20 AND ANC ≥500 cells/μL	12/71(16.9)	13/74 (17.6)	-0.7 (-13.2, 12.0)
Missing	1/3 (33.3)	0	
APACHE II Score			
≥20	5/12 (41.7)	7/17 (41.2)	0.5 (-33.8, 35.7)
<20	16/80 (20.0)	13/77 (16.9)	3.1 (-9.3, 15.4)
10-19	13/42 (31.0)	8/40 (20.0)	11 (-8.3, 29.5)
<10	3/38 (7.9)	5/37 (13.5)	-5.6 (-21.5, 9.5)
Missing	1/1 (100)	0	
ANC, cells/μL			
<500	4/7 (57.1)	1/5 (20.0)	37.1 (-21.3, 74.8)
≥500	18/83 (21.7)	19/89 (21.3)	0.3 (-12.0, 12.9)
Missing	0/3 (0)	0	

Source: Table 14.2.1.3 to Table 14.2.1.10 of the Study Report and Statistics Reviewer's analysis.
Abbreviations: ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; mITT, modified intent-to-treat

3.1.1.2 Phase 2 Study

3.1.1.2.1 Phase 2 Study Design

The phase 2 study, which was exploratory, provided supportive evidence of efficacy. It was a multicenter, randomized, double-blind study of safety, tolerability, and efficacy in the treatment of subjects with candidemia and/or IC.

Eligible subjects were ≥18 years of age with at least one systemic sign attributable to candidemia and/or IC. Diagnosis was based on a recent (≤96 hours before randomization) sample and required a blood culture positive for yeast or *Candida* or positive test for *Candida* by rapid in vitro diagnostic or positive Gram stain for yeast or positive culture for *Candida* spp. in a specimen from a normally sterile site.

The study was essentially adaptive. It was initially designed to have Part A only. Part B was added late to increase the sample size. In Part A, subjects were randomized in a 1:1:1 ratio to receive rezafungin treatment (400/400 mg or 400/200 mg) or caspofungin. After 107 subjects were enrolled in Part A, enrollment into Part A closed and Part B began. In Part B, subjects were randomized 2:1 to receive rezafungin treatment or IV caspofungin for 100 additional subjects. For the first part of Part B, subjects were randomized to rezafungin (400/400 mg) or caspofungin. After a complete review of unblinded Part A data, Protocol Amendment 6 defined Part B treatment as rezafungin (400/200 mg) or caspofungin.

Efficacy Endpoints

The primary efficacy outcome was overall response at Day 14 with success defined as resolution of signs of candidemia/IC and mycological eradication. Secondary efficacy endpoints included mycological response, and Investigator's assessment of clinical response.

All-cause mortality through Day 30 and follow-up was an additional efficacy outcome. Day 30 all-cause mortality was a post hoc efficacy endpoint.

3.1.1.2.2 Phase 2 Efficacy Results

In this section, overall response, mycological response, and all-cause mortality results are presented. Other efficacy endpoints are included in the Appendix.

Overall Response at Day 5 and Day 14

The overall response at Day 14 was the primary efficacy endpoint. At Day 5, the 400/200 mg rezafungin arm achieved a markedly higher proportion of success than the 400/400 mg rezafungin arm, even though the two rezafungin arms received the same dose in Week 1 (Table 10). This effect was not explainable from a clinical and pharmacological perspective and could be due to chance. At Day 14, the proportion of subjects assessed as having an overall response of success in the 400/200 mg rezafungin arm was 76.1%, higher than in the other two arms.

Table 10. Overall Response at Days 5 and 14, mITT Population, Phase 2 Study

Visit	Response	Statistic	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61
Day 5	Success	n (%)	42 (55.3)	34 (73.9)	34 (55.7)
		95% CI	43.4, 66.7	58.9, 85.7	42.4, 68.5
	Failure/indeterminate	n (%)	34 (44.7)	12 (26.1)	27 (44.3)
	Failure		24 (31.6)	10 (21.7)	24 (39.3)
	Indeterminate		10 (13.2)	2 (4.3)	3 (4.9)

Day 14	Success	n (%)	46 (60.5)	35 (76.1)	41 (67.2)
		95% CI	48.6, 71.6	61.2, 87.4	54.0, 78.7
	Failure/indeterminate	n (%)	30 (39.5)	11 (23.9)	20 (32.8)
	Failure	n (%)	20 (26.3)	8 (17.4)	17 (27.9)
	Indeterminate	n (%)	10 (13.2)	3 (6.5)	3 (4.9)

Source: Tables 20 and 26 of the Study Report and Statistics Reviewer's analysis.
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; N, number of subjects in the mITT population; n, number of subjects in the specified category

Mycological Response

The proportion of subjects with mycological success was highest in the 400/200 mg rezafungin arm and was 76.1% at Day 5 and Day 14 (Table 11). However, there were no statistically significant differences between this group and the caspofungin group at both visits. Note that at Day 5, the two rezafungin groups received the same dose, but the 400/200 mg group showed a numerically better result.

Table 11. Mycological Response at Day 5 and Day 14 (mITT Population), Phase 2 Study

Visit	Mycological Response	Statistic	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61
Day 5	Success (eradication)	n (%)	50 (65.8)	35 (76.1)	38 (62.3)
		95% CI	54.0, 76.3	61.2, 87.4	49.0, 74.4
	Failure/indeterminate	n (%)	26 (34.2)	11 (23.9)	23 (37.7)
	Failure	n (%)	17 (22.4)	9 (19.6)	21 (34.4)
	Indeterminate	n (%)	9 (11.8)	2 (4.3)	2 (3.3)
Day 14	Success (eradication)	n (%)	50 (65.8)	35 (76.1)	42 (68.9)
		95% CI	54.0, 76.3	61.2, 87.4	55.7, 80.1
	Failure/indeterminate	n (%)	26 (34.2)	11 (23.9)	19 (31.1)
	Failure	n (%)	19 (25.0)	8 (17.4)	17 (27.9)
	Indeterminate	n (%)	7 (9.2)	3 (6.5)	2 (3.3)

Source: Table 27 of the Study Report and Statistics Reviewer's analysis.
Percentages were based on the number of subjects in the mITT population.
Abbreviation: CI, confidence interval; mITT, modified intent-to-treat

All-Cause Mortality

Table 12 shows ACM through the follow-up visit (Days 45 to 52 for subjects with candidemia only or Days 52 to 59 for subjects with IC, with or without candidemia) in the mITT population. At the follow-up visit, the lowest ACM rate was observed in the 400/200 mg rezafungin arm (10.9% [5 of 46]). Of note, only five deaths had occurred in this arm by Day 30.

Table 12. All-Cause Mortality Through the Follow-up Visit, mITT Population, Phase 2 Study

Parameter	Statistic	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61
Events (deaths)	n (%)	14 (18.4)	5 (10.9)	12 (19.7)
Censored	n (%)	62 (81.6)	41 (89.1)	49 (80.3)
	n (%)	12 (15.8)	2 (4.3)	8 (13.1)
Death at Day 30	Probability	0.166	0.044	0.133
	95% CI	0.080, 0.251	0.000, 0.105	0.047, 0.219

Source: Table 33 of the Study Report and Statistics Reviewer's analysis.
Probability and 95% CI were based on the Kaplan-Meier method.
Abbreviation: CI, confidence interval; mITT, modified intent-to-treat

A post hoc analysis of Day 30 ACM was conducted. If it was unknown whether a subject was alive or deceased, the subject was considered deceased for this analysis. This was an exploratory study with no inferential analyses. Type I error control for multiplicity, interim analysis, adaptive design (different randomization ratios at different parts, stopping and reopening of the 400/200 mg rezafungin arm) were not considered for this post hoc analysis (Table 13).

Table 13. All-Cause Mortality at Day 30, mITT Population, Phase 2 Study

Parameter	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61
Survival	58 (76.3)	42 (91.3)	51 (83.6)
Deceased and unknown	18 (23.7)	4 (8.7)	10 (16.4)
Deceased	12 (15.8)	2 (4.3)	8 (13.1)
Unknown	6 (7.9)	2 (4.3)	2 (3.3)

Source: Statistics Reviewer's analysis of the adeff data from the Integrated Summary of Efficacy.
Abbreviation: mITT, modified intent-to-treat

3.1.2 Efficacy Summary

The phase 3 study demonstrated that 400/200 mg rezafungin was not inferior to caspofungin using a 20%, but not a 10%, NI margin. The phase 2 study provided supportive evidence for efficacy, although it was designed as an exploratory dose-ranging study with no inferential analyses.

3.1.3 Efficacy Issues in Detail

3.1.3.1 Evaluation of Efficacy Data Supporting the NI Assessment of Rezafungin Versus Caspofungin Comparator for the Primary Endpoint of Day 30 All-Cause Mortality

The rezafungin clinical development program consisted of a phase 2 dose-finding study and a single phase 3 study. The Applicant was informed that a single adequate controlled study showing NI of rezafungin compared to an echinocandin-based regimen with respect to Day 30 ACM would be acceptable for consideration of approval with supportive evidence provided by the phase 2 dose-finding study.

In 2017, the Division indicated it was willing to consider a smaller development program using a wider NI margin to support a limited use indication than would typically be considered for a program intended to support a candidemia/IC treatment indication for a broad patient population. A review of the literature was conducted to identify data from clinical studies or other historical evidence on the effect of placebo, no treatment, or inadequate treatment and treatment with an echinocandin-based regimen in patients with candidemia and IC. Based on this review, a data-driven estimate of the treatment effect of an echinocandin-based regimen on Day 30 ACM was approximately 31%. Therefore, it was determined that an NI margin of 20% for an endpoint of Day 30 ACM would be acceptable to obtain a limited use indication. However, noting the importance of preserving the treatment effect for ACM in patients with candidemia/IC from a clinical perspective, the Division stated that a study with a 10% NI margin using the ACM endpoint was recommended to obtain an indication without a limited use statement.

The phase 3 study submitted with this NDA was designed based on the 20% NI margin. The upper limit of the 95% CI for the difference in Day 30 ACM rates between treatment arms was <20% but >10%. Therefore, the study achieved its objective and can be used to support a limited use indication.

However, in the NDA submission, the Applicant proposes an indication without a limited use statement because the upper limit of the 95% CI for the difference in Day 30 ACM analysis of the pooled phase 2 and phase 3 studies conducted for the Integrated Summary of Efficacy is <10%.

We are concerned that the integrated efficacy analysis has potentially inflated the estimate of the treatment effect. As stated above, the basis of approval was to be the phase 3 study with supportive evidence from the phase 2 study. Therefore, the primary assessment was not prespecified to be the integrated analysis. It is rarely, especially without prespecification, acceptable from a statistical perspective to use the pooled results from studies as the primary assessment of efficacy for a marketing application.

Additionally, the phase 2 study was designed as an exploratory dose-ranging study (Section 6.2.2). Following protocol amendments, the study essentially became an adaptive study in which the 400/200 mg rezafungin treatment arm was terminated for the second part following preliminary analysis of the first part of the study, but was reinitiated after completion of the unblinded analysis of the first part. According to the FDA adaptive design guidance: "for studies intended to provide substantial evidence of effectiveness, statistical hypothesis testing methods should account for the adaptive selection of a best dose or doses from among the multiple doses evaluated in the study" (FDA 2019).

Furthermore, in the phase 2 study, at Day 5, when the rezafungin dose received for Week 1 was identical in the 400/200 mg and 400/400 mg rezafungin arms, the 400/200 mg arm achieved a numerically higher proportion of subjects with mycological eradication of 82.6% (38 of 46) versus 71.7% (54 of 76) for the 400/400 mg arm. Since both rezafungin treatment arms had received the same Week 1 rezafungin dose, no difference would be expected to be seen at this timepoint. Thus, it is our opinion that the Day 30 ACM results observed for the 400/200 mg rezafungin arm could be due to overestimation of a treatment effect in the clinical study, where a better result in one treatment arm occurred by chance, as it could not be explained from the pharmacological and clinical perspectives.

We do not consider the phase 2 study adequate and well-controlled (21 CFR 314.126). According to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-E9, studies intended to provide firm evidence in support of claims should be adequately controlled in which hypotheses are stated in advance and evaluated. In such studies, the key hypothesis of interest follows directly from the study's primary objective, which is always predefined. It is clearly stated in the phase 2 study report that the study was "an exploratory study" and "no inferential statistical analyses were conducted." Also, the primary efficacy endpoint for the phase 2 study was overall response at Day 14 (resolution of systemic signs and mycological eradication), rather than the ACM endpoint of interest.

We acknowledge that the phase 2 and phase 3 studies had similar designs (but different primary endpoints) and restricting the primary efficacy assessment to the phase 3 study may mean ignoring information that could provide a more precise estimate, given the phase 2 study contained a substantial fraction of mITT subjects in the Integrated Summary of Efficacy submitted by the Applicant. However, it is our opinion that pooling results from the phase 2 and phase 3 studies potentially leads to an overestimation of the treatment effect rather than a more precise estimate.

In conclusion, we do not agree with the pooling of the phase 2 and phase 3 studies as the primary assessment of efficacy in support of the indication claim. The primary assessment of efficacy should be

based on the results of the phase 3 study with supportive evidence provided by the phase 2 study results. Although the phase 3 study was designed with a 20% NI margin, the results would support an NI margin of 15%. This is still greater than the 10% margin which was recommended from a clinical standpoint to support approval of an indication without a limited use statement.

3.1.3.2 *Additional Considerations for Efficacy Assessment*

Assessment of Rezafungin's Antimicrobial Activity Relative to FDA-Approved Echinocandins

Rezafungin, a derivative of anidulafungin, is a second-generation echinocandin. The changes in the structure of anidulafungin, primarily at the C-5 ornithine position, provide improved chemical stability to host degradation pathways and a better PK profile with a longer half-life. Similar to other echinocandins, rezafungin targets the β-(1,3)-D-glucan synthase enzyme (Ong et al. 2016; Krishnan et al. 2017), resulting in inhibition of synthesis of β-(1,3)-D-glucan, a major polysaccharide component of the cell wall of some pathogenic fungi. Inhibition of this enzyme makes rezafungin and other echinocandins fungicidal against many *Candida* spp. In general, echinocandins including rezafungin have demonstrated in vitro activity against most isolates of *Candida* spp. and some filamentous fungi, e.g., *Aspergillus* spp.

The catalytic subunits of 1,3-β-D-glucan synthase are encoded by three homologous genes—*fks*1, *fks*2, and *fks*3—point mutations in certain areas of which increase minimum inhibitory concentration (MIC) values. There are two highly conserved 'hot spot' regions (HS1 and HS2) in both FKS1 and FKS2 among *Candida* spp. Mutations in these two regions of *fks* typically confer echinocandin resistance. These mutations influence glucan biosynthesis, thereby altering cell-wall components.

Clinical microbiological and PK-pharmacodynamic (PD) analyses comparing rezafungin's antimicrobial activity to FDA-approved echinocandins are summarized below.

Clinical Microbiological Analyses

In the NDA submission, the Applicant provided in vitro data for rezafungin and the FDA-approved echinocandins against *Candida* species. The in vitro MIC data from 2018 to 2020 surveillance (NC-188, NC-194, and NC-214) and CDC data for *C. auris* (NC-142) are summarized in Table 14. Overall, rezafungin's in vitro activity appears comparable to the other echinocandins against *Candida* species.

Table 14. In Vitro MIC_{90} of Rezafungin and Comparator Echinocandins Against *Candida* spp.

	MIC_{90} Values (µg/mL) of *Candida spp.* Isolates From 2018--2020 Surveillance Studies					CDC Study
Echinocandin Drug	***C. albicans* (n=943)**	***C. glabrata* (n=407)**	***C. tropicalis* (n=244)**	***C. parapsilosis* (n=356)**	***C. krusei* (n=147)**	***C. auris* (n=100)**
Rezafungin	0.06	0.06	0.06	2	0.06	0.5
Anidulafungin	0.06	0.12	0.06	4	0.06	2
Caspofungin	0.03	0.06	0.06	0.5	0.25	0.5
Micafungin	0.03	0.03	0.06	1	0.12	2

Source: Clinical Microbiology Reviewer using data from NDA 217417 (NC-188, NC-194, and NC-214).
Abbreviations: CDC, Centers for Disease Control; MIC_{90}, minimum concentration needed to inhibit 90% of tested isolates; NDA, new drug application

In the NDA submission, the Applicant stated that rezafungin has greater in vitro activity against echinocandin-resistant isolates compared to the FDA-approved echinocandins. In vitro MIC data were provided for caspofungin, anidulafungin, and rezafungin against a subset of 27 isolates. No MIC data

were provided for micafungin. These isolates consisted of four *Candida* species with *fks* mutations in the *fks*1 or *fks*2 gene. Overall, rezafungin had in vitro activity similar to anidulafungin but better than caspofungin against these mutant isolates (Table 15).

Table 15. In Vitro Activities (µg/mL) of Anidulafungin, Caspofungin, and Rezafungin Against Isolates of *Candida* spp. With *fks* Mutations (n=27)

Echinocandin Drug	0.06	0.12	0.25	0.50	1.0	2.0	4.0	8.0	16	Total
Rezafungin	2	3	11	4	6	1	x	x	x	27
Anidulafungin	1	3	10	3	6	3	1	x	x	27
Caspofungin	0	1	4	9	7	4	x	1	1	27

Source: Clinical Microbiology Reviewer using data from the NDA 217417.
Abbreviations: x, no isolate available at this minimum inhibitory concentration.

The in vitro activities of rezafungin, anidulafungin, caspofungin, and micafungin were also evaluated against azole-susceptible and -nonsusceptible isolates of *Candida* spp. Rezafungin exhibited in vitro activities similar to those of other echinocandins (Table 16). However, against fluconazole-nonsusceptible isolates, micafungin had slightly higher activities compared to other echinocandins. MIC_{90} values against fluconazole-nonsusceptible isolates were 0.03, 0.5, 1.0, and 0.5 µg/mL for micafungin, anidulafungin , caspofungin, and rezafungin, respectively (source, 2.7.2 Summary of Clinical Pharmacology, p. 315; Appendix 1; Table MIC distributions by fluconazole phenotype).

Table 16. In Vitro Activities of Rezafungin, Anidulafungin, and Caspofungin Against Azole-Susceptible and -Nonsusceptible *Candida* spp. Isolates

Organism	Type	N	Drug	MIC (µg/mL)		
				Range	MIC_{50}	MIC_{90}
C. albicans	AZL-NS	12	RZF	0.015 - 1	0.12	1
	AZL-S	13		≤0.008 - 0.5	0.015	0.03
	AZL-NS	12	ANI	≤0.008 - 2	0.12	1
	AZL-S	13		≤0.008 - 1	0.015	0.25
	AZL-NS	12	CAS	0.03 - 2	0.5	1
	AZL-S	13		0.06 - 1	0.12	1
C. glabrata	AZL-NS	11	RZF	0.015 - 2	0.12	1
	AZL-S	14		0.03 - 1	0.06	0.25
	AZL-NS	11	ANI	0.03 - 4	0.25	1
	AZL-S	14		≤0.008 - 2	0.06	0.25
	AZL-NS	11	CAS	0.12 - 16	0.25	2
	AZL-S	14		0.03 - 1	0.12	0.25
C. tropicalis	AZL-NS	6	RZF	≤0.008 – 0.03	0.03	-
	AZL-S	15		0.015 - 1	0.015	0.5
	AZL-NS	6	ANI	≤0.008 - 0.25	0.03	-
	AZL-S	15		≤0.008 - 1	0.03	1
	AZL-NS	6	CAS	0.06 - 0.25	0.12	-
	AZL-S	15		0.06 - 2	0.5	0.5
C. parapsilosis	AZL-NS	4	RZF	0.5 - 2	-	-
	AZL-S	11		0.5 - 2	1	1
	AZL-NS	4	ANI	1 - 2	-	-
	AZL-S	11		0.5 - 2	1	2
	AZL-NS	4	CAS	0.5 - 1	-	-
	AZL-S	11		0.12 - 0.5	0.5	0.5

AZL, azole; RZF, rezafungin; ANI, anidulafungin; CAS, caspofungin; MCF, micafungin. Source: NC-031.

Source: NDA 217417 submission.
Abbreviations: ANI, anidulafungin; AZL, azole; CAS, caspofungin; NDA, new drug application; NS, nonsusceptible; RZF, rezafungin; S, susceptible

The in vitro spontaneous mutation frequency for rezafungin was compared to anidulafungin and caspofungin. In general, echinocandins have a lower propensity to develop resistance than other antifungal classes. The spontaneous mutation frequencies to rezafungin against tested isolates of *Candida* spp. appear comparable to other echinocandins, ranging from 1.35×10^{-8} to 3.86×10^{-9} for *C. albicans*, *C. glabrata* (n=2), *C. parapsilosis*, and *C. krusei* (Table 17).

Table 17. Median Spontaneous Mutation Frequencies for Rezafungin and Comparators

Organism	RZF	ANI	CAS
C. albicans NRRL Y-477	5.00E-08	1.59E-07	1.14E-08
C. glabrata ATCC 90030	1.35E-08	9.01E-09	3.45E-07
C. glabrata ATCC 2001	3.16E-08	7.02E-08	3.16E-08
C. parapsilosis CP02	2.08E-08	<1.04E-08	<1.04E-08
C. krusei ATCC 6258	3.86E-09	<3.38E-09	<3.86E-09

RZF, rezafungin; ANI, anidulafungin; CAS, caspofungin. Source: NC-036, Table 4B.
Source: NDA 217417 submission.

In vivo studies to evaluate the activity of rezafungin in systemic fungal infections with *C. albicans*, *C. auris*, *A. fumigatus*, and *Pneumocystis murina* were conducted in mice. Rezafungin administration was compared to either untreated control, anidulafungin, micafungin, fluconazole, or amphotericin B. Overall, rezafungin demonstrated better in vivo activity compared to fluconazole, and similar activity to other echinocandins Additionally, in three in vivo studies (NC-056, -087, and -088), rezafungin demonstrated better activity compared to micafungin; however, rezafungin was administered at higher doses in these studies. Studies conducted in mouse models of *C. albicans* infection comparing rezafungin with other echinocandins are summarized in Table 18.

Table 18. In Vivo Efficacy of Rezafungin and Comparator Echinocandins in Disseminated Candidiasis Mouse Model of Animal Studies

Study#	Pathogen/MIC Values	Comparator(s) Route and Dosing(s)	Rezafungin Route and Dosing	Results
NC-035	*C. albicans* K1/RZF MIC 0.06; ANF MIC 0.015	ANF, IP: 0.25, 1, 4 mg/kg	IP: 0.25, 1, and 4 mg/kg	The 1 and 4 mg/kg doses yielded substantial reductions (>3 log) relative to controls at both 24 h and 48 h. Similar reductions were observed for ANF.
NC-040	*C. albicans* R303/RZF MIC 0.03; ANF MIC 0.0078	ANF, IV: 1 and 5 mg/kg	IV: 0.2, 1, and 5 mg/kg	Rezafungin treatment elicited significant (>2 log fungal burden reduction) anti-*Candida* effects in the 1 and 5 mg/kg treatment groups. Similar reductions were observed for ANF.
NC-042	*C. albicans* R303/RZF MIC 0.03; ANF MIC 0.0078	ANF, IV: 0.6 mg/kg	IV: 0.2, 0.4, 0.6, and 0.8 mg/kg	Rezafungin treatment elicited significant (>2 log fungal burden reduction) in the 0.6 and 0.8 mg/kg treatment groups at 24, 48, and 72 h. Significant effect was observed for ANF at 24 h and 48 h but not at 72 h.
NC-128	*C. albicans* SC5314 (ATCC MYA-2876)/ RZF MIC 0.015; MCF MIC ≤0.015	MCF, IP: 5 mg/kg (administered post-infection challenge so was not a true prophylaxis comparator)	SC: 3, 10, or 30 mg/kg given prophylactically up to 5 days prior to infection challenge (Days -5, -3, -1)	Animals receiving 10 mg/kg or 30 mg/kg CD101 (rezafungin) cleared the infection. MCF treatment also reduced fungal burden.
NC-130	*C. albicans* SC5314 (ATCC MYA-2876)/ RZF MIC 0.015; MCF MIC ≤0.015	MCF, IP: 5 mg/kg (administered post-infection challenge so was not a true prophylaxis comparator)	SC: 5, 10, or 20 mg/kg given prophylactically up to 5 days prior to infection challenge (Days -5, -3, -1)	Kidney CFU burden was completely cleared in all animals (except one) given 20 mg/kg. No measurable CFU in the groups given 10 mg/kg on Day -3 or -1. Significant decreases in CFU were seen with 5 mg/kg given on Day -3 or -1. MCF treatment also reduced fungal burden.

Study#	Pathogen/MIC Values	Comparator(s) Route and Dosing(s)	Rezafungin Route and Dosing	Results
NC-056	*C. albicans* ATCC 90028/ RZF MIC ≤0.03; MCF MIC ≤0.03 *C. albicans* DPL22/ RZF MIC 0.5; MCF MIC 0.5	MCF, IP: 5 mg/kg	IP: 20, 40, 60 mg/kg	Against wild-type *C. albicans*, rezafungin was significantly more active than MCF at all doses at 24 h and at 60 mg/kg at 48 h. For *fks*/FKS mutant *C. albicans*, rezafungin was significantly more active than MCF at all dose levels at 48 h but not 24 h.
NC-087	*C. albicans* ATCC 90028/ RZF MIC ≤0.03; MCF MIC ≤0.03 *C. albicans* DPL20/ RZF MIC 1; MCF MIC 1	MCF, IP: 5 mg/kg	IP: 10, 20, 40, 60 mg/kg	Against wild-type *C. albicans* better efficacy of rezafungin at all doses vs. MCF was demonstrated by reduced kidney burdens (>3 logs) at 24 h and 48 h. Against Fks1 S645P *C. albicans* 24 h kidney burdens were not significantly different in treatment groups, but survival at 48 h was observed in the 60 mg/kg rezafungin group, and not for MCF.
NC-088	*C. albicans* ATCC 90028/ RZF MIC ≤0.03; MCF MIC ≤0.03 *C. albicans* DPL20/ RZF MIC 1; MCF MIC 1 *C. albicans* DPL22/ RZF MIC 0.5; MCF MIC 0.5	MCF, IP: 5 mg/kg	IP: 20 and 60 mg/kg	Against WT C. *albicans* treated with rezafungin, mice had reduced fungal burden (1.5 logs), but not MCF. In *FKS/fks* mutant infected mice, rezafungin had ~2 log lower kidney counts vs controls; no treatment was effective at 24 h but, rezafungin doses reduced kidney burdens by ~1 log at 48 h, significantly better than MCF. In mice infected with the highly resistant fks mutant, no treatment was effective at either time point, but at 48 h rezafungin at 60 mg/kg had the lowest fungal kidney counts.

Source: Clinical Microbiology Reviewer using data from NDA 217417.
Abbreviations: CFU, colony-forming units; IP, intraperitoneal; IV, intravenous; MIC, minimum inhibitory concentration; NDA, new drug application; SC, subcutaneous; ANF, anidulafungin; MCF, micafungin

Overall, rezafungin's in vitro activity appears comparable to the other FDA-approved echinocandins against all *Candida* spp. While rezafungin had slightly higher in vitro activities than caspofungin against some isolates of *Candida* spp. with *fks* mutations, its activities were comparable to those of anidulafungin. The in vitro mutation frequencies of rezafungin against *Candida* isolates appears comparable to other echinocandins. Against both azole-resistant and -susceptible isolates, rezafungin demonstrated similar in vitro activity. This phenomenon was also observed with the other echinocandins. Comparable in vivo activities were observed in murine animal infection models when similar doses of rezafungin and the other echinocandins were administered.

PK-PD Analyses

The Applicant submitted PTA analyses based on nonclinical PK-PD efficacy targets for comparing rezafungin's antimicrobial activity to FDA-approved echinocandins.

Nonclinical PK-PD Targets

The nonclinical PK-PD targets used in PTA analyses were associated with net fungal stasis (no change in fungal burden over the treatment period) in the kidney in a neutropenic murine model of disseminated candidiasis. The infection model evaluated several *Candida* strains, including *C. albicans* (n=4; MIC range, 0.03 to 0.06 µg/mL) and *C. glabrata* (n=3; MIC range, 0.125 to 1 µg/mL).

PTA Analyses

PTA analyses relied on the abovementioned nonclinical PK-PD targets and were estimated for the predicted/simulated concentrations in virtual subjects receiving 400 mg rezafungin followed by 200 mg weekly. The estimated rezafungin PTAs at the proposed dosing regimen were compared to those for other echinocandins at FDA-approved dosing regimens. Based on this comparison, it is the Applicant's position that the proposed rezafungin dosage provides at least a three-dilution MIC improvement in PTA over the currently approved echinocandins.

The Applicant's PTA analyses and position are currently being reviewed; however, it is noteworthy that the FDA-approved echinocandins do not always achieve 90% PTA at their FDA-recognized breakpoints. These breakpoints are derived based on publicly available reports of clinical success rates against isolates of *C. albicans* and *C. glabrata* (Pfaller et al. 2011). The following are selected examples of reported clinical success rates for *C. albicans* from (Pfaller et al. 2011) compared to the PTA findings for the three FDA-approved echinocandins:

- Caspofungin: At a 0.25 mg/L caspofungin MIC against *C. albicans*, clinical success was reported to be 91% (21 of 23) compared to the 35.7% PTA forecasting clinical failure.
- Anidulafungin: At 0.03 and 0.06 mg/L anidulafungin MICs against *C. albicans,* clinical success was reported to be 91% (10 of 11) and 87% (6 of 7) compared to the 52.7% and 0.9% PTA, respectively, forecasting clinical failure.
- Micafungin: At a 0.03 mg/L micafungin MIC against *C. albicans*, clinical success was reported to be 79% (135 of 170) compared to the 10.1% PTA forecasting clinical failure.

These findings show that there are uncertainties regarding to what extent the improvement in PTA over the currently approved echinocandins would translate into an improved clinical outcome.

In addition, the Applicant's PTA findings show that the proposed rezafungin dosage provides improved PTA (>90%) against *C. albicans* and *C. glabrata* at MIC of up to 0.5 and 8 µg/mL, respectively, which is a

3-dilution improvement in MIC compared to caspofungin at the approved dosage (i.e., >90% PTA at MIC up to 0.12 and 1 µg/mL, respectively). However, the rezafungin clinical development program provides limited information on clinical efficacy/failure rates or mycological data (Table 19) to allow the determination of concordance between PTA findings and clinical outcome. Therefore, the clinical relevance of any potential PTA differences based on nonclinical PK-PD targets between rezafungin and the FDA-approved echinocandins is unknown.

Table 19. Maximum MIC for Study Drug Received by Baseline *Candida* Species (Number of Patients in mITT Population) With Available Data on Mycological Response at Day 14

***Candida* Species**	**Rezafungin Arm (Total N=137) µg/mL**	**Caspofungin Arm (Total N=157) µg/mL**
Candida albicans	0.12 (n=8)	0.12 (n=2)
Candida glabrata	0.5 (n=1)	0.12 (n=2)

Source: Applicant's Integrated Summary of Efficacy, Appendix 1, Table 2.2.13 (p. 386).
Abbreviations: MIC, minimum inhibitory concentration; mITT, modified intent-to-treat

Overall, the clinical microbiological data and PK-PD analyses do not demonstrate that rezafungin has better microbiological activity against *Candida* spp. likely to cause IC and candidemia compared to the FDA-approved echinocandins. Therefore, the review team concludes that: (1) overall, rezafungin has similar in vitro and in vivo activities to other echinocandins, and (2) it is unknown if the postulated improvement in PTA for rezafungin compared to FDA-approved echinocandins translates into clinically significant differences in rezafungin's ability to treat infections caused by *Candida* spp.

Assessment of Rezafungin's Tissue Penetration Relative to FDA-Approved Echinocandins

IC is characterized by infection of deep-seated tissues or organs that may or may not be at exclusive sites (e.g., prostate or brain) or in compartments formed by inflammation (e.g., abscess). Effective IC treatment requires adequate drug penetration into the site of infection to achieve microbe-eliminating concentrations.

The Applicant references a murine intra-abdominal candidiasis study to suggest that rezafungin may achieve better tissue penetration than FDA-approved echinocandins and therefore might overcome their shortcomings. The study compared rezafungin and micafungin liver tissue and infection-site concentrations using matrix-assisted laser desorption ionization mass spectrometry imaging (Zhao et al. 2017) (Study Report NC-141). The findings show that compared with micafungin (5 mg/kg), rezafungin (20 mg/kg) had greater absolute concentrations in the liver at the infection site, in lesions, and in uninvolved surrounding tissue. Consistent with this finding, mice treated with rezafungin (20 mg/kg) had significantly lower liver fungal burdens than mice treated with micafungin (5 mg/kg) (P=0.047), largely due to liver sterilization in four of five mice in the rezafungin (20 mg/kg) arm but none in the micafungin (5 mg/kg) arm. The extent of rezafungin penetration was dose-proportional. Importantly, no substantial differences were detected in tissue and infection-site exposure nor in liver fungal burden between micafungin (5 mg/kg) and rezafungin (5 mg/kg). Rezafungin (5 mg/kg) systemic exposures (maximum concentration and area under the concentration-time curve [$AUC_{0\text{-}168h}$]) and micafungin (5 mg/kg) systemic exposures (steady-state maximum concentration and $AUC_{0\text{-}24h}$) reported in mice were comparable to the reported systemic exposures in subjects with candidemia and IC after administration of the proposed initial 400 mg rezafungin dose or 100 mg daily micafungin doses (Study Reports NC-200, NC-05, NC-122, and NC-095) (Andes et al. 2008; NIH 2022).

It is noteworthy that a published systematic review of single-dose rat echinocandin PK and tissue distribution studies reported drug penetration ratios (ratios measured for drug $AUC_{0\text{-}24h}$ estimates in liver, kidney, lung to that of AUC estimates in serum) of rezafungin (4.14, 4.62, 4.33), micafungin (7.8, 3.2, 3.6), anidulafungin (12.4, 10.7, 10.4), and caspofungin (12.4, 10.7, 10.4) (Ong et al. 2017). From these data, anidulafungin has greater drug penetration of tissue than micafungin or rezafungin. Therefore, it is not clear that the positive rezafungin findings from the murine intra-abdominal candidiasis model against micafungin can be generalized to all approved echinocandins. We acknowledge that accounting for the drug fraction unbound in plasma is typically advocated when determining relative penetration ratios; however, each of these echinocandins exhibits high plasma-protein binding (>97%). Also, assay technical differences (e.g., methodological and/or interlaboratory differences) and measurement variability can strongly influence calculated estimates, hampering interpretation.

The above data do not suggest that the absolute concentrations in the liver are greater for rezafungin than micafungin when comparing the humanized doses in mice that simulate drug concentrations in patients with candidemia and IC. In addition, publicly available data do not suggest that rezafungin has a unique distinguishing tissue penetration property when compared to the other FDA-approved echinocandins, as measured by drug penetration ratios. The Applicant has not provided data to address the publicly available data. Importantly, the above data are limited to eliminating organs. Whether rezafungin would demonstrate any difference in tissue penetration compared to other echinocandins for more exclusive sites (e.g., central nervous system, eye, prostate) is unknown.

No human tissue or infection-site rezafungin PK data have been submitted to make comparative echinocandin PK analyses. Whether similar PK findings would be observed in infected humans as in infected mice remains to be demonstrated. Moreover, to our knowledge, there are no nonclinical animal infection model reports/literature that have characterized an echinocandin tissue-site PK or PK-PD target thought necessary to achieve clinical success. We also note that in the analysis of clinical data there was no substantial difference in Day 30 ACM rates between subjects with IC treated with rezafungin or caspofungin (Table 3 and Table 9).

In conclusion, the above nonclinical data submitted by the Applicant are not adequate to demonstrate that rezafungin achieves better tissue penetration/antifungal activity than the FDA-approved echinocandins. In addition, at the present time, the clinical relevance of any potential differences in absolute infection-site echinocandin drug concentrations is unclear due to the lack of target-site specific PK and/or PD data.

3.2 Safety Issues

- Assessment of neurotoxicity safety signal from nonhuman primate studies of rezafungin.
- Assessment of the DDI potential of rezafungin compared to FDA-approved echinocandins.

3.2.1 Sources of Data for Safety

The Applicant conducted eight phase 1 studies, seven in healthy adults and one in subjects with hepatic impairment. These studies enrolled 150 subjects who received rezafungin (Table 24). The rezafungin dose in these studies ranged from 50 to 1400 mg and ranged in duration from a single dose to four weekly doses of rezafungin.

The ISS dataset was pooled from the phase 2 and 3 studies (Table 25) and comprised 151 subjects with candidemia/IC receiving the proposed rezafungin dosage, consisting of a 400 mg loading dose followed by 200 mg weekly doses. An additional 81 subjects in the phase 2 study received 400 mg of rezafungin as a loading dose followed by 400 mg weekly; the safety data from these subjects were analyzed separately. The median duration of rezafungin use in the subjects included in the ISS was 14 days, with a maximum duration of 28 days (Table 20). These subjects form the basis of the safety data for the proposed indication.

Table 20. Duration of Exposure, Safety Population, ISS

	Pooled	
Parameter	**Reza (400/200 mg) N=151 n (%)**	**Caspo N=166 n (%)**
Duration of treatment, days		
Mean (SD)	12.6 (6.3)	13.8 (6.4)
Median (Q1, Q3)	14 (9, 14)	14 (13, 15)
Minimum, maximum	1, 28	1, 28
Total exposure (person-years)	5	6
Subjects treated, by duration, n (%)		
<1 day	0	0
≥1 to <7 days	33 (21.9)	26 (15.7)
≥7 to <14 days	14 (9.3)	22 (13.3)
≥14 to <28 days	97 (64.2)	107 (64.5)
28 days	7 (4.6)	11 (6.6)

Source: adex.xpt and adsl.xpt; software: R.
Duration of exposure reflects intravenous and oral therapy combined.
Abbreviations: Reza, rezafungin; Caspo, caspofungin; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

The Applicant has also provided safety data from eight subjects receiving rezafungin through expanded access in the United States and Europe. These subjects had invasive fungal diseases with limited treatment options and did not otherwise qualify for participation in ongoing clinical studies; narratives of these subjects were provided.

The Applicant is currently conducting two clinical studies of rezafungin: an extension of the phase 3 candidemia/IC study enrolling subjects in China only and a phase 3 prophylaxis study enrolling subjects to receive 13 weeks of rezafungin or comparator for the prevention of invasive fungal diseases in the allogeneic blood and bone-marrow transplant population. Blinded safety data related to these subjects was provided in the most recent Development Safety Update Report (in lieu of a 120-day Safety Update); see Section 6.3.5.

3.2.2 Safety Summary

Overview of Treatment-Emergent Adverse Events

In the ISS dataset, treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), were common in both treatment arms, which is expected in this population of seriously ill subjects receiving treatment for candidemia/IC. TEAEs and SAEs occurred at slightly higher frequencies in the

rezafungin arm (Table 21). Treatment discontinuations due to TEAEs occurred at similar rates in the two arms.

Table 21. Overview of AEs, Safety Population, ISS

Event Category	Reza (400/200 mg) N=151 n (%)	Caspo N=166 n (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
SAE	83 (55.0)	81 (48.8)	6.2 (-4.8, 17.2)
SAEs with fatal outcome	35 (23.2)	40 (24.1)	-0.9 (-10.3, 8.4)
Life-threatening SAEs	0	0	0 (0, 0)
AE leading to permanent discontinuation of study drug	14 (9.3)	15 (9.0)	0.2 (-6.1, 6.6)
AE leading to dose modification of study drug	3 (2.0)	4 (2.4)	-0.4 (-3.6, 2.8)
AE leading to interruption of study drug	3 (2.0)	4 (2.4)	-0.4 (-3.6, 2.8)
AE leading to reduction of study drug	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)
Other	0	0	0 (0, 0)
Any AE	138 (91.4)	138 (83.1)	8.3 (1.0, 15.5)[a]
Severe and worse	75 (49.7)	85 (51.2)	-1.5 (-12.6, 9.5)
Moderate	38 (25.2)	30 (18.1)	7.1 (-2.0, 16.2)
Mild	25 (16.6)	23 (13.9)	2.7 (-5.2, 10.6)

Source: adae.xpt; software: R.
Treatment-emergent AEs are defined as AEs that occurred during or after study drug administration and through the follow-up visit.
Risk difference (with 95% CI) is shown between total treatment and comparator.
Severity as assessed by the investigator.
[a] 95% CI excludes zero.
Abbreviations: AE, adverse event; Caspo, caspofungin; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of subjects in treatment arm; n, number of subjects with at least one event; Reza, rezafungin; SAE, serious adverse event

Adverse Events of Special Interest

Adverse events of special interest (AESIs) monitored by the Applicant during the clinical development program included phototoxicity, infusion-related reactions, and neurotoxicity (including tremor and peripheral neuropathy). The neurotoxicity AEs are discussed in Section 3.2.3.1.

Phototoxicity

Nonclinical studies (both in vitro and a rat study) suggested that rezafungin had phototoxic potential, and this was explored further in a phase 1 study. In this study, subjects were randomized to receive four weekly infusions of 400 mg rezafungin, placebo, or oral ciprofloxacin (as a positive control) while also being exposed to ultraviolet light at baseline and at multiple timepoints after the fourth infusion. Ultraviolet light was administered to simulate midday summer outdoor sun exposure and indoor exposure behind window glass. Subjects were examined for a minimal erythema dosage (defined as the lowest irradiation dose that produced uniform redness at the borders of the ultraviolet-light exposure site), and a photosensitivity index was calculated based on the minimal erythema dosage both with and without drug exposure. Results demonstrated mild phototoxicity in the rezafungin arm.

In the phase 2 study, a subject who received a single 400 mg infusion of rezafungin developed a sunburn/burning sensation on the head and neck with 4 hours of sun exposure 4 days after the infusion. The event was described as mild and resolved the next day. The event was confounded by the subject's

unprotected skin exposure (no hat or sunscreen) and use of concomitant medications such as fluoxetine and colchicine. No such cases were noted in the phase 3 study.

Infusion Reactions

Infusion reactions are known adverse reactions of the echinocandin drug class. This has also been noted in the rezafungin clinical development program. In phase 1 studies, infusion reactions were noted in healthy volunteers with associated symptoms of flushing, warmth, nausea/abdominal discomfort, and chest tightness/dyspnea. These symptoms generally occurred within minutes of study drug administration and resolved either without discontinuation of the infusion or by discontinuation of the infusion and restarting it at a lower rate once symptoms had resolved.

In the phase 2 study, one subject had an infusion reaction 3 minutes after starting the fourth infusion of rezafungin (400 mg/400 mg cohort). The infusion was stopped and symptoms resolved within 10 minutes of discontinuation. No rechallenge was given. No such reactions were noted in the caspofungin arm.

In the phase 3 study, four subjects in the rezafungin arm were noted to have infusion reactions; none was noted in the caspofungin arm. One subject was noted to have symptoms including flushing, warmth, and abdominal discomfort 1 minute after starting both the first and second rezafungin infusions. Symptoms resolved within minutes and the infusion was continued without interruption. Another subject had symptoms of presyncope, warmth, and dyspnea 2 minutes after starting the first rezafungin infusion. The infusion was discontinued and symptoms resolved 40 minutes later. Two rezafungin subjects were noted to have an infusion reaction on Day 3 (a day they would have received placebo rather than a rezafungin infusion). In one case, the subject had rash and wheezing 30 minutes into the infusion and required discontinuation of infusion as well as dexamethasone. In the other case, a subject had a scarlatiniform rash of the trunk and face, hypotension, and bronchospasm 30 minutes into the infusion, and symptoms resolved after stopping the infusion.

Common Treatment-Emergent Adverse Events

TEAEs occurred in 138 subjects (138 of 151; 91.4%) in the rezafungin 400 mg/200 mg treatment arm and in 138 subjects (138 of 166; 83.1%) in the caspofungin arm of the ISS dataset. The TEAEs occurring with ≥10% frequency in the rezafungin arm were hypokalemia (14.6%), pyrexia (11.9%), and diarrhea (11.3%). TEAEs that occurred in the rezafungin arm at a rate that was at least 5% greater than in the caspofungin arm were pyrexia and vomiting. Table 22 summarizes other common TEAEs that occurred at a ≥2% rate in the rezafungin arm, including erythema and tremor.

Table 22. Common AEs Occurring at ≥2% Frequency in the Rezafungin Arm and a ≥2% Risk Difference Compared to the Caspofungin Arm, Safety Population, ISS

	Pooled		
Preferred Term	Reza (400/200 mg) N=151 n (%)	Caspo N=166 n (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
Any AE	138 (91.4)	138 (83.1)	8.3 (1.0, 15.5)[a]
Pyrexia	18 (11.9)	11 (6.6)	5.3 (-1.1, 11.7)
Vomiting	14 (9.3)	7 (4.2)	5.1 (-0.5, 10.6)
Hypomagnesemia	12 (7.9)	5 (3.0)	4.9 (-0.1, 10.0)
Hypokalemia	22 (14.6)	17 (10.2)	4.3 (-2.9, 11.6)
Nausea	13 (8.6)	8 (4.8)	3.8 (-1.7, 9.3)
Pneumonia	12 (7.9)	7 (4.2)	3.7 (-1.6, 9.0)
Fluid overload	7 (4.6)	3 (1.8)	2.8 (-1.1, 6.7)
Insomnia	7 (4.6)	3 (1.8)	2.8 (-1.1, 6.7)
Dehydration	6 (4.0)	2 (1.2)	2.8 (-0.8, 6.3)
Dysphagia	5 (3.3)	1 (0.6)	2.7 (-0.4, 5.8)
Malnutrition	5 (3.3)	1 (0.6)	2.7 (-0.4, 5.8)
Erythema	4 (2.6)	0	2.6 (0.1, 5.2)[a]
Tremor	4 (2.6)	0	2.6 (0.1, 5.2)[a]
Hypophosphatemia	8 (5.3)	5 (3.0)	2.3 (-2.1, 6.7)
Anemia	15 (9.9)	13 (7.8)	2.1 (-4.2, 8.4)
Staphylococcal bacteremia	4 (2.6)	1 (0.6)	2.0 (-0.8, 4.9)
Disseminated intravascular coagulation	3 (2.0)	0	2.0 (-0.2, 4.2)
Gastrointestinal hemorrhage	3 (2.0)	0	2.0 (-0.2, 4.2)
Infusion-related reaction	3 (2.0)	0	2.0 (-0.2, 4.2)

Source: adae.xpt; software: R.
Treatment-emergent AEs are defined as AEs that occur during or after study drug administration and through the follow-up visit.
Coded as Medical Dictionary for Regulatory Activities preferred terms.
Risk difference (with 95% CI) is shown between total treatment and comparator.
[a] 95% CI excludes zero.
Abbreviations: AE, adverse event; Caspo, caspofungin; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of subjects in treatment arm; n, number of subjects with adverse event; Reza, rezafungin

3.2.3 Safety Issues in Detail

3.2.3.1 Assessment of Neurotoxicity Safety Signal From Nonhuman Primate Studies of Rezafungin

Analyses of Nonclinical Data

Rezafungin is a cationic amphiphilic compound and echinocandin. Although 4-week studies of rezafungin in nonhuman primates did not show clear evidence of neurotoxicity, a subchronic dosing study with rezafungin showed neurotoxic effects (tremors, cytoplasmic inclusions in Schwann cells, hypercellularity in Schwann cells, thin myelin, and axonal degeneration) at doses of ≥30 mg/kg when primates were dosed every 3 days for 3 months. A 13-week follow-up study was subsequently conducted in female primates, which showed that some of these effects were not reversible up to 13 weeks after cessation of dosing at the 30 mg/kg dose. A 6-month follow-up study of weekly rezafungin in 6- to 10-year-old monkeys confirmed the presence of drug-related tremors.

Three-Month Nonhuman Primate Study With a 4-Week Recovery Period

In Study NC-118, a 3-month once every 3 days IV infusion toxicity and toxicokinetic study in cynomolgus monkeys with a 4-week recovery period, rezafungin was administered by IV infusion (at 0, 3, 10, 30, or 60 mg/kg) to 3 to 5 male and female cynomolgus monkeys, over 20 to 40 minutes, once every third day for 13 weeks followed by a 4-week recovery period. Due to excessive toxicity starting on Day 42 (piloerection, unkempt appearance, hunched posture, labored breathing, vocalization, thin body, swollen abdominal area), the dose level for Arm 5 was reduced from 60 mg/kg/dose to 45 mg/kg/dose. Isolated tremors (but no intention tremors) were observed at the two lower doses. Of note, tremors were defined as involuntary twitching or trembling of muscles characterized by small contractions of a localized area of the body which may be continuous or intermittent. Intention tremors were defined as tremors which were more pronounced when movements were initiated. In the 30 mg/kg/dose arm males, intention tremors were observed in three of five males and tremors were observed in one male. In the 30 mg/kg/dose arm females, intention tremors were observed in four of five females and tremors were seen in all females. The incidence of both tremors and intention tremors in the 60/45 mg/kg/dose arm was markedly higher compared to the 30 mg/kg arm, occurring as early as Day 35/36 and continuing consistently throughout the remainder of the dosing period for both sexes. During recovery, no tremors or intention tremors were seen in the 30 mg/kg/dose arm, but tremors persisted to the end of the 28-day reversibility period in the 60/45 mg/kg dose arm.

Increased cellularity/hyperplasia of Schwann cells was observed in some sensory ganglia and peripheral nerves in a few animals at the 30 mg/kg/dose and all animals at 60/45 mg/kg. Schwann cell hyperplasia persisted through the recovery necropsy. Schwann cell hyperplasia is a common, very prominent feature of nerve fiber degeneration. Severe axonal degeneration of multiple fascicles in the right sciatic nerve was observed at the terminal necropsy in one male in the 60/45 mg/kg arm. After recovery, one 60/45 mg/kg male had moderate axonal degeneration in the left sural nerve. Demyelination of mild to moderate severity was observed at ≥30 mg/kg at the end of dosing and in recovery animals. Electron microscopy confirmed thinning, loss, and splitting of the compact myelin sheath, in the 30 and 60/45 mg/kg/dose arms but with higher incidence and severity in the 60/45 mg/kg/dose arm. Other histopathological findings observed in this study included intracytoplasmic inclusions, (minimal to marked) in the peripheral nerves at all dose levels, highest in the 30 and 60/45 mg/kg/dose arms. Inclusions persisted in peripheral nerves in recovery animals at 30 and 60/45 mg/kg. Electron microscopy revealed these inclusions to be concentrically lamellated or whorled, accumulations of osmiophilic membranous/lipid rich material, consistent with lysosomal accumulation of membranous material (e.g., degraded myelin), and phospholipidosis (not considered adverse). On Day 84, the $AUC_{0\text{-}168h}$ for 30 mg/kg rezafungin was 6930 µg·hour/mL (9-fold the clinical exposure) for males and females combined and was 11,270 µg·hour/mL, (15-fold the clinical exposure) for males at 45 mg/kg.

Thirteen-Week Nonhuman Primate Study With a 13-Week Recovery Period

Study NC 154, a 13-week investigative repeat-dose IV (20-minute) infusion neurotoxicity study, was conducted to provide more detailed information on the onset and reversibility of the neurotoxicity of rezafungin. Females were used, because this sex appeared to be more sensitive to the neurotoxicity observed in the previous 13-week toxicity study. Rezafungin was administered by intravenous infusion over 20 minutes to female cynomolgus monkeys once every third day for 13 weeks at 0 (vehicle) or 30 mg/kg, followed by a 13-week recovery period. Monkeys were subjected to detailed neurobehavioral evaluations including proprioception positioning, placing reactions, head movement, muscle tone, flexor

reflex, quantitative measures of nerve conduction velocities and histopathology assessments. Tremors were observed starting on Day 22 and persisted up to 44 days after cessation of dosing. Slight tremors of the limbs were detected in 7 of 10 animals (beginning in 1 animal during Week 4), with observations of moderate limb tremors in 2 of these 7 animals beginning during Week 7. Slight whole-body tremors were seen in some animals beginning during Week 9. During the recovery period, slight to moderate tremors of the limbs were observed with the last observations noting slight tremors of the limbs in two animals on Day 134. No abnormalities were identified in the control arm. Marginal reductions in nerve conduction velocity were detected in the peroneal nerve (-9%) and the sural nerve (-6%) in the rezafungin-treated animals during Week 13 of dosing, but these reductions did not persist to the end of the 13-week reversibility period. Cytoplasmic inclusions consistent with phospholipidosis were observed in Schwann cells after dosing and persisted 13 weeks after cessation of dosing. One rezafungin-treated animal showed neurotoxicity in the sciatic, tibial, sural, and medial plantar nerves, including Schwann cell hyperplasia, axonal degeneration, and demyelination.

Twenty-Six-Week Nonhuman Primate Study With a 52-Week Recovery Period

NC-190, a 26-week, once-weekly, intravenous infusion toxicity and toxicokinetic study of rezafungin in mature cynomolgus monkeys with a 52-week recovery period, was conducted to further characterize the potential toxicity of weekly rezafungin in adult (6 to 10 years old) monkeys. Monkeys were dosed at 0 (vehicle), 5, 15, or 30 mg/kg for 60 minutes initially but the infusion duration was reduced to 20 minutes due to injection site reactions. The incidence of tremor in concurrent (6 to 10 years old) control animals in this study was greatly increased compared to the incidence in (younger, 2 to 5 years old) control animals in previous primate studies of rezafungin. This high incidence of background tremors made it difficult to interpret tremor data. While tremors were observed in all study groups, the vast majority of the whole body/generalized tremors, hindlimb tremors and locomotor-associated tremors were observed in rezafungin-treated animals. Moderate tremors were only observed in treated male monkeys, beginning around Day 63, and including one animal with tremors so strong that he was unable to consistently bring treats to his mouth on a couple of occasions.

Sensory and motor nerve conduction velocity were within normal physiological range at baseline, Week 13, Week 25, and Week 53 in all animals. Lysosomes filled with lipid/membranous material in the cytoplasm of Schwann cells were observed in the dorsal spinal nerve root (cervical, thoracic, and lumbar), peripheral nerves (sciatic, tibial, sural, and medial plantar), sympathetic nerves (in the cervicothoracic ganglia sections), and/or trigeminal nerve (in the trigeminal ganglion section) in the 5, 15, and 30 mg/kg arms of males and females. These inclusions were considered to be nonadverse. Minimal axonal degeneration was noted in the resin section of the medial plantar nerve of one 30 mg/kg arm male and minimal degeneration of the axon was diagnosed in the sural nerve of a single 5 mg/kg female and the medial plantar nerve of a single 30 mg/kg female. In these monkeys, the dose of 30 mg/kg (AUC 4355 µg hour/mL) provides an exposure six-fold the clinical exposure. Human plasma $AUC_{0\text{-}168h}$ is 753 µg hour/mL estimated in subjects following an IV dose of 400 mg.

Additional Studies

In a tissue distribution study, NC-162 PK: Excretion mass balance, PK, and tissue distribution by quantitative whole-body autoradiography in monkey, elimination/tissue release of radioactivity from all tissues was shown to be very slow. The half-life value in the spinal nerve was estimated at 874 hours.

The tissues with greatest exposure to rezafungin were the spinal nerves (dorsal root ganglia), followed by the liver and adrenal gland cortex.

Pharmacology studies showed that, at 10µM, rezafungin interacted with several receptor/transporter sites, notably including the dopamine transporter (antagonist), glucocorticoid receptor (agonist) and the µ opioid receptor (agonist). Since perturbations of dopamine homeostasis have been linked to tremors (Kalia and Lang 2015), interactions with the dopamine transporter could theoretically contribute to the tremors observed.

Additional repeat-dose nonclinical safety studies were performed in rats. There was no evidence of tremors in rats treated with rezafungin every 3 days for 13 weeks or every 7 days for 26 weeks. In the 26-week study, at the end of the dosing period, in 45 mg/kg females, there was a slight increase in the incidence of minimal nerve fiber degeneration in the dorsal nerve root of the cervical spine, which persisted at the end of the recovery period. In 25 and 45 mg/kg males at the end of the recovery period, there was a slight increase in the incidence of minimal nerve fiber degeneration in the dorsal nerve root of the cervical spine. The Applicant considered these findings nonadverse since the severity of the nerve fiber degeneration was mostly minimal (<1% of the fibers affected), which is within the range of nerve fiber degeneration observed in control rats in studies performed at this testing facility. Rezafungin administration was associated with signs of histamine release (low carriage; decreased activity, swelling (forelimb, hindlimb, cranium, muzzle), increased respiration rate, labored breathing, incoordination, blue, discolored skin on forelimb, forepaw, hindlimb, hind paw, pinna, and urogenital areas).

Analysis of Clinical Data

After the identification of the neurotoxicity signal in the nonhuman primate studies, the eligibility criteria for the planned phase 3 clinical studies were revised to exclude subjects at increased risk for neurologic AEs and enhanced monitoring for neurologic AEs was implemented. In the phase 3 candidemia/IC study, subjects were not eligible for enrollment if they met the National Cancer Institute Common Terminology Criteria for Adverse Events Grade 2 or higher criteria for ataxia, tremor, motor neuropathy, or sensory neuropathy; had a history of severe ataxia, tremor, or neuropathy; had a history of multiple sclerosis or a movement disorder; or were receiving ongoing or planned therapy with a known severe neurotoxic medication (or a moderate neurotoxic medication in the case of subjects with Grade 1 ataxia, tremor, or neuropathy). Also, subjects in the phase 3 study were assessed for signs and symptoms of tremor, ataxia, and peripheral neuropathy by neurologic examination at the Screening Visit and at the End-of-Treatment Visit (within 2 days of the last dose of study treatment), at a minimum. In the phase 2 and 3 studies, tremor, ataxia, and peripheral neuropathy were identified as AESIs.

In the ISS dataset, the incidence of AEs in the *nervous system disorders* system organ class between the rezafungin arm (22 of 151; 14.6%) and the caspofungin arm (20 of 166; 12.0%) was similar. An imbalance in the incidence of tremors was noted, with a higher incidence in the rezafungin arm (see below). Other neurological AESIs occurred at similar rates in both treatment arms. Details of the findings from the neurological AESI cases are discussed below.

Tremors

In the ISS dataset, four cases of tremor were noted in the rezafungin treatment arm (see narratives in Section 6.3.4) and no cases were noted in the caspofungin treatment arm. No cases of tremor were seen in the 400 mg/400 mg rezafungin treatment arm of the phase 2 study. The majority of the tremor cases

have alternative plausible etiologies. In two of the tremor cases, rezafungin was postulated to indirectly cause tremor via electrolyte disturbances, but such disturbances were also seen in the caspofungin-treated subjects and no tremor cases were seen in the caspofungin arm. In another case, the subject had extensive neurologic comorbidities including Parkinson's disease and stroke. It should be noted that tremor is listed as an adverse reaction in the caspofungin and anidulafungin labeling (occurring in <5% of study subjects). Therefore, a direct relationship between rezafungin administration and tremor development cannot be dismissed.

Peripheral Neuropathy

Peripheral neuropathy is also a potential risk given the findings in the nonhuman primate study. A grouped query was used to identify TEAEs consistent with peripheral neuropathy (preferred terms included peroneal nerve palsy, neuropathy peripheral, and polyneuropathy). Only one case (preferred term, peroneal neuropathy) was seen in the pooled 400 mg/200 mg rezafungin arm and three cases were seen in the caspofungin arm of the ISS dataset. No cases of peripheral neuropathy occurred in the 400 mg/400 mg rezafungin arm of the phase 2 study. The Applicant also identified one rezafungin-treated subject in the ISS dataset with an AE reported as "intensive care unit (ICU)-acquired weakness." Narratives for the two potential peripheral neuropathy adverse reactions in the rezafungin arm (peroneal nerve palsy case and ICU-acquired weakness case) were reviewed but were considered by the clinical reviewer to be unlikely to be related to rezafungin treatment.

Ataxia

No ataxia cases were reported in the rezafungin arm.

3.2.3.2 Assessment of DDI Potential of Rezafungin Compared to FDA-Approved Antifungals for Candidemia and IC

The candidemia and IC patient populations are at higher risk of medication-related harmful effects due to changes in PK associated with polypharmacy to treat their high number of comorbidities. Cancer, postsurgical and post-transplantation status, older age, use of immunosuppressives and broad-spectrum antimicrobial agents, and comorbidities such as diabetes mellitus are risk factors for candidemia and IC.

To treat candidemia and IC, systemic antifungal therapy often consists of azoles, echinocandins, or amphotericin B when deemed necessary. FDA-approved azole antifungal agents to treat candidemia and IC include fluconazole and voriconazole. FDA-approved echinocandin antifungal agents to treat candidemia and IC include caspofungin, anidulafungin, and micafungin.

The echinocandins are recommended as first-line therapy by the Infectious Diseases Society of America for the treatment of candidemia and IC, except when affecting the central nervous system, the eyes, or the urinary tract (Pappas et al. 2016). Echinocandins are only available as IV formulations; transition to oral azole antifungals is recommended in patients with azole-susceptible isolates once they are clinically stable.

Compared to echinocandins, the azole antifungal drugs have significant PK interactions with other drugs based on their United States prescription drug labeling information. Thus, the numerous concomitant medications of patients with IC increases their risk of DDIs when transitioning from echinocandins to oral azoles. These interactions may result in increased toxicity, or may lead to reduced efficacy of the antifungal as well as the drugs used to treat the underlying diseases.

To evaluate the DDI potential of rezafungin, the Applicant conducted in vitro and clinical DDI studies to assess its potential as a victim (effect of other drugs on rezafungin) or perpetrator (effect of rezafungin on concomitant drugs) of DDIs.

Rezafungin as a Victim of PK Drug Interactions

Rezafungin undergoes minimal cytochrome P450 (CYP)-mediated metabolism and is not a substrate of drug transporters, so it is unlikely that other drugs alter rezafungin exposure. Rezafungin was stable when incubated with human hepatocytes, as well as liver and intestinal microsomes (Applicant Study Reports NC-010, NC-011, and NC-048). This was confirmed by a radiolabeled mass-balance study in humans, in which the rezafungin AUC accounted for the vast majority (~77%) of the radiocarbon AUC in plasma (Applicant Study Report CD101.IV.1.12). In addition, observed rezafungin maximum concentration and AUC values following administration of rezafungin with concomitant medication were similar to predicted values following administration of rezafungin alone.

Rezafungin as a Perpetrator of PK Drug Interactions

Rezafungin does not, to a clinically meaningful extent, inhibit or induce major drug-metabolizing enzymes or major drug transporters. We agree with the Applicant's conclusion that rezafungin has a low potential for clinically relevant DDIs in the general patient population. The Applicant's DDI evaluations and assessments are consistent with the in vitro and clinical DDI FDA guidance documents (FDA 2020b; FDA 2020a). Results of clinical DDI studies (CD101.IV.1.09 and CD101.IV.1.17) are listed in Table 23. The rezafungin dosing regimen used in these studies resulted in rezafungin exposures equal to or greater than those anticipated in the indicated treatment population. The concomitant drugs studied included those commonly prescribed to patients diagnosed with candidemia and IC as well as drugs that can be used to predict interactions mediated by CYP drug-metabolizing enzymes and drug transporters.

Table 23. Effect of Rezafungin on the PK of Coadministered Drugs (GMR [90% CI])

		Observations[a]	
Drug	**Possible Mechanism(s)**	**C_{max}**	**AUC**
Tacrolimus	CYP3A4, P-gp	↔	0.86 (0.75-0.99)
Repaglinide	CYP2C8, OATP	↔	1.16 (1.06-1.26)
Metformin	OCT, MATEs	↔	↔
Rosuvastatin	BCRP, OATP	↔	1.13 (1.02-1.27)
Pitavastatin	OATP	↔	↔
Caffeine	CYP1A2	↔	↔
Efavirenz	CYP2B6	↔	↔
Midazolam	CYP3A	↔	↔
Digoxin	P-gp	↔	↔
Cyclosporine	CYP3A4, P-gp	↔	↔
Ibrutinib	CYP3A4, P-gp, BCRP	0.83 (0.72-0.97)	↔
Mycophenolate Mofetil	Other[b]	0.81 (0.63-1.05)	↔
Venetoclax	CYP3A4, P-gp	↔	↔

Source: Clinical Pharmacology Summary, Tables 10,12, and 19. Slight modifications by the FDA Reviewer.
[a] Magnitude of change indicates ratio of geometric mean PK parameter for test (with rezafungin) relative to reference (drug alone).
[b] Drugs affecting absorption or enterohepatic recirculation.
Abbreviations: AUC, area under the concentration time curve (refers to both from time zero to last quantifiable sample and extrapolated to time infinity, unless otherwise noted); BCRP, breast cancer resistance protein; CI, confidence interval; C_{max}, maximum concentration; CYP, cytochrome P450; FDA, Food and Drug Administration; GMR, geometric mean ratio; MATE multidrug and toxin extrusion; OATP, organic anion transporter peptide; OCT, organic cation transporter; P-gp, P-glycoprotein; PK, pharmacokinetics; ↔, no change (ratio of PK parameter value varies by up to ~10%, and/or 90% CI is within 80-125%), ↓, decrease in exposure; ↑, increase in exposure

Rezafungin is not anticipated to be an inducer of CYP3A4 enzyme and/or P-glycoprotein (P-gp) transporter at the Applicant-proposed dosing regimen (400 mg, then 200 mg weekly) based on in vitro and in vivo DDI assessments. As shown in Table 23, rezafungin reduced tacrolimus (substrate of CYP3A and P-gp) systemic exposure by <20%; however, the dosing regimen for rezafungin used was 600 mg on Day 1, then 400 mg on Days 8 and 15, which is higher than the Applicant-proposed dose. In addition, rezafungin at the Applicant-proposed dosing did not alter the PK of cyclosporine or venetoclax (substrates of CYP3A and P-gp), midazolam (CYP3A clinical index substrate drug), and digoxin (P-gp clinical index substrate drug).

DDI Comparisons Across Antifungals

To assess and compare DDI potential between rezafungin and the FDA-approved azole and echinocandin antifungal drug products indicated to treat candidemia and IC, DDI information was compiled (Table 45 and Table 46). Based on a comparison of rezafungin's DDI potential with the abovementioned antifungals (Table 45 and Table 46), we agree with the Applicant that rezafungin has a lower DDI potential than azole antifungal drug products. Indeed, the majority of clinically significant DDIs (requiring dose adjustment or increased monitoring) associated with azole antifungal drugs involve the common drug metabolizing CYP enzyme system per the respective United States Prescribing Information. All azole drugs are both victims and perpetrators of PK DDIs to varying degrees, posing potentially frequent DDI risks. For echinocandins, rezafungin may have a slightly better DDI profile compared to caspofungin. Indeed, caspofungin's United States Prescribing Information recommends an alternative dosing regimen when administered concomitantly with drugs that are CYP enzyme inducers. However, rezafungin appears to have a similar DDI profile to anidulafungin and micafungin.

3.3 Risk Mitigation

Based on the safety review to date, the review team's current assessment is that the data concerning tremor will be described in labeling, but additional risk mitigation strategies are not anticipated at this time.

4 Benefit-Risk Framework

Disclaimer: This predecisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	Invasive candidiasis and candidemia are serious conditions often affecting immunosuppressed individuals and individuals with significant comorbidities. Based on review of published literature, a conservative estimate of Day-30 all-cause mortality in patients with candidemia/invasive candidiasis receiving no treatment or inadequate treatment is approximately 70%.	Invasive candidiasis and candidemia are serious conditions associated with significant morbidity and mortality.
Current Treatment Options	Echinocandins, such as caspofungin, micafungin, and anidulafungin, are considered standard of care for treatment of invasive candidiasis and candidemia. Alternative options include azole drugs and amphotericin B. Generally, an intravenous antifungal is given initially for 3-5 days with a switch to an oral formulation upon clinical improvement. Increasing resistance among *Candida* species is limiting current treatment options, and existing treatment options can be associated with adverse effects including infusion reactions, hepatotoxicity, and significant drug-drug interactions. Treatment duration is prolonged (generally continues for 2 weeks after clearance of infection) and can involve daily intravenous infusions. The only available oral stepdown therapies belong to the azole class of antifungals; therefore, patients who are intolerant of azoles, are taking concomitant medications that have pharmacokinetic drug-drug interactions with azoles, or who are infected with an azole-resistant pathogen must continue intravenous antifungal therapy for the full duration of treatment.	Though treatment options exist for the proposed indication, changes in the pathogen profile as well as limitations with current drug administration highlight the need for alternative treatment options. New treatments should maintain or improve upon the efficacy and safety of standard of care therapy while addressing the rising incidence of resistance as well as providing alternative therapeutic options.

	Evidence and Uncertainties	Comments to the Advisory Committee
Benefits	A phase 3, randomized, controlled, blinded study found that rezafungin met the primary endpoint of demonstrating noninferiority to caspofungin on the primary endpoint of Day-30 all-cause mortality within the prespecified noninferiority margin of 20%. The rezafungin arm of the phase 3 study had a Day-30 all-cause mortality rate of 23.7% (22/93), while the caspofungin arm had a mortality rate of 21.3% (20/94); the difference (95% CI) was 2.4% (-9.7%, 14.4%). Supportive evidence was provided by a phase 2 study that was not designed for hypothesis testing, but did measure mortality outcomes similar to the phase 3 study.	The phase 3 study met the agreed primary endpoint for this serious infection. However, there is a higher degree of uncertainty for the treatment effect compared with a study designed with a narrower prespecified NI margin. Point to consider: Does rezafungin possess characteristics to support a limited use indication, such as improved spectrum of activity, enhanced pharmacokinetic profile, or a significantly enhanced ease of usage/administration relative to current treatment options? What is (are) the population(s) of unmet need?
Risks and Risk Management	Common treatment-emergent adverse events for rezafungin are hypokalemia, pyrexia, diarrhea, and vomiting. Echinocandin-associated adverse effects including infusion reactions were similarly demonstrated by rezafungin. Phototoxicity was demonstrated in nonclinical studies. A neurotoxicity signal, including tremors, was demonstrated in nonclinical studies (at 9- and 6-fold the clinical dose) and in clinical studies though the clinical implications of this are unclear (i.e., severity of effects).	The safety profile of rezafungin is generally acceptable considering the seriousness of the infection and the current safety profile of existing antifungal therapy. Point to consider: Do any of the safety findings offset the anticipated benefits of rezafungin and are there any safety findings warranting other strategies to mitigate risk?

Summary of Benefit-Risk

For a drug to be approved for marketing in the United States, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. A benefit-risk assessment for rezafungin requires careful consideration of the evidence and remaining uncertainties about the key benefits of a product (as demonstrated in the development program) and potential key risks, as well as the ability to adequately mitigate such risks. This assessment should also consider whether the product is able to address a significant unmet need for patients with this serious disease.

During the course of our review, FDA identified potential key benefits and risks of rezafungin. The key issues for consideration in the benefit-risk assessment of rezafungin include the presumed ability to meet an unmet need in the context of generally similar (to current treatment options) effects on survival, the ability to mitigate any identified risks such as neurotoxicity, and the acceptable tradeoffs between the benefits and risks to patients.

Points to Consider

- Is the overall benefit-risk assessment favorable for the use of rezafungin for the treatment of candidemia/IC in adult patients with limited or no alternative treatment options?
  - If not, what additional information would be needed for the benefit-risk assessment to be favorable for the use of rezafungin in this/these population(s)?

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6 Appendix

6.1 Clinical Studies of Rezafungin

Table 24. Phase 1 Studies of Rezafungin

Study Number	Study Design	Target Population	Dose of Rezafungin for Injection	Number of Subjects (M/F)	Mean Age (Range), Years
CD101.IV.1.01 (NCT02516904)	Randomized, double-blind, single ascending dose	Healthy adults	Single dose: Cohort 1: 50 mg Cohort 2: 100 mg Cohort 3: 200 mg Cohort 4: 400 mg	24 rezafungin 8 placebo (17 M/15 F)	43.2 (25, 54)
CD101.IV.1.02 (NCT02551549)	Randomized, double-blind, multiple ascending dose	Healthy adults	Cohort 1: 100 mg ×2 weekly doses Cohort 2: 200 mg ×2 weekly doses Cohort 3: 400 mg ×3 weekly doses	18 rezafungin 6 placebo (12 M/12 F)	42.8 (22, 54)
CD101.IV.1.06	Randomized, double-blind, to determine effect on ECG parameters	Healthy adults	Single dose Cohort 1: 600 mg Cohort 2: 1400 mg	24 rezafungin 24 moxifloxacin 12 placebo (26 M/34 F)	33.9 (20, 51)
CD101.IV.1.07	Randomized, assessor-blind, to assess photosensitivity	Healthy adults	400 mg ×4 weekly doses	12 rezafungin) 12 ciprofloxacin 12 placebo (5 M/7 F)	44.1 (24, 54)
CD101.IV.1.09	Open-label crossover, to assess DDI	Healthy adults	600 mg on Day 1 400 mg on Day 10 400 mg on Day 15	26 rezafungin (24 M/2 F)	39.0 (26, 55)
CD101.IV.1.12	Open-label to assess metabolism and excretion	Healthy adults	Single dose of 400 mg	9 rezafungin (9 M/0 F)	41 (30, 54)
CD101.IV.1.15	Open-label to assess HI	Subjects with normal hepatic function, or moderate or severe HI	Single dose of 400 mg	Normal hepatic function: 16 Moderate HI: 8 Severe HI: 8 (20 M/12 F)	57.1 (41, 68)
CD101.IV.1.17	Open-label crossover, to assess DDI	Healthy adults	400 mg on Day 1 200 mg on Day 8 200 mg on Day 15	34 rezafungin (16 M/16 F)	38.6 (21, 59)

Source:
Abbreviations: DDI, drug-drug interaction; ECG, electrocardiogram; F, female; HI, hepatic impairment; M, male; NCT, National Clinical Trial

Table 25. Clinical Studies Submitted in Support of Efficacy and Safety Determinations for Rezafungin

Study Identifier	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
CD101-IV-2-03 (STRIVE) Phase 2	Subjects ≥18 years of age with ≥1 systemic sign attributable to candidemia or IC and seeking to treat this infection	Control Type: Active concurrent noninferiority Randomization: Block randomization with stratification based on the method used at screening to establish the diagnosis indicating whether the subject had candidemia or IC Part A: 1:1:1 ratio (rezafungin group 1 vs. rezafungin group 2 vs. caspofungin) Part B: 2:1 ratio (rezafungin[a] vs. caspofungin) Blinding: Double-blind Biomarkers: No biomarkers Key design features: None	Drug (established name): Rezafungin Rezafungin Group 1: 400 mg Day 1 and Day 8; optional 400 mg on Day 15, optional for subjects with IC 400 mg Day 22. Rezafungin Group 2: 400 mg Day 1, 200 mg Day 8; optional 200 mg on Day 15, optional for subjects with IC 200 mg Day 22. Caspofungin: 70 mg Day 1, 50 mg/day for 14 days, optional 50 mg/day Days 15-21, optional for subjects with IC 50 mg/day Days 22-28 Oral step-down: (see footnote[b]) Number treated: Part A: 35 Reza Group 1; 35 Reza Group 2; 34 Caspofungin Part B: 46 Reza Group 1; 18 Reza Group 2; 34 Caspofungin Duration (quantity and units): 28 days (Days 1-14 required; Days 15-28 optional for subjects with IC)	Primary: Overall response at Day 14 (±1 day) defined as resolution of attributable systemic signs of candidemia and/or IC that were present at baseline Secondary[c]: Mycological response Investigator's assessment of clinical response 30-Day all-cause mortality Time to first of two negative blood cultures	Planned: Part A: 114 Part B: 45 to 120 Actual: Part A: 107 Part B: 100	Centers: 68 Countries: 10

Study Identifier	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
CD101-IV-3-05 (ReSTORE) Phase 3	Subjects ≥18 years of age with ≥1 systemic sign attributable to candidemia or IC and seeking to treat this infection	Control Type: Active concurrent noninferiority Randomization: Stratified randomization with a 1:1 ratio (rezafungin vs. caspofungin) Blinding: Double-blind Biomarkers: No biomarkers Key design features: None	Drug (established name): Rezafungin 400 mg dose IV Week 1, followed by 200 mg once weekly for a total of 2-4 doses. Caspofungin 70 mg loading dose IV day 1, followed by 50 mg IV once daily, with option to continue for 28 days.[d] Number treated: 98 Rezafungin, 98 Caspofungin Duration: 28 days (Days 1-14 required; Days 15-28 optional for subjects with IC)	Primary: ACM at Day 30 (2 days) Secondary[e]: Global response at Day 14 for the EMA Mycological response Investigators' assessment of clinical response Radiological response	Planned: 218 Actual: 199	Centers: 66 Countries: 17

Source: Clinical Study Report and adsl.xpt.

[a] Under Protocol Amendment 5, subjects were enrolled into Part B and were randomized to rezafungin 400 mg every week or caspofungin (Reza group 1). After a complete review of unblinded Part A data, Amendment 6 defined Part B treatment as rezafungin 400 mg loading/200 mg weekly (Reza group 2) or caspofungin. Subjects enrolled under Amendment 5 continued receiving their originally assigned study drug regardless of subsequent approval of Amendment 6.

[b] Oral step-down: oral placebo (saline; rezafungin groups) or oral fluconazole of 800 mg on the first day, followed by 400 mg/day thereafter.

[c] Overall response at Day 5, Day 28 (±2) and follow-up, mycological response at Day 5, Day 14 (±1), Day 28 (±2), and follow-up, investigator's assessment of clinical response at Day 14 (±1), Day 28 (±2), and the follow-up visit.

[d] After ≥3 days (or the minimum duration of IV therapy advised by the site's national/regional/local guidelines, whichever is greater) of caspofungin treatment, subjects who meet the stepdown therapy eligibility criteria could be switched to oral fluconazole at a dose of 6 mg/kg administered once daily (rounded to the nearest 200 mg increment) with a maximum daily dose of 800 mg (e.g., a subject weighing 73 kg would receive fluconazole 400 mg dose (two capsules of 200 mg each) based on a 6 mg/kg target dose (73 kg × 6 mg/kg=438 mg).

[e] Global cure (based on clinical cure as assessed by the investigator, radiological cure for qualifying invasive candidiasis subjects], and mycological eradication), confirmed by an independent DRC, at Day 14 (±1 day).

Abbreviations: ACM, all-cause mortality; Caspo, caspofungin; DRC, Data Review Committee; EMA, European Medicines Agency; IC, invasive candidiasis; IV, intravenous; Reza, rezafungin

6.2 Additional Details of Efficacy Analyses

6.2.1 Phase 3 Study

6.2.1.1 Analysis Populations

Two of the efficacy-related analysis populations were as follows:

- The ITT population included all randomized subjects.
- The mITT population included all subjects 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 at least one dose of study drug.

6.2.1.2 Secondary Efficacy Endpoint Definitions

Table 26. Global Response Definitions

	Definition		
Global Response	**Mycological Response**	**Clinical Response as Assessed by the Investigator**	**Radiological Response[b]**
Cure	Eradication/presumed eradication[a]	Cure	Cure
Failure	Eradication/presumed eradication[a]	Cure	Failure
	Eradication/presumed eradication[a]	Failure	Cure, failure, or indeterminate
	Eradication/presumed eradication[a]	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[a]	Cure	Indeterminate
	Eradication/presumed eradication[a]	Indeterminate	Cure or indeterminate
	Indeterminate	Cure	Cure or indeterminate
	Indeterminate	Indeterminate	Cure or indeterminate

Source: Table 8 of the Clinical Study Report.
[a] Presumed eradication is defined only for a culture from a normally sterile site and is not defined for a blood culture.
[b] For those subjects with invasive candidiasis documented by radiologic/imaging evidence at baseline.

Table 27. Mycological Response Definitions

Mycological Response	Definition
Eradication[a]	If positive blood culture at baseline: 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): *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 *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 subject 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 subject 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 subject was 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 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: *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 *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 subject 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 subject required a change of antifungal therapy to treat candidemia and/or invasive candidiasis, OR The subject 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 postbaseline 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. Subject was lost to follow-up on the day of assessment.

Source: Table 9 of the Clinical Study Report.

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

Table 28. Investigator's Assessment of Clinical Response Definitions

Clinical Response	Definition
Cure	Resolution of attributable systemic signs and symptoms of candidemia and/or invasive candidiasis that were present at baseline, AND No new systemic signs or symptoms attributable to candidemia and/or invasive candidiasis, AND No new systemic antifungal therapy to treat candidemia and/or invasive candidiasis, AND The subject was alive.
Failure	Progression or recurrence of attributable systemic signs or symptoms of candidemia and/or invasive candidiasis, OR Lack of resolution of attributable systemic signs or symptoms of candidemia and/or invasive candidiasis, OR Requirement for new systemic antifungal or prolonged therapy to treat candidemia and/or invasive candidiasis[a], OR An AE required discontinuation of study drug therapy (IV and IV/oral) on or prior to the day of assessment, OR The subject died of any cause.
Indeterminate	Study data were not available for the evaluation of efficacy for any reason including: Lost to follow-up, Withdrawal of consent, Extenuating circumstances that precluded the classification of clinical outcome of candidemia and/or invasive candidiasis.

Source: Table 10 of the Clinical Study Report.
[a] Prolonged antifungal therapy was defined as therapy for candidemia and/or invasive candidiasis extending beyond the allowable 28 days of study drug. The determination of prolonged therapy only applied to the follow-up visit clinical response assessment.
Abbreviations: AE, adverse event; IV, intravenous

Table 29. Radiological Response Definitions

Radiological Response	Definition[a]
Cure	Improvement or resolution of radiological or other imaging findings of invasive candidiasis that were present at baseline (i.e., the radiograph/imaging study that documented evidence of the invasive candidiasis) AND No new radiological or other imaging findings attributable to invasive candidiasis, AND The subject was alive.
Failure	Progression of or new radiological or other imaging findings of invasive candidiasis, OR Lack of improvement of radiological or other imaging findings of invasive candidiasis, OR The subject died of any cause.

Radiological Response	Definition[a]
Indeterminate	Radiological or imaging data are not available for the evaluation of efficacy for any reason including: Lost to follow-up, Withdrawal of consent, Radiology/imaging not completed Extenuating circumstances that precluded the classification of a radiological outcome of invasive candidiasis

Source: Table 11 of the Clinical Study Report.
Includes radiological or other imaging studies. Only for invasive candidiasis subjects with imaging performed at baseline who had radiological or other imaging studies that documented evidence of invasive candidiasis.

6.2.1.3 Baseline Demographics and Clinical Characteristics

Table 30. Baseline Demographics, ITT Population, Phase 3 Study

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
Sex, n (%)			
Female	33 (33.0)	43 (43.4)	76 (38.2)
Male	67 (67.0)	56 (56.6)	123 (61.8)
Age, years			
Mean (SD)	59.5 (15.80)	62.0 (14.57)	60.7 (15.22)
Median	59.0	62.0	61.0
IQR	48.5, 71.0	53.0, 73.0	50.0, 72.0
Minimum, maximum	19.0, 89.0	20.0, 91.0	19.0, 91.0
Age category, n (%)			
<65 years	60 (60.0)	58 (58.6)	118 (59.3)
≥65 years	40 (40.0)	41 (41.4)	81 (40.7)
Race, n (%)			
American Indian or Alaska Native	1 (1.0)	1 (1.0)	2 (1.0)
Asian	27 (27.0)	31 (31.3)	58 (29.1)
Black or African American	5 (5.0)	4 (4.0)	9 (4.5)
Other	1 (1.0)	2 (2.0)	3 (1.5)
White	61 (61.0)	60 (60.6)	121 (60.8)
Not reported	5 (5.0)	1 (1.0)	6 (3.0)
Weight at baseline, kg			
Mean (SD)	73.5 (23.25)	69.8 (22.60)	71.7 (22.95)
Median	68.0	66.2	67.9
IQR	55.0, 84.0	56.0, 80.0	56.0, 82.0
Minimum, maximum	37.2, 149.9	33.0, 153.6	33.0, 153.6
Missing	5	8	13
Height at baseline (cm)			
Mean (SD)	169.5 (9.98)	167.3 (11.40)	168.4 (10.73)
Median	170.0	168.0	168.0
IQR	160.0, 177.0	160.0, 176.0	160.0, 176.8
Minimum, maximum	137.0, 190.0	115.0, 192.0	115.0, 192.0
Missing	6	9	15
BMI, kg/m^2			
Mean (SD)	25.4 (7.04)	24.5 (6.46)	25.0 (6.76)
Median	23.6	24.1	24.0
IQR	20.8, 28.4	20.7, 26.7	20.8, 27.7
Minimum, maximum	13.7, 51.9	12.9, 47.6	12.9, 51.9
Missing	6	11	17

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
Child-bearing potential, n (%)			
No	21 (21.0)	36 (36.4)	57 (28.6)
Yes	12 (12.0)	7 (7.1)	19 (9.5)
Missing (male subjects)	67 (67.0)	56 (56.6)	123 (61.8)
Country, n (%)			
Australia	8 (8.0)	5 (5.1)	13 (6.5)
Belgium	5 (5.0)	7 (7.1)	12 (6.0)
Bulgaria	6 (6.0)	4 (4.0)	10 (5.0)
China	6 (6.0)	5 (5.1)	11 (5.5)
Colombia	1 (1.0)	0	1 (<1)
Spain	12 (12.0)	12 (12.1)	24 (12.1)
France	5 (5.0)	1 (1.0)	6 (3.0)
Greece	6 (6.0)	11 (11.1)	17 (8.5)
Israel	3 (3.0)	2 (2.0)	5 (2.5)
Italy	2 (2.0)	3 (3.0)	5 (2.5)
South Korea	6 (6.0)	6 (6.1)	12 (6.0)
Singapore	3 (3.0)	0	3 (1.5)
Thailand	8 (8.0)	17 (17.2)	25 (12.6)
Taiwan	3 (3.0)	1 (1.0)	4 (2.0)
United States	26 (26.0)	25 (25.3)	51 (25.6)
Geographic region, n (%)			
Asia-Pacific (excluding China/Taiwan)	25 (25.0)	28 (28.3)	53 (26.6)
China/Taiwan	9 (9.0)	6 (6.1)	15 (7.5)
Europe/Israel/Turkey	39 (39.0)	40 (40.4)	79 (39.7)
South America	1 (1.0)	0	1 (<1)
North America	26 (26.0)	25 (25.3)	51 (25.6)

Source: Statistical Reviewer's analysis; adsl.xpt.
Abbreviations: IQR, interquartile range; ITT, intent-to-treat; SD, standard deviation

Baseline clinical characteristics are summarized in Table 31. Most subjects had a final diagnosis of candidemia only (69.3%). The two treatment arms were similar in these clinical characteristics.

Table 31. Baseline Clinical Characteristics, ITT Population, Phase 3 Study

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
Diagnosis at randomization, n (%)			
Candidemia only	73 (73.0)	68 (68.7)	141 (70.9)
Invasive candidiasis	27 (27.0)	31 (31.3)	58 (29.1)
Final diagnosis, n (%)[a]			
Candidemia only	70 (70.0)	68 (68.7)	138 (69.3)
Invasive candidiasis	30 (30.0)	31 (31.3)	61 (30.7)
Diagnosis methodology, n (%)[b]			
Blood culture	70 (70.0)	69 (69.7)	139 (69.8)
Gram stain	30 (30.0)	31 (31.3)	61 (30.7)
Tissue culture	29 (29.0)	31 (31.3)	60 (30.2)
Missing	5 (5.0)	4 (4.0)	9 (4.5)

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
APACHE II Score			
Mean (SD)	12.5 (8.01)	13.1 (7.11)	12.8 (7.56)
Median	12.0	12.0	12.0
IQR	7.0, 16.0	7.0, 19.0	7.0, 18.0
Minimum, maximum	0.0, 40.0	0.0, 37.0	0.0, 40.0
Missing	1	0	1
APACHE II Score group 1, n (%)			
<20	84 (84.0)	81 (81.8)	165 (82.9)
≥20	15 (15.0)	18 (18.2)	33 (16.6)
Missing	1 (1.0)	0	1 (<1)
APACHE II Score group 2, n (%)			
10-19	43 (43.0)	44 (44.4)	87 (43.7)
<10	41 (41.0)	37 (37.4)	78 (39.2)
≥20	15 (15.0)	18 (18.2)	33 (16.6)
Missing	1 (1.0)	0	1 (<1)
ANC at randomization (/µL)			
Mean (SD)	8082.0 (6754.49)	8692.7 (6289.79)	8390.5 (6514.34)
Median	7263.6	7300.0	7267.2
IQR	4130, 9900	4800, 11,100	4380, 10,915
Minimum, maximum	0, 41,174	0, 37,220	0, 41,174
Missing	3	0	3
ANC at randomization (µL) group, n (%)			
<500	9 (9.0)	6 (6.1)	15 (7.5)
≥500	88 (88.0)	93 (93.9)	181 (91.0)
Missing	3 (3.0)	0	3 (1.5)
APACHE II/ANC at randomization, n (%)			
APACHE II score ≥20 or ANC <500 cells/µL	22 (22.0)	21 (21.2)	43 (21.6)
APACHE II score <20 and ANC ≥500 cells/µL	75 (75.0)	78 (78.8)	153 (76.9)
Missing	3 (3.0)	0	3 (1.5)
Randomization strata, n (%)			
Candidemia only, APACHE II score <20 and ANC ≥500/µL	51 (51.0)	53 (53.5)	104 (52.3)
Candidemia only, APACHE II score ≥20 or ANC <500/µL	19 (19.0)	17 (17.2)	36 (18.1)
Invasive candidiasis, APACHE II score <20 and ANC ≥500/µL	25 (25.0)	24 (24.2)	49 (24.6)
Invasive candidiasis, APACHE II score ≥20 or ANC <500/µL	5 (5.0)	5 (5.1)	10 (5.0)
eCrCl at baseline (mL/min)			
Mean (SD)	93.7 (109.49)	81.8 (62.33)	88.0 (89.79)
Median	78.4	64.9	72.0
IQR	38.3, 112.5	40.9, 108.9	39.3, 110.5
Minimum, maximum	9.4, 949.6	0.4, 314.0	0.4, 949.6
Missing	6	11	17

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
Child-Pugh score Group 1, n (%)			
<7	5 (5.0)	5 (5.1)	10 (5.0)
7-9	14 (14.0)	15 (15.2)	29 (14.6)
>9	1 (1.0)	0	1 (<1)
Missing	80 (80.0)	79 (79.8)	159 (79.9)

Source: Table 20 of the Study Report and Statistics Reviewer's analysis; adsl.xpt.
[a] Final diagnosis of invasive candidiasis was determined based on the investigator's response of the tissue/fluid culture assessment and radiologic test CRF pages.
[b] Categories were not mutually exclusive.
Abbreviations: CRF, clinical report form; IQR, interquartile range; ITT, intent-to-treat; SD, standard deviation; ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation II; eCrCl, estimated creatinine clearance

Candida pathogens isolated from baseline blood and sterile site cultures in the mITT population are summarized in Table 32. The most common fungal pathogen was *C. albicans*, which was detected in 41.9% and 42.6% of subjects in the rezafungin and caspofungin treatment arms, respectively. The two treatment arms were comparable in terms of these *Candida* pathogens at baseline.

Table 32. Baseline *Candida* Pathogens From Blood and Sterile Site Cultures, mITT Population, Phase 3 Study

Fungal Pathogen, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Total N=187
Candida albicans	39 (41.9)	40 (42.6)	79 (42.2)
Candida dubliniensis	3 (3.2)	1 (1.1)	4 (2.1)
Candida glabrata	24 (25.8)	25 (26.6)	49 (26.2)
Candida guilliermondii	2 (2.2)	0	2 (1.1)
Candida krusei	2 (2.2)	2 (2.1)	4 (2.1)
Candida lusitaniae	1 (1.1)	1 (1.1)	2 (1.1)
Candida metapsilosis	1 (1.1)	0	1 (0.5)
Candida nivariensis	0	1 (1.1)	1 (0.5)
Candida parapsilosis	8 (8.6)	17 (18.1)	25 (13.4)
Candida tropicalis	20 (21.5)	17 (18.1)	37 (19.8)

Source: Table 31 of the Study Report and Reviewer's analysis.
Abbreviations: mITT, modified intent-to-treat; N, number of subjects; n, number of subjects in the category

6.2.1.4 FDA's Sensitivity Analyses

There were eight subjects (three and five in the rezafungin and caspofungin arms, respectively) who did not meet the inclusion criteria or who met the exclusion criteria but were included in the mITT population. If those eight subjects were excluded from the analysis of the primary efficacy endpoint of Day 30 ACM, the upper limit of the 95% CI met the NI margin of 20%. See Table 33.

There were 43 subjects (23 and 20 in the two treatment arms, respectively) who took systemic antifungal treatment for candidemia/IC in addition to the assigned study treatment. Twelve of these subjects (eight and four subjects in the two arms) died by Day 30. If all of the subjects who received non-study systemic antifungals were considered failures in the analysis of Day 30 ACM, the upper limit of the 95% CI was 15.5%, meeting a 20% NI margin.

If the primary endpoint is analyzed excluding the eight subjects not meeting the inclusion/exclusion criteria and considering concomitant antifungal users as deceased, the upper limit of the 95% CI was higher than 15%, but meets a 20% NI margin.

Table 33. FDA's Sensitivity Analysis of All-Cause Mortality at Day 30 (-2 Days), mITT Population, Phase 3 Study

Parameter	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
Excluding subjects who did not meet inclusion and exclusion criteria (IE)	22/90 (24.4)	18/89 (20.2)	4.3 (-8.0, 16.4)
Considering concomitant systemic antimycotics users as failures	37/93 (39.8)	36/94 (38.3)	1.5 (-12.5, 15.5)
Both excluding IE subjects and considering concomitant systemic antimycotics users as failures	36/90 (40.0)	33/89 (37.1)	2.9 (-11.3, 17.2)

Source: Statistical Reviewer's analysis.
Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; mITT, modified intent-to-treat

6.2.2 Phase 2 Study

6.2.2.1 Data Sets Analyzed

The data sets analyzed in the phase 2 study are listed in Table 34. Totals of 92 and 98 subjects in Part A and B were included in the mITT population.

Table 34. Data Sets Analyzed, Phase 2 Study

Parameter	Rezafungin 400/400 mg	Rezafungin 400/200 mg	Caspofungin	Total
Part A				
Randomized (ITT population)	35 (100.0)	36 (100.0)	36 (100.0)	107 (100.0)
Received ≥1 dose (safety population)	35 (100.0)	36 (100.0)	33 (91.7)	104 (97.2)
mITT	33 (94.3)	31 (86.1)	28 (77.8)	92 (86.0)
Reason for exclusion from the mITT population				
Did not have a blood culture within 96 hours of randomization	2 (5.7)	5 (13.9)	6 (16.7)	13 (12.1)
Did not have documented *Candida* infection	2 (5.7)	5 (13.9)	6 (16.7)	13 (12.1)
Did not receive ≥1 dose of study drug	0	0	3 (8.3)	3 (2.8)
Part B				
Randomized (ITT population)	46 (100.0)	21 (100.0)	33 (100.0)	100 (100.0)
Received ≥1 dose (safety population)	46 (100.0)	19 (90.5)	33 (100.0)	98 (98.0)
mITT	43 (93.5)	15 (71.4)	33 (100.0)	91 (91.0)
Reason for exclusion from mITT				
Did not have a blood culture within 96 hours of randomization	3 (6.5)	5 (23.8)	0	8 (8.0)
Did not have documented *Candida* infection	3 (6.5)	5 (23.8)	0	8 (8.0)
Did not receive ≥1 dose of study drug	0	2 (9.5)	0	2 (2.0)

Source: Table 9 of the Study Report and Statistics Reviewer's analysis.
Abbreviations: n, number of subjects in the specified category; ITT, intent to treat; mITT, modified intent-to-treat

6.2.2.2 Baseline Demographics and Clinical Characteristics

In the ITT population, 57% of the subjects were male. Baseline demographics were well-balanced among the three arms (Table 35).

Table 35. Baseline Demographics and Clinical Characteristics, ITT Population, Phase 2 Study

Parameter	Rezafungin 400/400 mg N=81	Rezafungin 400/200 mg N=57	Caspofungin N=69	Total N=207
Sex, n (%)				
Male	44 (54.3)	36 (63.2)	38 (55.1)	118 (57.0)
Female	37 (45.7)	21 (36.8)	31 (44.9)	89 (43.0)
Age, years				
Mean (SD)	59.4 (15.86)	60.0 (15.90)	59.4 (15.85)	59.6 (15.79)
Median	61	63	63	62
IQR	50, 69	49, 70	52, 70	49, 70
Minimum, maximum	24, 88	24, 91	24, 93	24, 93
Age category, n (%)				
<65 years	49 (60.5)	32 (56.1)	40 (58.0)	121 (58.5)
≥65 years	32 (39.5)	25 (43.9)	29 (42.0)	86 (41.5)
Race, n (%)				
Asian	0	1 (1.8)	3 (4.3)	4 (1.9)
Black or African American	8 (9.9)	7 (12.3)	4 (5.8)	19 (9.2)
Other	4 (4.9)	2 (3.5)	0	6 (2.9)
White	69 (85.2)	44 (77.2)	59 (85.5)	172 (83.1)
Missing	0	3 (5.3)	3 (4.3)	6 (2.9)
Ethnicity, n (%)				
Hispanic or Latino	8 (9.9)	9 (15.8)	7 (10.1)	24 (11.6)
Not Hispanic or Latino	73 (90.1)	46 (80.7)	59 (85.5)	178 (86.0)
Not reported	0	2 (3.5)	3 (4.3)	5 (2.4)
Weight at baseline, kg				
Mean (SD)	77.6 (23.57)	75.7 (23.78)	75.5 (17.73)	76.4 (21.80)
Median	77.2	71.0	73.7	74.6
IQR	62.7, 88.1	58.7, 89.0	67.0, 84.3	62.3, 88.8
Minimum, maximum	41.8, 218.7	34.0, 154.5	47.4, 150.0	34.0, 218.7
Missing	1	2	3	6
Height at baseline (cm)				
Mean (SD)	169.4 (9.42)	167.9 (10.47)	168.3 (8.03)	168.7 (9.27)
Median	170.0	170.0	169.5	170.0
IQR	162.3, 177.8	160.0, 176.0	162.0, 173.0	162.0, 175.0
Minimum, maximum	150.0, 190.0	145.0, 187.9	154.0, 188.0	145.0, 190.0
Missing	1	3	3	7
BMI, kg/m^2				
Mean (SD)	26.9 (7.17)	26.8 (8.57)	26.6 (5.63)	26.8 (7.09)
Median	25.8	25.5	26.4	25.9
IQR	22.9, 30.4	21.5, 30.7	22.7, 30.5	22.5, 30.6
Minimum, maximum	13.9, 69.2	14.7, 64.4	15.9, 44.8	13.9, 69.2
Missing	1	3	3	7
Subject child-bearing potential, n (%)				
No	29 (35.8)	19 (33.3)	24 (34.8)	72 (34.8)
Yes	8 (9.9)	2 (3.5)	7 (10.1)	17 (8.2)

Parameter	Rezafungin 400/400 mg N=81	Rezafungin 400/200 mg N=57	Caspofungin N=69	Total N=207
Country, n (%)				
Belgium	9 (11.1)	9 (15.8)	12 (17.4)	30 (14.5)
Bulgaria	4 (4.9)	1 (1.8)	2 (2.9)	7 (3.4)
Canada	1 (1.2)	1 (1.8)	3 (4.3)	5 (2.4)
Spain	22 (27.2)	15 (26.3)	13 (18.8)	50 (24.2)
Greece	6 (7.4)	6 (10.5)	8 (11.6)	20 (9.7)
Hungary	2 (2.5)	0	0	2 (1.0)
Italy	7 (8.6)	2 (3.5)	5 (7.2)	14 (6.8)
Romania	2 (2.5)	0	3 (4.3)	5 (2.4)
Russia	2 (2.5)	1 (1.8)	0	3 (1.4)
United States	26 (32.1)	22 (38.6)	23 (33.3)	71 (34.3)
Geographic region, n (%)				
Europe	54 (66.7)	34 (59.6)	43 (62.3)	131 (63.3)
North America	27 (33.3)	23 (40.4)	26 (37.7)	76 (36.7)
Diagnosis, n (%)				
Candidemia	62 (76.5)	46 (80.7)	56 (81.2)	164 (79.2)
Invasive candidiasis	19 (23.5)	11 (19.3)	13 (18.8)	43 (20.8)
APACHE II Score				
Mean (SD)	13.4 (7.13)	14.1 (6.72)	14.0 (7.39)	13.8 (7.07)
Median	12	14	13	12.0
IQR	9.0, 17	8.0, 20	9.0, 17.0	9.0, 17.0
Minimum, maximum	2.0, 31	2.0, 28	1.0, 35.0	1.0, 35.0
Missing	2	2	6	10
eCrCl at baseline (mL/min)				
Mean (SD)	111.1 (63.98)	84.7 (55.62)	105.1 (70.70)	102.2 (64.84)
Median	101.9	72.4	95.1	89.7
IQR	67.7, 151.5	43.4, 110.1	51.2, 138.3	54.4, 141.7
Minimum, maximum	7.1, 331.8	5.6, 252.5	8.6, 293.3	5.6, 331.8
Missing	2	6	5	13

Source: Statistics Reviewer's analysis.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; eCrCl, estimated creatine clearance; IQR, interquartile range; ITT, intent-to-treat population; SD, standard deviation

Fungal pathogens at baseline in the mITT population in the phase 2 study are listed in Table 36. The most common pathogens were *C. albicans, C. glabrata,* and *C. parapsilosis*. The proportion of subjects with *C. albicans* in the rezafungin 400/200 mg arm was numerically lower; and the proportion of subjects with *C. glabrata* in this arm was numerically higher (Table 36).

Table 36. Fungal Pathogens at Baseline, mITT Population, Phase 2 Study

Candida Species	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61	Total N=183
Candida albicans	38 (50.0)	19 (41.3)	34 (55.7)	91 (49.7)
Candida dubliniensis	4 (5.3)	0	1 (1.6)	5 (2.7)
Candida fermentati	0	0	1 (1.6)	1 (0.5)
Candida glabrata	13 (17.1)	14 (30.4)	10 (16.4)	37 (20.2)
Candida guilliermondii	2 (2.6)	0	0	2 (1.1)
Candida intermedia	0	0	1 (1.6)	1 (0.5)
Candida kefyr	0	0	1 (1.6)	1 (0.5)
Candida krusei	1 (1.3)	3 (6.5)	1 (1.6)	5 (2.7)
Candida metapsilosis	0	1 (2.2)	0	1 (0.5)
Candida parapsilosis	10 (13.2)	7 (15.2)	11 (18.0)	28 (15.3)
Candida rugosa	1 (1.3)	0	0	1 (0.5)
Candida tropicalis	9 (11.8)	7 (15.2)	6 (9.8)	22 (12)
Candida utilis	1 (1.3)	0	0	1 (0.5)

Source: Table 12 of the Study Report and Reviewer's analysis.
Subjects with more than one *Candida* species at baseline were counted for each species; thus, numbers may not sum to the totals.
Abbreviations: mITT, modified intent-to-treat; N, number of subjects in the mITT population

6.2.2.3 Additional Efficacy Results

Reasons for Failure or Indeterminate Overall Response at Day 14

The reasons for failure or indeterminate overall response at Day 14 are listed in Table 37. The main reason for failure was mycological failure. The reasons for indeterminate overall response were primarily due to inadequate mycological culture data or assessment of systemic signs.

Table 37. Reasons for Failure or Indeterminate Overall Response at Day 14, mITT Population, Phase 2 Study

Reason	Statistic	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61
Failure	n	20	8	17
Death	n (%)	7 (9.2)	2 (4.3)	4 (6.6)
Mycological failure	n (%)	12 (15.8)	6 (13.0)	13 (21.3)
Recurrence of attributable SS	n (%)	2 (2.6)	0	2 (3.3)
Fever	n/N1 (%)	1/39 (2.6)	0/18 (0.0)	1/31 (3.2)
Hypothermia	n/N1 (%)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)
Hypotension	n/N1 (%)	1/15 (6.7)	0/11 (0.0)	1/14 (7.1)
Tachycardia	n/N1 (%)	2/52 (3.8)	0/25 (0.0)	1/37 (2.7)
Tachypnea	n/N1 (%)	1/44 (2.3)	0/26 (0.0)	1/34 (2.9)
Indeterminate	n	10	3	3
Inadequate number of mycological cultures	n (%)	7 (9.2)	3 (6.5)	2 (3.3)
Assessment of SS not completed	n (%)	6 (7.9)	2 (4.3)	1 (1.6)
Attributable SS not reported at baseline	n (%)	1 (1.3)	0	0

Source: Table 23 and Statistics Reviewer's analysis.
Reasons for failure or indeterminate response are not mutually exclusive.
Mycological failure includes subjects with a change in antifungal therapy for the treatment of candidemia and/or IC.
Abbreviations: mITT, modified intent-to-treat; N, number of subjects in the mITT population; n, number of subjects in the specified category; N1, number of subjects with the specified sign at baseline; SS, systemic signs

Investigator Assessment of Clinical Response

Clinical response was not assessed at Day 5. At Day 14, the 400/200 mg rezafungin arm achieved the highest proportion of clinical cure in the investigator assessment of clinical response (Table 38).

Table 38. Investigator Assessment of Clinical Response at Day 14 and Follow-up, mITT Population, Phase 2 Study

Visit	Clinical Response	Statistic	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61
Day 14	Clinical cure	n (%)	53 (69.7)	37 (80.4)	43 (70.5)
		95% CI	58.1, 79.8	66.1, 90.6	57.4, 81.5
	Clinical failure/indeterminate	n (%)	23 (30.3)	9 (19.6)	18 (29.5)
	Clinical failure	n (%)	18 (23.7)	6 (13.0)	17 (27.9)
	Indeterminate	n (%)	5 (6.6)	3 (6.5)	1 (1.6)
Follow-up	Clinical cure	n (%)	42 (55.3)	32 (69.6)	38 (62.3)
		95% CI	43.4, 66.7	54.2, 82.3	49.0, 74.4
	Clinical failure/indeterminate	n (%)	34 (44.7)	14 (30.4)	23 (37.7)
	Clinical failure	n (%)	25 (32.9)	10 (21.7)	21 (34.4)
	Indeterminate	n (%)	9 (11.8)	4 (8.7)	2 (3.3)

Source: Table 30 of the Study Report and Statistics Reviewer's analysis.
Abbreviation: CI, confidence interval; mITT, modified intent-to-treat

The reasons for failure or an indeterminate investigator assessment of clinical response at Day 14 are listed in Table 39. The most common reasons for failure were death and requirement for new/prolonged therapy to treat the candidemia/IC.

Table 39. Reasons for Failure or Indeterminate Investigator Assessment of Clinical Response at Day 14, mITT Population, Phase 2 Study

Evaluation/Reason	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61
Failure	18 (23.7)	6 (13.0)	17 (27.9)
Progression or recurrence of attributable SS of candidemia/IC	1 (1.3)	0	2 (3.3)
Lack of resolution of attributable SS of candidemia/IC	5 (6.6)	0	8 (13.1)
Requirement for new/prolonged therapy to treat candidemia/IC	4 (5.3)	4 (8.7)	8 (13.1)
An AE requires discontinuation of study drug on or prior to the day of assessment	4 (5.3)	0	4 (6.6)
Subject died of any cause	7 (9.2)	2 (4.3)	3 (4.9)
Indeterminate	5 (6.6)	3 (6.5)	1 (1.6)
Lost to follow up	0	1 (2.2)	0
Assessment not completed (reason not specified)	3 (3.9)	1 (2.2)	0
Other	2 (2.6)	1 (2.2)	1 (1.6)

Source: Table 31 of the Study Report and Statistics Reviewer's analysis.
Abbreviations: AE, adverse event; IC, invasive candidiasis; mITT, modified intent-to-treat; SS, systemic signs or symptoms

Table 40 shows the results of subgroup analysis of Day 30 ACM by age, sex, and race. If it was unknown whether a subject was alive or deceased, the subject was considered deceased for this analysis. By age, there was a trend towards a better treatment effect in subjects ≥65 years old, but this effect (age-

treatment interaction) was not statistically significant according to the Breslow-Day test. The sample size was too small to reach reliable conclusions.

Table 40. Subgroup Analysis of All-Cause Mortality at Day 30 by Age, Sex, and Race, Phase 2 Study

Parameter	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61
Age (years)			
<65	11/45 (24.4)	3/27 (11.1)	2/36 (5.6)
≥65	7/31 (22.6)	1/19 (5.3)	8/25 (32.0)
Sex			
Male	9/42 (21.4)	2/28 (7.1)	6/34 (17.6)
Female	9/34 (26.5)	2/18 (11.1)	4/27 (14.8)
Race			
Asian	0	0/1 (0)	1/3 (33.3)
Black or African American	0/6 (0)	1/6 (16.7)	2/4 (50)
Other	1/4 (25)	1/2 (50)	2/6 (33.3)
White	17/66 (25.8)	2/36 (5.6)	7/51 (13.7)
Missing	0	0/1 (0)	0/3 (0)

Source: Statistics Reviewer's analysis of the adeff data from the Integrated Summary of Efficacy.

Overall, in this phase 2 study, the Day 30 ACM (including subjects with unknown survival status) was 8.7% in the 400/200 mg rezafungin arm, lower than in the caspofungin arm (16.4%), providing supportive information for the efficacy of rezafungin.

6.2.3 Phase 2 and Phase 3 Studies Pooled

Table 41 presents the Applicant's analysis results of ACM at Day 30 for the phase 2 and phase 3 studies as well as the 400/200 mg rezafungin and caspofungin groups pooled, as presented in the NDA submission. See the discussion in Section 3.1.3.1.

Table 41. All-Cause Mortality at Day 30, mITT Population, Phase 2, Phase 3, and Pooled Data

	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
Characteristic, n (%)	**Rezafungin 400/400 mg N=76**	**Rezafungin 400/200 mg N=46**	**Caspofungin N=61**	**Rezafungin 400/200 mg N=93**	**Caspofungin N=94**	**Rezafungin 400/200 mg N=139**	**Caspofungin N=155**
Deceased[a]	18 (23.7)	4 (8.7)	10 (16.4)	22 (23.7)	20 (21.3)	26 (18.7)	30 (19.4)
Known deceased	12 (15.8)	2 (4.3)	8 (13.1)	19 (20.4)	17 (18.1)	21 (15.1)	25 (16.1)
Unknown survival status	6 (7.9)	2 (4.3)	2 (3.3)	3 (3.2)	3 (3.2)	5 (3.6)	5 (3.2)
Alive	58 (76.3)	42 (91.3)	51 (83.6)	71 (76.3)	74 (78.7)	113 (81.3)	125 (80.6)
Difference in death rate (95% CI)[b,c,d]	-	-7.0 (-21.2, 7.3)		2.4 (-9.7, 14.4)		-1.5 (-10.7, 7.7)	

Source: Adapted from Table 8 of the Integrated Summary of Efficacy.
Subjects who died on or before Day 30, or with unknown survival status.
Phase 2 STRIVE: Two-sided 95% CI for the weighted (by part A and B) treatment difference estimate in death rates, rezafungin for injection minus caspofungin, was calculated using the stratified (by part A and B) methodology of Miettinen and Nurminen.
Phase 3 ReSTORE: 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.
Pooled: Two-sided 95% CI for the weighted (by study and parts A and B) treatment difference estimate in death rates, rezafungin for injection minus caspofungin, was calculated using the stratified (by study and part A and B) methodology of Miettinen and Nurminen.
Note: Percentages were calculated using the total number of subjects in each treatment group (N) as the denominator.
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; N, number of subjects; n, number of subjects in the category.

6.3 Additional Clinical Safety Analyses

6.3.1 Deaths

In the ISS pooled safety analysis, deaths occurred at similar rates in the rezafungin 400 mg/200 mg arm and caspofungin arm. There were 35 (35 of 151; 23.2%) deaths in the rezafungin arm and 40 deaths (40 of 166; 24.1%) in the caspofungin arm (Table 42). Septic shock, multiple organ dysfunction syndrome, and sepsis were the preferred terms most commonly associated with deaths; however, no deaths were considered related to study drug. The clinical reviewer examined the case narratives for all deaths occurring in the rezafungin arm of the ISS, as well as those occurring in the 400 mg/400 mg arm of the phase 2 study, and agrees that no deaths could be clearly attributed to study drug. Subjects presented with multiple comorbidities and were often coinfected with other pathogens, making attribution of cause of death extremely difficult. Moreover, in many cases, the deaths occurred after comfort measures/hospice had been initiated by the medical team.

Table 42. Deaths, Safety Population, ISS

	Pooled		
Preferred Term	**Reza (400/200 mg) N=151 n (%)**	**Caspo N=166 n (%)**	**Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)**
Any AE leading to death	35 (23.2)	40 (24.1)	-0.9 (-10.3, 8.4)
Multiple organ dysfunction syndrome	5 (3.3)	3 (1.8)	1.5 (-2.0, 5.0)
Cardiac arrest	3 (2.0)	1 (0.6)	1.4 (-1.1, 3.9)
Shock	2 (1.3)	0	1.3 (-0.5, 3.1)
Bronchopulmonary aspergillosis	1 (0.7)	0	0.7 (-0.6, 2.0)
Cardiopulmonary failure	1 (0.7)	0	0.7 (-0.6, 2.0)
Catheter bacteremia	1 (0.7)	0	0.7 (-0.6, 2.0)
Death	1 (0.7)	0	0.7 (-0.6, 2.0)
Death nos	1 (0.7)	0	0.7 (-0.6, 2.0)
Device related sepsis	1 (0.7)	0	0.7 (-0.6, 2.0)
Gastric cancer stage IV	1 (0.7)	0	0.7 (-0.6, 2.0)
Hypoxia	1 (0.7)	0	0.7 (-0.6, 2.0)
Lymphoma	1 (0.7)	0	0.7 (-0.6, 2.0)
Myocarditis	1 (0.7)	0	0.7 (-0.6, 2.0)
Neurodegenerative disorder	1 (0.7)	0	0.7 (-0.6, 2.0)
Pneumonia	1 (0.7)	0	0.7 (-0.6, 2.0)
Pneumonia aspiration	1 (0.7)	0	0.7 (-0.6, 2.0)
Pneumonia pseudomonal	1 (0.7)	0	0.7 (-0.6, 2.0)
Squamous cell carcinoma of the tongue	1 (0.7)	0	0.7 (-0.6, 2.0)
Sepsis	3 (2.0)	3 (1.8)	0.2 (-2.8, 3.2)
Acute respiratory distress syndrome	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Acute respiratory failure	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Candida sepsis	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Cardio-respiratory arrest	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Malignant neoplasm progression	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Neoplasm malignant	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Ventricular tachycardia	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Acinetobacter sepsis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Aspiration	0	1 (0.6)	-0.6 (-1.8, 0.6)

Preferred Term	Pooled Reza (400/200 mg) N=151 n (%)	Pooled Caspo N=166 n (%)	Pooled Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
Bacterial sepsis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Bronchitis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Cardiac failure	0	1 (0.6)	-0.6 (-1.8, 0.6)
COVID-19	0	1 (0.6)	-0.6 (-1.8, 0.6)
Endocarditis candida	0	1 (0.6)	-0.6 (-1.8, 0.6)
Intestinal ischemia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Intra-abdominal hemorrhage	0	1 (0.6)	-0.6 (-1.8, 0.6)
Klebsiella sepsis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Metastases to central nervous system	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pleural effusion	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pneumonia *Klebsiella*	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pneumonia lipoid	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pneumothorax	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pulmonary sepsis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Septic shock	8 (5.3)	10 (6.0)	-0.7 (-5.8, 4.4)
Respiratory failure	1 (0.7)	3 (1.8)	-1.1 (-3.5, 1.3)
COVID-19 pneumonia	0	2 (1.2)	-1.2 (-2.9, 0.5)

Source: adae.xpt; software: R.
Treatment-emergent AEs are defined as AEs that occurred during or after study drug administration through the follow-up visit.
Risk difference (with 95% CI) is shown between total treatment and comparator. Table sorted by risk difference.
Abbreviations: AE, adverse event; Caspo, caspofungin; CI, confidence interval; COVID-19, coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event; Reza, rezafungin

6.3.2 Serious Adverse Events

Given the treatment indication and underlying severe illness in the study population, SAEs were common in the phase 2 and 3 studies. In the rezafungin 400 mg/200 mg treatment arm and caspofungin arm of the ISS, 83 subjects (83 of 151; 55%) and 81 subjects (81 of 166; 48.8%), respectively, had SAEs. The most frequently reported SAEs in the rezafungin treatment (400 mg/200 mg) arm were septic shock, multiple organ dysfunction syndrome, sepsis, pneumonia, and bacteremia (Table 43).

Table 43. Subjects With SAEs by SOC and Preferred Term, Safety Population, ISS

System Organ Class Preferred Term	Pooled Reza (400/200 mg) N=151 n (%)	Pooled Caspo N=166 n (%)	Pooled Reza (400/200 mg) vs. Pooled Caspo Risk Difference (%) (95% CI)
Any SAE	83 (55.0)	81 (48.8)	6.2 (-4.8, 17.2)
Blood and lymphatic system disorders (SOC)	2 (1.3)	2 (1.2)	0.1 (-2.3, 2.6)
Disseminated intravascular coagulation	1 (0.7)	0	0.7 (-0.6, 2.0)
Iron deficiency anemia	1 (0.7)	0	0.7 (-0.6, 2.0)
Blood loss anemia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Splenic hemorrhage	0	1 (0.6)	-0.6 (-1.8, 0.6)

System Organ Class Preferred Term	Pooled Pooled Reza (400/200 mg) N=151 n (%)	Pooled Pooled Caspo N=166 n (%)	Pooled Pooled Reza (400/200 mg) vs. Pooled Caspo Risk Difference (%) (95% CI)
Cardiac disorders (SOC)	11 (7.3)	8 (4.8)	2.5 (-2.8, 7.7)
Cardiac arrest	3 (2.0)	1 (0.6)	1.4 (-1.1, 3.9)
Atrioventricular block first degree	1 (0.7)	0	0.7 (-0.6, 2.0)
Bradycardia	1 (0.7)	0	0.7 (-0.6, 2.0)
Cardiac failure congestive	1 (0.7)	0	0.7 (-0.6, 2.0)
Cardiopulmonary failure	1 (0.7)	0	0.7 (-0.6, 2.0)
Left ventricular dysfunction	1 (0.7)	0	0.7 (-0.6, 2.0)
Myocarditis	1 (0.7)	0	0.7 (-0.6, 2.0)
Cardiac failure	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Cardio-respiratory arrest	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Ventricular tachycardia	1 (0.7)	2 (1.2)	-0.5 (-2.6, 1.6)
Atrial fibrillation	0	1 (0.6)	-0.6 (-1.8, 0.6)
Right ventricular failure	0	1 (0.6)	-0.6 (-1.8, 0.6)
Supraventricular tachycardia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Death nos (SOC)	1 (0.7)	0	0.7 (-0.6, 2.0)
Death nos	1 (0.7)	0	0.7 (-0.6, 2.0)
Gastrointestinal disorders (SOC)	10 (6.6)	13 (7.8)	-1.2 (-6.9, 4.5)
Gastrointestinal hemorrhage	2 (1.3)	0	1.3 (-0.5, 3.1)
Upper gastrointestinal hemorrhage	2 (1.3)	0	1.3 (-0.5, 3.1)
Abdominal pain lower	1 (0.7)	0	0.7 (-0.6, 2.0)
Colonic fistula	1 (0.7)	0	0.7 (-0.6, 2.0)
Dysphagia	1 (0.7)	0	0.7 (-0.6, 2.0)
Gastric ulcer hemorrhage	1 (0.7)	0	0.7 (-0.6, 2.0)
Hemoperitoneum	1 (0.7)	0	0.7 (-0.6, 2.0)
Abdominal pain	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Intestinal obstruction	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Colitis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Diarrhea	0	1 (0.6)	-0.6 (-1.8, 0.6)
Diverticulum	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hematochezia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hemorrhagic ascites	0	1 (0.6)	-0.6 (-1.8, 0.6)
Intestinal ischemia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Large intestine perforation	0	1 (0.6)	-0.6 (-1.8, 0.6)
Proctitis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Rectal hemorrhage	0	1 (0.6)	-0.6 (-1.8, 0.6)
Vomiting	0	1 (0.6)	-0.6 (-1.8, 0.6)
Intra-abdominal hemorrhage	0	2 (1.2)	-1.2 (-2.9, 0.5)
General disorders and administration site conditions (SOC)	8 (5.3)	7 (4.2)	1.1 (-3.6, 5.8)
Multiple organ dysfunction syndrome	5 (3.3)	4 (2.4)	0.9 (-2.8, 4.6)
Complication associated with device	1 (0.7)	0	0.7 (-0.6, 2.0)
Death	1 (0.7)	0	0.7 (-0.6, 2.0)
Fatigue	1 (0.7)	0	0.7 (-0.6, 2.0)
Asthenia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Generalized edema	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hernia	0	1 (0.6)	-0.6 (-1.8, 0.6)

System Organ Class Preferred Term	Pooled Pooled Reza (400/200 mg) N=151 n (%)	Pooled Pooled Caspo N=166 n (%)	Pooled Pooled Reza (400/200 mg) vs. Pooled Caspo Risk Difference (%) (95% CI)
Hepatobiliary disorders (SOC)	2 (1.3)	3 (1.8)	-0.5 (-3.2, 2.2)
Biloma	1 (0.7)	0	0.7 (-0.6, 2.0)
Hepatic hemorrhage	1 (0.7)	0	0.7 (-0.6, 2.0)
Hepatic infarction	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hypertransaminasemia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Liver injury	0	1 (0.6)	-0.6 (-1.8, 0.6)
Immune system disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Anaphylactic shock	0	1 (0.6)	-0.6 (-1.8, 0.6)
Infections and infestations (SOC)	35 (23.2)	40 (24.1)	-0.9 (-10.3, 8.4)
Bacteremia	4 (2.6)	2 (1.2)	1.4 (-1.6, 4.5)
Staphylococcal bacteremia	2 (1.3)	0	1.3 (-0.5, 3.1)
Pneumonia	4 (2.6)	3 (1.8)	0.8 (-2.4, 4.1)
Bronchopulmonary aspergillosis	1 (0.7)	0	0.7 (-0.6, 2.0)
Catheter bacteremia	1 (0.7)	0	0.7 (-0.6, 2.0)
Cellulitis	1 (0.7)	0	0.7 (-0.6, 2.0)
Cryptococcosis	1 (0.7)	0	0.7 (-0.6, 2.0)
Device-related sepsis	1 (0.7)	0	0.7 (-0.6, 2.0)
Endocarditis	1 (0.7)	0	0.7 (-0.6, 2.0)
Escherichia bacteremia	1 (0.7)	0	0.7 (-0.6, 2.0)
Fusarium infection	1 (0.7)	0	0.7 (-0.6, 2.0)
Peritonitis	1 (0.7)	0	0.7 (-0.6, 2.0)
Pneumonia pseudomonal	1 (0.7)	0	0.7 (-0.6, 2.0)
Systemic *Candida*	1 (0.7)	0	0.7 (-0.6, 2.0)
Urinary tract infection	1 (0.7)	0	0.7 (-0.6, 2.0)
Urosepsis	1 (0.7)	0	0.7 (-0.6, 2.0)
Candida sepsis	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Septic pulmonary embolism	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Septic shock	9 (6.0)	10 (6.0)	-0.1 (-5.3, 5.2)
Abdominal abscess	2 (1.3)	3 (1.8)	-0.5 (-3.2, 2.2)
Abdominal infection	0	1 (0.6)	-0.6 (-1.8, 0.6)
Acinetobacter sepsis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Bronchitis	0	1 (0.6)	-0.6 (-1.8, 0.6)
COVID-19	0	1 (0.6)	-0.6 (-1.8, 0.6)
Diverticulitis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Endocarditis *Candida*	0	1 (0.6)	-0.6 (-1.8, 0.6)
Enterococcal sepsis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Meningitis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pneumonia *Klebsiella*	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pseudomonal sepsis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pulmonary sepsis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pyelonephritis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Vascular device infection	0	1 (0.6)	-0.6 (-1.8, 0.6)
Sepsis	4 (2.6)	6 (3.6)	-1.0 (-4.8, 2.9)
Bacterial sepsis	0	2 (1.2)	-1.2 (-2.9, 0.5)
COVID-19 pneumonia	0	2 (1.2)	-1.2 (-2.9, 0.5)
Klebsiella sepsis	0	3 (1.8)	-1.8 (-3.8, 0.2)

System Organ Class Preferred Term	Pooled Pooled Reza (400/200 mg) N=151 n (%)	Pooled Pooled Caspo N=166 n (%)	Pooled Pooled Reza (400/200 mg) vs. Pooled Caspo Risk Difference (%) (95% CI)
Injury, poisoning and procedural complications (SOC)	5 (3.3)	3 (1.8)	1.5 (-2.0, 5.0)
Abdominal wound dehiscence	1 (0.7)	0	0.7 (-0.6, 2.0)
Fall	1 (0.7)	0	0.7 (-0.6, 2.0)
Gastrointestinal anastomotic leak	1 (0.7)	0	0.7 (-0.6, 2.0)
Infusion-related reaction	1 (0.7)	0	0.7 (-0.6, 2.0)
Wound dehiscence	1 (0.7)	0	0.7 (-0.6, 2.0)
Drain site complication	0	1 (0.6)	-0.6 (-1.8, 0.6)
Gastrointestinal stoma complication	0	1 (0.6)	-0.6 (-1.8, 0.6)
Tracheal hemorrhage	0	1 (0.6)	-0.6 (-1.8, 0.6)
Investigations (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Weight decreased	0	1 (0.6)	-0.6 (-1.8, 0.6)
Metabolism and nutrition disorders (SOC)	2 (1.3)	5 (3.0)	-1.7 (-4.9, 1.5)
Alkalosis hypochloremic	1 (0.7)	0	0.7 (-0.6, 2.0)
Hypokalemia	1 (0.7)	0	0.7 (-0.6, 2.0)
Hyponatremia	1 (0.7)	0	0.7 (-0.6, 2.0)
Dehydration	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hyperglycemic hyperosmolar nonketotic syndrome	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hyperkalemia	0	3 (1.8)	-1.8 (-3.8, 0.2)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hematoma muscle	0	1 (0.6)	-0.6 (-1.8, 0.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (SOC)	7 (4.6)	4 (2.4)	2.2 (-1.9, 6.3)
Gastric cancer stage IV	1 (0.7)	0	0.7 (-0.6, 2.0)
Lymphoma	1 (0.7)	0	0.7 (-0.6, 2.0)
Metastases to meninges	1 (0.7)	0	0.7 (-0.6, 2.0)
Post-transplant lymphoproliferative disorder	1 (0.7)	0	0.7 (-0.6, 2.0)
Squamous cell carcinoma of the tongue	1 (0.7)	0	0.7 (-0.6, 2.0)
Malignant neoplasm progression	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Neoplasm malignant	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Malignant pleural effusion	0	1 (0.6)	-0.6 (-1.8, 0.6)
Metastases to central nervous system	0	1 (0.6)	-0.6 (-1.8, 0.6)
Nervous system disorders (SOC)	5 (3.3)	2 (1.2)	2.1 (-1.2, 5.4)
Cerebral hemorrhage	1 (0.7)	0	0.7 (-0.6, 2.0)
Neurodegenerative disorder	1 (0.7)	0	0.7 (-0.6, 2.0)
Neurological symptom	1 (0.7)	0	0.7 (-0.6, 2.0)
Peroneal nerve palsy	1 (0.7)	0	0.7 (-0.6, 2.0)
Subarachnoid hemorrhage	1 (0.7)	0	0.7 (-0.6, 2.0)
Encephalopathy	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hypertensive encephalopathy	0	1 (0.6)	-0.6 (-1.8, 0.6)
Renal and urinary disorders (SOC)	4 (2.6)	4 (2.4)	0.2 (-3.2, 3.7)
Hydronephrosis	1 (0.7)	0	0.7 (-0.6, 2.0)
Renal failure	1 (0.7)	0	0.7 (-0.6, 2.0)
Acute kidney injury	2 (1.3)	3 (1.8)	-0.5 (-3.2, 2.2)
Hematuria	0	1 (0.6)	-0.6 (-1.8, 0.6)

System Organ Class Preferred Term	Pooled Pooled Reza (400/200 mg) N=151 n (%)	Pooled Pooled Caspo N=166 n (%)	Pooled Pooled Reza (400/200 mg) vs. Pooled Caspo Risk Difference (%) (95% CI)
Respiratory, thoracic and mediastinal disorders (SOC)	10 (6.6)	19 (11.4)	-4.8 (-11.1, 1.4)
Pneumonia aspiration	2 (1.3)	1 (0.6)	0.7 (-1.4, 2.9)
Acute pulmonary edema	1 (0.7)	0	0.7 (-0.6, 2.0)
Dyspnea	1 (0.7)	0	0.7 (-0.6, 2.0)
Hypoxia	1 (0.7)	0	0.7 (-0.6, 2.0)
Pulmonary embolism	1 (0.7)	0	0.7 (-0.6, 2.0)
Acute respiratory distress syndrome	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Apnea	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pneumonia lipoid	0	1 (0.6)	-0.6 (-1.8, 0.6)
Respiratory arrest	0	1 (0.6)	-0.6 (-1.8, 0.6)
Aspiration	1 (0.7)	3 (1.8)	-1.1 (-3.5, 1.3)
Pleural effusion	0	2 (1.2)	-1.2 (-2.9, 0.5)
Pneumothorax	0	2 (1.2)	-1.2 (-2.9, 0.5)
Acute respiratory failure	1 (0.7)	4 (2.4)	-1.7 (-4.4, 0.9)
Respiratory failure	1 (0.7)	5 (3.0)	-2.3 (-5.3, 0.6)
Skin and subcutaneous tissue disorders (SOC)	2 (1.3)	0	1.3 (-0.5, 3.1)
Henoch-Schonlein purpura	1 (0.7)	0	0.7 (-0.6, 2.0)
Red man syndrome	1 (0.7)	0	0.7 (-0.6, 2.0)
Urticaria	1 (0.7)	0	0.7 (-0.6, 2.0)
Vascular disorders (SOC)	7 (4.6)	1 (0.6)	4.0 (0.5, 7.6) *
Shock	2 (1.3)	0	1.3 (-0.5, 3.1)
Arterial hemorrhage	1 (0.7)	0	0.7 (-0.6, 2.0)
Circulatory collapse	1 (0.7)	0	0.7 (-0.6, 2.0)
Hypotension	1 (0.7)	0	0.7 (-0.6, 2.0)
Hypovolemic shock	1 (0.7)	0	0.7 (-0.6, 2.0)
Deep vein thrombosis	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)

Source: adae.xpt; software: R.
Risk difference (with 95% CI) is shown between total treatment and comparator.
Abbreviations: Caspo, caspofungin; COVID-19, coronavirus disease 2019; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of subjects in treatment arm; n, number of subjects with adverse event; Reza, rezafungin; SAE, serious adverse event; SOC, system organ class

There were four potentially treatment-related SAEs reported in the rezafungin arm. There was one in the phase 2 arm in a subject receiving high-dose rezafungin (400/400 mg) and three in the 400/200 mg dose arm across the phase 2 and 3 studies:

- Infusion-related reaction (400 mg/200 mg rezafungin arm): A 64-year-old male was 30 minutes into the Day 3 study infusion (which was saline placebo on that day given the once weekly rezafungin dosing schedule) when he experienced scarlatiniform erythema of the trunk and face associated with hypotension and bronchospasm. The infusion was stopped and the infusion-related reaction resolved without additional treatment. A tryptase assay was negative and no eyelid or lip swelling was observed.
- Urticaria (400 mg/200 mg rezafungin arm): A 57-year-old male was receiving the last study infusion (third weekly dose of rezafungin) when he developed a generalized urticarial rash. Study treatment was stopped and the rash fully resolved the same day without additional treatment. Notably, the subject had a hypersensitivity reaction to vancomycin 5 days prior.

- Atrioventricular block (400 mg/200 mg rezafungin arm): An 84-year-old male had a PR interval of 220 ms on a routine electrocardiogram 1 day after the third weekly rezafungin infusion. This resulted in a prolongation of the subject's hospitalization. An electrocardiogram 11 days later showed resolution of the atrioventricular block.
- Atrial flutter (400 mg/400 mg rezafungin arm): A 61-year-old female developed supraventricular tachycardia associated with hypotension 10 minutes after the start of Day 3 study infusion (which was saline placebo given the once weekly rezafungin dosing schedule). The infusion was immediately discontinued. An electrocardiogram showed a complex supraventricular tachycardia with possible atrial flutter with 2:1 conduction. Study treatment was discontinued and fluconazole started.

6.3.3 AEs Leading to Treatment Discontinuation

AEs leading to treatment discontinuation occurred evenly in the rezafungin and caspofungin treatment arms (14 [9.3%] and 15 [9.0%] subjects, respectively) in the ISS (Table 44). Infusion-related reaction is the only TEAE in the rezafungin arm that resulted in discontinuation in more than one subject.

Table 44. Subjects With AEs Leading to Treatment Discontinuation by SOC and Preferred Term, Safety Population, ISS

	Pooled		
System Organ Class Preferred Term	**Reza (400/200 mg) N=151 n (%)**	**Caspo N=166 n (%)**	**Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)**
Any AE leading to discontinuation	14 (9.3)	15 (9.0)	0.2 (-6.1, 6.6)
Cardiac disorders (SOC)	2 (1.3)	1 (0.6)	0.7 (-1.4, 2.9)
Cardiac arrest	1 (0.7)	0	0.7 (-0.6, 2.0)
Left ventricular dysfunction	1 (0.7)	0	0.7 (-0.6, 2.0)
Ventricular tachycardia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Gastrointestinal disorders (SOC)	1 (0.7)	2 (1.2)	-0.5 (-2.6, 1.6)
Abdominal pain	1 (0.7)	0	0.7 (-0.6, 2.0)
Diverticulum	0	1 (0.6)	-0.6 (-1.8, 0.6)
Intra-abdominal hemorrhage	0	1 (0.6)	-0.6 (-1.8, 0.6)
General disorders and administration site conditions (SOC)	1 (0.7)	0	0.7 (-0.6, 2.0)
Adverse drug reaction	1 (0.7)	0	0.7 (-0.6, 2.0)
Hepatobiliary disorders (SOC)	1 (0.7)	3 (1.8)	-1.1 (-3.5, 1.3)
Hyperbilirubinemia	1 (0.7)	0	0.7 (-0.6, 2.0)
Hepatocellular injury	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hypertransaminsemia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Liver injury	0	1 (0.6)	-0.6 (-1.8, 0.6)
Immune system disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Anaphylactic shock	0	1 (0.6)	-0.6 (-1.8, 0.6)

System Organ Class Preferred Term	Pooled Reza (400/200 mg) N=151 n (%)	Pooled Caspo N=166 n (%)	Pooled Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
Infections and infestations (SOC)	5 (3.3)	6 (3.6)	-0.3 (-4.3, 3.7)
Cryptococcosis	1 (0.7)	0	0.7 (-0.6, 2.0)
Endocarditis	1 (0.7)	0	0.7 (-0.6, 2.0)
Fusarium infection	1 (0.7)	0	0.7 (-0.6, 2.0)
Septic shock	1 (0.7)	0	0.7 (-0.6, 2.0)
Systemic *Candida*	1 (0.7)	0	0.7 (-0.6, 2.0)
Endocarditis *Candida*	0	1 (0.6)	-0.6 (-1.8, 0.6)
Pneumonia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Chorioretinitis	0	2 (1.2)	-1.2 (-2.9, 0.5)
Endophthalmitis	0	2 (1.2)	-1.2 (-2.9, 0.5)
Injury, poisoning and procedural complications (SOC)	2 (1.3)	0	1.3 (-0.5, 3.1)
Infusion-related reaction	2 (1.3)	0	1.3 (-0.5, 3.1)
Investigations (SOC)	2 (1.3)	0	1.3 (-0.5, 3.1)
Blood alkaline phosphatase increased	1 (0.7)	0	0.7 (-0.6, 2.0)
Hepatic enzyme increased	1 (0.7)	0	0.7 (-0.6, 2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.7)	0	0.7 (-0.6, 2.0)
Malignant neoplasm progression	1 (0.7)	0	0.7 (-0.6, 2.0)
Nervous system disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Headache	0	1 (0.6)	-0.6 (-1.8, 0.6)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Wheezing	1 (0.7)	0	0.7 (-0.6, 2.0)
Pleural effusion	0	1 (0.6)	-0.6 (-1.8, 0.6)
Skin and subcutaneous tissue disorders (SOC)	1 (0.7)	0	0.7 (-0.6, 2.0)
Urticaria	1 (0.7)	0	0.7 (-0.6, 2.0)

Source: adae.xpt; software: R.
Treatment-emergent AEs are defined as AEs that occurred during or after study drug administration and through the follow-up visit.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; Caspo, caspofungin; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients with adverse event; Reza, rezafungin; SOC, system organ class

6.3.4 Narratives From Rezafungin-Treated Patients With Tremor, ISS

Narratives of the four rezafungin-treated patients in the ISS who reported tremor after initiation of study treatment are provided below.

Phase 2 Study

- Subject (b) (6) : An 84-year-old white female in the 400 mg/200 mg rezafungin treatment arm received four weekly infusions of rezafungin for IC and candidemia (cleared by Day 2). Her 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.

— On Day 11 (3 days after the second rezafungin infusion), she developed mild rest and intention tremors in the upper extremities without paresthesia. Study drug was continued and the subject was discharged home 5 days later. At a follow-up visit >1 month later, the tremors had resolved completely without any specific therapy. There was no neurological consultation and no neurological tests were performed. The investigator and the Applicant's medical monitor considered the tremor to be related to study drug, given that the subject did not have a prior history of neurological disease and the AE started during the administration of the study drug.

— The FDA Clinical Reviewer agrees that the tremor was likely related to rezafungin therapy.

- Subject (b) (6) : A 67-year-old African-American male in the 400 mg/200 mg rezafungin arm received two weekly doses of rezafungin for candidemia. His medical history 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.

  — On Day 20 (12 days after the second rezafungin infusion), he developed left eye deviation, facial and left eyelid twitching, and mild tremors (shaking) of both upper extremities. The tremors resolved on the next day. The investigator and the Applicant's medical monitor considered the tremors to be unrelated to study drug.

  — The FDA Clinical Reviewer agrees with the Applicant's assessment given the subject's extensive neurologic comorbidities and the significant interval between study drug administration and start of the AE.

Phase 3 Study

- Subject (b) (6) : A 77-year-old white female in the 400 mg/200 mg rezafungin arm received two weekly rezafungin infusions for treatment of IC. Her past medical history included hypertension, GERD, hypothyroidism, bilateral lung nodules, and she was admitted for diverticulitis with perforation requiring surgical management. Concomitant medications included: amlodipine, gabapentin, levothyroxine, losartan, metronidazole, Senna plus (docusate sodium, sennoside A+B), and famotidine as well as a single dose of fluconazole given prior to starting to rezafungin.

  — On Day 21 (13 days after receiving the second rezafungin infusion), she developed mild tremors of both hands, which interfered with the application of eye makeup but not with drinking, eating, or writing. The tremor did not occur at rest and resolved 1 month later. The investigator assessed the tremor as possibly related to study drug but stated that concomitant hypokalemia was a possible alternate cause for the tremor since the hypokalemia had resolved at the same time the tremor was noted to have resolved. The Applicant's medical monitor concurred with the Investigator's assessment and considered the event possibly related to the study drug while also noting that hypokalemia, age, and concomitant levothyroxine and amlodipine usage could have been alternative etiologies. An expert neurologist review concluded that rezafungin was indirectly related to the development of tremor by possibly causing hypokalemia (e.g., rezafungin usage led to hypokalemia, which led to tremor). The neurologist noted that

spironolactone was used to address the hypokalemia and both hypokalemia and tremor appeared to resolve simultaneously.

  - The FDA Clinical Reviewer agrees that though a direct relationship between rezafungin administration and tremor development cannot be ruled out, there is a long duration between last study drug administration and tremor development and plausible alternative etiologies (including indirect toxicity) exist.

- Subject (b) (6): A 28-year-old Chinese female in the 400 mg/200 mg rezafungin arm received two weekly rezafungin infusions for treatment of candidemia. Her past medical history included recently diagnosed acute B-lymphoblastic leukemia, gestational diabetes mellitus, fistula-in-ano, constipation, whole-body numbness related to hypocalcemia, and a drug-induced liver injury related to chemotherapy.
  - Concomitant medications included dexamethasone sodium phosphate injection, sodium methylprednisolone succinate injection, ibuprofen tablet, imipenem and cilastatin injection, meropenem injection, xuebijing injection, cefoperazone sodium and sulbactam sodium injection, terbutaline sulfate Injection, budesonide suspension for inhalation, vidarabine monophosphate injection, recombinant human granulocyte macrophage stimulating factor injection, furosemide injection, injections of human immunoglobulin, potassium chloride tablets, calcium gluconate injection, and sodium glycerophosphate injection.
  - On Day 12 (4 days after her second rezafungin infusion), she was noted to have spontaneous mild tremor of the hands and feet. The tremor resolved 2 days later without specific treatment. The investigator considered the tremor to be not related to study drug but rather due to concomitant hypocalcemia. It should be noted the subject remained hypocalcemic on the day the tremors resolved, however she received calcium gluconate that same day and was not found to be hypocalcemic or have tremors at subsequent visits.
  - The FDA Clinical Reviewer finds that though a relationship between study drug and tremor development cannot be ruled out given the temporal relationship between study drug administration and the AE, alternative etiologies including electrolyte disturbances and concomitant medication use (such as terbutaline) could be alternative explanations.

6.3.5 Blinded Safety Data From Ongoing Clinical Studies

A Development Safety Update Report covering the period from July 11, 2021 to July 10, 2022 was submitted by the Applicant and included blinded safety data from ongoing clinical studies. Regarding the China study extension of the phase 3 candidemia/IC study, currently only seven subjects have been randomized. From these subjects, one SAE (gastric cancer) as well as one death (sudden cardiac arrest) were reported; no discontinuation from the study due to AEs was reported. The phase 3 ReSPECT prophylaxis study is ongoing and 166 subjects were randomized (an estimated 110 subjects to rezafungin). Ten deaths have been reported (four of which occurred after the last study visit) and eight subjects discontinued from the study due to AEs. Causes of death included respiratory distress/failure, intracranial hemorrhage, and progression of underlying malignancy. Causes of study discontinuation included respiratory distress, intracranial hemorrhage, and liver dysfunction. One SAE of polyneuropathy was reported in this study.

6.3.6 Safety Data From Expanded-Access Patients

There were eight patients with invasive fungal diseases and limited treatment options who received rezafungin under an Expanded Access Program in the United States and Europe because they were not eligible for any other rezafungin clinical study. The duration of treatment was 2 to 115 weeks (and in some cases is expected to be indefinite) and treatment was generally well-tolerated. No deaths or treatment-related tremors, ataxia, or neuropathy have been reported. Treatment indications included several *Candida* endocarditis cases, *Candida* infection of retained mediastinal hardware, adverse reaction to azoles, *Candida* prosthetic hip and knee infections, and failure of previous echinocandin therapy.

6.4 Additional Details of DDI Assessment

Table 45. DDI Comparisons: As Victim of PK Drug Interactions

Drug	Risk	Key Highlights
Fluconazole	No or low	Fluconazole is cleared primarily by renal excretion as unchanged drug, with only 11% as metabolites. The strong CYP-inducer rifampin has only limited effects on fluconazole exposure, decreasing its AUC by 23%.
Voriconazole	High	Voriconazole is extensively metabolized, primarily by CYP2C19, and to a lesser extent, CYP3A and CYP2C9. Voriconazole pharmacokinetics is substantially influenced by the CYP2C19 genotype, with PMs of CYP2C19 having on average 4-fold higher voriconazole exposure (AUC) than homozygous EMs. Potent CYP3A inhibition by ritonavir in subjects PM of CYP2C19 (representing a situation where both CYP2C19 and CYP3A activities are impaired) leads to a 9-fold increase in voriconazole AUC. Coadministration with strong CYP inducers such as rifampin, ritonavir or rifabutin, result in more than 5-fold AUC reduction (<20% of fluconazole AUC when administered alone).
Caspofungin	No or low	70 mg caspofungin once daily (rather than 70 mg on Day 1 and 50 mg daily thereafter) is recommended in USPI when administered concomitant hepatic CYP inducers. Caspofungin trough concentrations are reduced 30% when coadministered with rifampin compared to caspofungin alone. Noteworthy, the AUC is the same or increased when coadministered with rifampin compared to caspofungin alone. The AUC has been proposed as the PK driver of efficacy.
Micafungin	No or low	No micafungin dose modifications are recommended in the USPI. Micafungin is poorly metabolized by CYP enzymes and is not a substrate of P-gp transporter.
Anidulafungin	No or low	No anidulafungin dose modifications are recommended in the USPI. Coadministration of voriconazole or tacrolimus with anidulafungin did not significantly alter the PK of either drug. Cyclosporine minimally increased the steady-state AUC of anidulafungin by 22%. Rifampin (CYP inducer, OATP1B1/3 inhibitor) did not significantly alter the PK of anidulafungin.
Rezafungin	No or low	No dose adjustments are proposed by the Applicant. Rezafungin does not undergo extensive CYP metabolism and is not a substrate of drug transporting proteins. (See *Rezafungin as an object of PK drug interactions)*

Sources: Drug product-specific USPI, University-of-Washington (2022), and Reviewer's assessment.
Abbreviations: AUC, area under the concentration-time curve; CYP, cytochrome P450; EM, extensive metabolizer; OATP, organic anion transporter peptide; P-gp, P-glycoprotein; PK, pharmacokinetics; PM, poor metabolizer; USPI, United States Prescribing Information

Table 46. DDI Comparisons: As Perpetrator of PK Drug Interactions

Drug	Risk	Key Highlights
Fluconazole	High	There are DDI management and dose modification recommendations in the USPI. Moderate CYP3A inhibitor. Interactions have been described with midazolam, cyclosporine, cisapride, eletriptan, eplerenone, terfenadine, nifedipine, triazolam, rifabutin, oral contraceptives, and saquinavir. Moderate CYP2C9 inhibitor. Interactions have also been described with warfarin, tolbutamide, phenytoin, losartan, ibuprofen, flurbiprofen, and several oral hypoglycemics. Strong CYP2C19 inhibitor. Interaction described with omeprazole. Glucuronidation inhibitor. Fluconazole coadministration increases the AUC of zidovudine 1.74-fold.
Voriconazole	High	There are DDI management and dose modification recommendations in the USPI. Strong CYP3A inhibitor. Interactions have been described with Alfentanil, fentanyl, oxycodone, cyclosporine, and tacrolimus. Moderate CYP2C19 inhibitor. Interactions have been described with omeprazole, ibuprofen, and diclofenac. Weak CYP2C9 inhibitor. Interaction described with warfarin. Of note, coadministration with warfarin, increases maximum prothrombin 2-fold.
Caspofungin	No or low	No DDI management strategies are recommended in the USPI. Studies in vitro showed that caspofungin is not an inhibitor nor an inducer of CYP enzymes.
Micafungin	No or low	Patients receiving CYP3A substrate drugs in combination with micafungin should be monitored for adverse reactions associated with the CYP3A substrate drug and its dosage reduced if necessary. Weak inhibitor of CYP3A, increasing the AUC of the CYP3A substrates sirolimus, nifedipine, and itraconazole by 21%, 18%, and 22%, respectively.
Anidulafungin	No or low	No DDI management strategies are recommended in USPI. In vitro studies showed that anidulafungin is not an inhibitor of CYP enzymes. Anidulafungin did not alter the PK of voriconazole, cyclosporine, or tacrolimus.
Rezafungin	No or low	No DDI management strategies are proposed in the draft USPI. Weak OATP1B1/3 inhibitor, increasing the AUC of the OATP1B1/3 substrate drugs repaglinide and rosuvastatin.

Sources: Drug product-specific USPI, University-of-Washington (2022), and Reviewer's assessment.
Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively.
Abbreviations: AUC, area under the concentration-time curve; CYP, cytochrome P450; DDI, drug-drug interaction; OATP, organic anion transporter peptide; P-gp, P-glycoprotein; PK, pharmacokinetics; PM, poor metabolizer; USPI, United States Prescribing Information