CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217417Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217417
Priority or standard	Priority
Submit date(s)	7/22/2022
Received date(s)	7/22/2022
PDUFA goal date	3/22/2023
Division/office	Division of Anti-Infectives (DAI)
Review completion date	3/21/2023
Established/proper name	Rezafungin for injection
(Proposed) proprietary name	REZZAYO
Pharmacologic class	echinocandin
Applicant	Cidara Therapeutics
Dosage form(s)/formulation(s)	solid (b) (4) (cake or powder) for reconstitution in a single-dose glass vial
Dosing regimen	administered once weekly by intravenous (IV) infusion, with an initial 400 mg loading dose, followed by a 200-mg dose once weekly thereafter, up to a maximum total of 4 weekly doses
Applicant-proposed indication(s)/ population(s)	Treatment of candidemia and invasive candidiasis in patients 18 years of age or older
SNOMED CT code for proposed indication disease term(s)[1]	432261003 Candidemia (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	Initial 400 mg loading dose, followed by a 200-mg dose once weekly thereafter, up to a maximum total of 4 weekly doses
Approved indication(s)/ population(s) (if applicable)	Indicated in patients 18 years of age or older who have limited or no alternative options for the treatment of candidemia and invasive candidiasis
SNOMED CT code for approved indication disease term(s)[1]	432261003 Candidemia (disorder)

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ACM	all-cause mortality
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APACHE	Acute Physiology and Chronic Health Evaluation
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BP	breakpoint
CAF	caffeine
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CFU	colony forming unit
CL	clearance
CL_{cr}	creatinine clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CYP	cytochrome P450
CYS	cyclosporine
DAI	Division of Anti-Infectives
DDI	drug-drug interaction
DIG	digoxin
E-R	exposure-response
ECV	epidemiological cutoff value
EFA	efavirenz
*f*AUC	free-drug area under the plasma concentration-time curve
fC_{max}	free-drug maximum plasma concentration
FDA	Food and Drug Administration
FU	follow-up
HI	hepatic impairment
HV	healthy volunteers
IBR	ibrutinib
IC	invasive candidiasis
IC_{50}	half maximal inhibitory concentration
IND	investigational new drug
ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
LFT	liver function test
MET	metformin
MIC	minimum inhibitory concentration
MID	midazolam
mITT	modified intent-to-treat

MPPRC	medical policy and program review council
MYC	mycophenolate mofetil
NCV	nerve conduction velocity
NDA	new drug application
NHP	nonhuman primate
NS	non-susceptible
OPQ	Office of Pharmaceutical Quality
OSIS	Office of Study Integrity and Surveillance
P-gp	P-glycoprotein
PD	pharmacodynamic
PI	Prescribing Information
PIT	pitavastatin
PK	pharmacokinetic
PK-PD	pharmacokinetic-pharmacodynamic
PMC	postmarketing commitment
PO	by mouth
PPB	plasma protein binding
PTA	probability of target attainment
QIDP	Qualified Infectious Disease Product
REP	repaglinide
REZ	rezafungin
ROS	rosuvastatin
SAE	serious adverse event
STIC	susceptibility test interpretive criteria
TAC	tacrolimus
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Prescribing Information
VEN	venetoclax
VPC	visual predictive check

I. Executive Summary

1. Summary of Regulatory Action

NDA 271417 for rezafungin (REZ) for injection was submitted by Cidara Therapeutics, Inc., with the proposed indication of treatment of candidemia and invasive candidiasis (IC) in patients 18 years of age or older. The application was reviewed by the multidisciplinary review team. The review team has recommended approval, and I, the signatory for this application, concur with this recommendation.

Rezafungin is an echinocandin, an established class of antifungals that includes three FDA-approved drugs for the treatment of candidemia/IC. Rezafungin has a similar spectrum of antifungal activity to the FDA-approved echinocandins, but it is distinguished by a longer half-life supporting once-weekly dosing. The Applicant submitted a single, randomized comparator-controlled noninferiority (NI) study of rezafungin in patients with candidemia/IC that met the prespecified 20% NI margin for the primary endpoint of Day 30 all-cause mortality (ACM). Supportive evidence of effectiveness was provided by a phase 2 dose-ranging study evaluating a similar patient population. The integrated summary of safety (ISS) dataset for rezafungin consists of 151 patients 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. An additional 81 patients were exposed to a higher rezafungin dose (400 mg weekly) in the phase 2 study.

Overall, the safety findings observed with rezafungin were consistent with the currently FDA-approved echinocandins. Of note, a neurotoxicity safety signal (tremors and/or axonal degeneration) was identified in subchronic dosing studies of rezafungin in nonhuman primates and rats administered rezafungin for 3 to 6 months. A higher incidence of tremors (4 in the rezafungin arm versus 0 in the caspofungin comparator arm) was observed in the phase 2 and 3 clinical studies, though all episodes were reported as mild and reversible. Given the limited clinical data on the safety of longer duration rezafungin dosing, the labeling will note that the safety of rezafungin has not been established beyond 4 weekly doses. The identified risks will be further evaluated in an ongoing clinical study assessing a longer duration of rezafungin dosing and through routine postmarketing pharmacovigilance.

Under 21 CFR part 312 subpart E, FDA may exercise flexibility in applying statutory standards for drugs intended to treat life-threatening and severely debilitating diseases, while preserving appropriate guarantees for safety and effectiveness (May 2022). Rezafungin was developed under a flexible development program given the unmet needs for treatment of candidemia/IC, a serious infection that often impacts patients with multiple comorbidities and requires at least two weeks of systemic antifungal therapy. Because the flexible development program consisted of a single phase 3 NI study supported by a phase 2 dose-ranging study, there is a greater reliance on nonclinical studies of rezafungin and the known safety and efficacy profile of the echinocandin drug class to inform the benefit-risk assessment for use of rezafungin in the indicated population.

The overall benefit-risk profile is favorable to support a limited use indication in adult patients with candidemia/IC who have limited, or no alternative treatment options as described in the benefit-risk framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this interdisciplinary assessment document and the product quality review.

2. Benefit–Risk Assessment

2.1. Benefit–Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Candidemia/IC 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%.	Candidemia/IC are serious infections with substantial mortality risks.
Current treatment options	• Echinocandins, such as caspofungin, micafungin, and anidulafungin, are considered standard of care for treatment of candidemia/IC. All require daily IV dosing. • Alternative options include azole drugs and amphotericin B. Generally, an intravenous antifungal is given initially for 3 to 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 daily intravenous antifungal therapy for the full duration of treatment.	Echinocandins are first-line treatment for candidemia/IC. Patients often transition to oral azoles once clinically stable to complete at least 2 weeks of systemic antifungal treatment for candidemia/IC. Patients unable to take oral azoles require daily IV therapy to complete candidemia/IC treatment which may necessitate placement of central lines and present other challenges to completing treatment in outpatient settings.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• A phase 3, randomized, controlled, blinded study found that rezafungin dosed weekly 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 with point estimates similar to the phase 3 study.	Rezafungin dosed weekly was noninferior to a regimen of daily caspofungin with optional stepdown to oral azole therapy within the prespecified 20% noninferiority margin for a Day 30 all-cause mortality endpoint. Rezafungin has demonstrated substantial evidence of effectiveness to support approval of an indication for treatment of candidemia/IC in patients with limited or no alternative treatment options. Patients unable to be transitioned to oral azole stepdown therapy and those with contraindications to central line placement to complete therapy for candidemia/IC may be most likely to benefit from rezafungin.
Risk 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 and a phase 1 study. • A neurotoxicity signal, including tremors and axonal degeneration, was identified in nonclinical studies of subchronic rezafungin dosing in nonhuman primates at doses ≥6-fold the clinical dose based on AUC comparisons. Neurotoxicity, including axonal/nerve fiber degeneration was also observed in rats dose weekly for 26 weeks at 2 to 4 fold the clinical dose based on AUC comparisons. • In clinical studies of rezafungin administered up to a maximum total of 4 weekly doses, tremor was observed at a higher incidence in the rezafungin arm than the comparator arm, but all cases were mild and reversible.	A neurotoxicity safety signal was identified in subchronic dosing studies of rezafungin in nonhuman primates and rats. When rezafungin was administered as a 400 mg loading dose followed by 200 mg weekly, up to a maximum total of 4 weekly doses in clinical studies, the safety profile was similar to the FDA-approved echinocandins. Given the limited clinical data on the safety of longer duration rezafungin dosing, the labeling will note that the safety of rezafungin has not been established beyond 4 weekly doses The identified risks will be further evaluated in an ongoing clinical study assessing a longer duration of rezafungin dosing and through routine postmarketing pharmacovigilance.

Abbreviations: AUC, area under the concentration-time curve; IC, invasive candidiasis; IV, intravenous

2.2. Conclusions Regarding Benefit-Risk

In NDA 217417 for rezafungin for injection, the Applicant is seeking an indication for treatment of candidemia/IC in adult patients. Rezafungin is a member of the echinocandin class of antifungals that has an extended half-life supporting once-weekly intravenous (IV) dosing.

Candidemia/IC are serious infections caused by the invasion of *Candida* spp. into the blood and/or deep tissues. Treatment requires systemic antifungal therapy for a least 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. Echinocandins are first-line initial therapy for candidemia/IC except for infections of the central nervous system, eye, or urinary tract. The three FDA-approved echinocandins require daily IV dosing. In clinical practice, most patients are transitioned to oral antifungal therapy once clinically stable. However, the only available oral therapies for candidemia/IC belong to the azole class of antifungals. 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 *Candida* spp. or are intolerant of azole therapy.

This 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 a total duration of therapy of up to 4 weeks. The primary endpoint was Day 30 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 population, a treatment difference of 2.4% (95% CI -9.7%, 14.4%). Supportive evidence of effectiveness is provided by a phase 2 dose-ranging study in a similar population.

A neurotoxicity safety signal was identified in subchronic rezafungin dosing studies in nonhuman primates and rats. Although 4-week studies of rezafungin in nonhuman primates did not show clear evidence of neurotoxicity, a 13-week dosing study with rezafungin showed neurotoxic effects (tremors, cytoplasmic inclusions in Schwann cells, hypercellularity in Schwann cells, thin myelin, and nerve fiber degeneration (affecting axons and/or myelin) at doses of ≥30 mg/kg dosed every 3 days for 3 months at 9-fold to 15-fold the expected clinical exposure (based on area under the concentration-time curve [AUC] comparison). Tremors and demyelination persisted in the fourth week of a 4-week reversibility period. A subsequent 26-week, nonhuman primate study using weekly rezafungin dosing showed a drug-related increase in tremors compared to controls beginning at doses similar to human exposures (5 mg/kg). In rats dosed weekly for 26 weeks, intravenous rezafungin was associated with neurotoxicity, including axonal/nerve fiber degeneration, at 25 and 45 mg/kg (about 2- and 4-fold the clinical dose based on AUC comparison) and these persisted to the end of the 26-week reversibility period.

The ISS dataset for rezafungin consists of 151 patients with candidemia or IC exposed to the proposed clinical dose for up to 4 weeks in the phase 2 and phase 3 studies. An additional 81 patients were exposed to a higher rezafungin dose (400 mg weekly) in the phase 2 study. Tremor

is reported as an uncommon adverse reaction (<5% of subjects in clinical trials) in the labeling of other FDA-approved echinocandins (Pfizer 2020; Merck 2021). In the ISS dataset, tremor was also uncommon but occurred at a higher incidence in the rezafungin-treated patients (2.6%) compared to caspofungin-treated patients (0%). The safety findings from clinical studies of rezafungin administered up to a maximum total of 4 weekly doses were otherwise consistent overall with the safety profile of the FDA-approved echinocandins. A clinical study using longer durations of rezafungin dosing is ongoing.

Rezafungin is primarily distinguished from the approved echinocandins (caspofungin, micafungin, and anidulafungin) by its prolonged half-life supporting once-weekly dosing. It has a similar spectrum of activity against the *Candida* spp. that are common causative pathogens of candidemia/IC. Rezafungin has a low DDI risk potential that is similar to the echinocandins micafungin and anidulafungin, but more favorable than the echinocandin caspofungin as well as the azole antifungal drugs.

Based on review of the available efficacy and safety data, NDA 217417 for rezafungin provides substantial evidence of effectiveness and a favorable benefit-risk profile for the treatment of adult patients who have limited or no alternative options for the treatment of candidemia/IC.

II. Interdisciplinary Assessment

3. Introduction

Rezafungin is an antifungal drug product being developed by Cidara Pharmaceuticals, Inc. for the treatment of candidemia and invasive candidiasis (IC) in adults. It is an echinocandin, a class of antifungals which inhibit the synthesis of the essential fungal cell wall component 1,3-β-D-glucan. Rezafungin is to be administered as an intravenous (IV) infusion and will be given as a 400-mg dose on Day 1 followed by a 200-mg dose once weekly thereafter (in the phase 2 and 3 studies, patients were given a total of 2 to 4 doses).

Candidemia and IC are serious infections caused by the invasion of *Candida* spp. 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. The echinocandin class of antifungals are currently considered first-line initial therapy for candidemia/IC except for infections of the central nervous system, eye, or urinary tract. There are three FDA-approved echinocandins, all of which are available only as 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 *Candida* spp., or are intolerant of azole therapy.

This NDA contains a single adequate and well-controlled phase 3 noninferiority (NI) study (ReSTORE) in adult subjects with candidemia/IC comparing IV rezafungin (REZ) 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% 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 (<10%).

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 once every 3 days 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 moderate tremors in rezafungin-treated monkeys compared to control animals. Neurotoxicity, including axonal/nerve fiber degeneration, was also observed in rats dose weekly for 26 weeks at 2- to 4-fold the clinical dose based on AUC comparisons.

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. An additional 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) and in none of the subjects receiving the caspofungin comparator. The safety findings from these clinical studies were otherwise consistent 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 the currently 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 NDA was brought to the Antimicrobial Drugs Advisory Committee meeting to discuss whether the data contained in the NDA for rezafungin support a favorable benefit-risk assessment for the treatment of candidemia/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 NI study and a limited safety database.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Evaluation of Efficacy Data Supporting the NI Assessment of Rezafungin Versus Caspofungin Comparator for the Primary Endpoint of Day 30 ACM

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

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

3.1.2. Key Safety Review Issues

3.1.2.1. Assessment of Neurotoxicity Safety Signal From Nonhuman Primate Studies of Rezafungin

3.1.2.2. Assessment of the DDI Potential of Rezafungin Compared to FDA-Approved Antifungals for Candidemia and IC

3.2. Approach to the Clinical Review

From an efficacy perspective, the phase 3 study (ReSTORE) was reviewed as the primary evidence of efficacy given its overall study design, and the phase 2 study (STRIVE) was reviewed as supportive data. As is described in further detail below, the phase 3 study was considered to be an adequate and well-controlled study with a prespecified primary endpoint that had been designed consistent with guidance from the Division. The phase 2 study was considered supportive given its descriptive design as well as other statistical caveats noted in this review. Thus, evidence of efficacy was provided by a single pivotal study, which was deemed acceptable given the seriousness of the indication, what is known about the study drug class to date, and the possibility of tailoring use to a limited population where the benefit-risk calculus is appropriate.

From a safety perspective, the phase 3 study data taken together with the data from the 400 mg/200 mg cohort of the phase 2 study were evaluated as the integrated safety database given that this total population provided safety information at the proposed dose in the proposed indication/study population. Supportive safety data were provided from multiple sources, including the 400 mg/400 mg cohort of the phase 2 study (which provided modest information on dose-dependent toxicities), phase 1 data (from eight studies, almost all in healthy volunteers),

and expanded access patients who were ineligible for the original studies. At the time of submission, as well as at the time of the 120-Day Safety Update, blinded, topline safety information was provided from two ongoing clinical studies: the 13-week randomized, controlled prophylaxis study against invasive fungal infections in patients undergoing blood and marrow transplantation (RESPECT study) and the extension of the phase 3 candidemia/IC study in China. Though the integrated safety database was small (151 rezafungin-treated patients), the NDA submission was considered adequate from a safety evaluation perspective given the supportive safety data noted above, the known drug safety profile of the echinocandin class, and the context of a limited use population for whom expected benefit outweighed a certain degree of safety uncertainty.

Table 3. Clinical Studies Submitted in Support of Efficacy and/or 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 to 21, optional for subjects with IC 50 mg/day Days 22 to 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 to 14 required; Days 15 to 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: 43 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 to 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 to 14 required; Days 15 to 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: 15

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 elig bility 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

4. Patient Experience Data

Outside the objective clinical data supporting the primary and secondary endpoints (such as all-cause mortality, mycological culture clearance, etc.), clinician-reported outcomes were used to assess clinical cure (a component of the secondary endpoint of global cure). No patient-reported outcomes were used in the studies for primary or exploratory purposes.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Section 15.2.1.1. Definitions of Secondary Endpoints
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Nonclinical REZ Pharmacokinetics-Pharmacodynamics (PK-PD) Information

The Applicant conducted several studies examining the nonclinical PK-PD of REZ in a neutropenic candidiasis murine model with *C. albicans, C. glabrata*, *C. parapsilosis*, *C. tropicalis*, or *C. dubliniensis.* Both free-drug (*f*)$AUC_{0\text{-}168}$/minimum inhibitory concentration (MIC) and *f* maximum plasma concentration (C_{max})/MIC of REZ were best correlated with kidney fungal burden reduction, indicating that the antifungal activity of REZ was concentration dependent, similar to other echinocandins. The Applicant chose the *f*$AUC_{0\text{-}168}$/MIC as the PK-PD index for REZ considering that REZ AUC and C_{max} would be highly correlated with the weekly dosing. In addition, species specific REZ *f*$AUC_{0\text{-}168}$/MIC targets associated with stasis and 1-log_{10} mycological kill in kidney tissue were identified (Table 5).

Table 5. Summary of *Candida* Species MICs and Murine Invasive Candidiasis PK-PD Targets by Applicant

	MICs (µg/mL)	*f*$AUC_{0\text{-}168}$/MIC[a,b] Median (Range)	
Organism	Range	Stasis	1-log_{10} kill
C. albicans	0.03-0.06	20.5 (14.2-25.9)	37.2 (21.3-48.1)
C. glabrata	0.125-1	0.5 (0.35-3.4)	2.9 (2.5-8.4)
C. parapsilosis	0.5-1	18.2 (9.7-26.7)	NA
C. auris	0.06-2	12.1 (4.6-23.8)	38.4 (27.4-55.3)
C. tropicalis	0.016-0.06	86.5 (44.7-108.6)	148.9 (73.5-214.5
C. dubliniensis	0.03-0.06	35.1 (21.5-175.3)	228.3 (30.1, 431.5)

Source: Reviewer's Table
[a] The fraction of REZ bound to plasma proteins in mice as measured by ultracentrifugation was 0.992 (NC-137 study report)
[b] The published *f*$AUC_{0\text{-}24}$/MIC target was multiplied by 7 to get weekly ratio to match all the rest.
Abbreviations: *f*$AUC_{0\text{-}168}$/MIC, area under the free rezafungin plasma concentration-time curve from time 0 to 168 hours relative to MIC; MIC, minimum inh bitory concentration; NA, not applicable/attained; PK-PD, pharmacokinetic/pharmacodynamic

During the review, the following concerns (for more details see Section 14.2.1) were identified:

- Adequate information in support of the 2-hr window between treatment initiation and post-inoculation is not provided. Therefore, there is a concern that the model may reflect a postexposure prophylaxis state more than a treatment state.
- Poor *C. glabrata* growth may lead to underestimation of the REZ *f*$AUC_{0\text{-}168}$/MIC targets associated with the fungal burden reduction endpoints.
- The MICs of *C. albicans*, *C. tropicalis*, and *C. parapsilosis* strains evaluated in nonclinical PK-PD assessments are below the Applicant proposed susceptibility test interpretive criteria (STIC). Therefore, to support the proposed respective STICs, REZ's

antifungal activity would need to be extrapolated beyond the information available from nonclinical PK-PD assessments.

- REZ PK-PD targets (associated with endpoints on Day 7) against *C. auris, C. tropicalis, C. dubliniensis* are difficult to interpret from an every three days dosing regimen in the absence of comparative murine PK data considering REZ is proposed to be administered once weekly and there is an apparent relationship between the shape of the concentration-time profile and mycological kill in nonclinical PK-PD studies.

The Applicant utilized nonclinical PK-PD information along with PTA analyses to inform dose selection for the phase 2 and 3 studies as well as to support a hypothesis that REZ may have improved activity in humans compared to other echinocandins (see Section 6 for more details). While these nonclinical findings might be valuable in rationalizing dosage selection for clinical study evaluation, the translational utility of these findings to candidemia/IC patient care remains to be determined; especially considering the lack of established animal models for candidiasis and IC (see Section 14.2.3 for more details).

5.2. Clinical Pharmacology/Pharmacokinetics

Clinical pharmacology properties of REZ are summarized in Table 6.

Table 6. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	REZ is an echinocandin antifungal
Mechanism of action	REZ inhibits 1,3-β-D-glucan synthase enzyme complex, which is present in fungal cell walls but not in mammalian cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall of many fungi, including *Candida* species (spp.).
Active moieties	REZ is the active moiety
QT prolongation	At a dose of 1400 mg (approximately 2.5 times the C_{max} of the proposed 400 mg loading dose), REZ does not prolong the QTc interval to any clinically relevant extent. The effect of REZ was evaluated in a phase 1, randomized, double-blind, comparative, placebo- and positive-controlled study conducted in healthy subjects. The QTc effect of REZ or moxifloxacin (positive control) was studied following single doses of 600 mg REZ infused over 1.5 hr, 1400 mg REZ infused over 3.5 hr, or 400 mg oral moxifloxacin. The primary endpoint was based on an analysis of the regression of ΔQTcF as a function of REZ plasma concentration to derive the estimated mean placebo-adjusted change of QTcF from baseline (ΔΔQTcF) for the REZ dose groups at the geometric mean C_{max} for each dose level. A secondary endpoint was determination of mean ΔΔQTcF at each time point by dose. The estimated mean ΔΔQTcF at the geometric mean plasma concentrations for the REZ doses had confidence interval upper bounds of <10 ms. This finding was further supported by nonclinical data as well as, central tendency and categorical analyses of clinical data.
General Information	
Bioanalysis	Validated HPLC-MS/MS methods were used to determine the concentrations of REZ in human plasma, urine, and feces (as applicable to individual studies). The bioanalytical methods' validation and performance met the criteria recommended in the Bioanalytical Method Validation Guidance for Industry.
Healthy subjects versus patients	Following the proposed loading 400 mg REZ IV dose, the geometric mean REZ $AUC_{0\text{-}168}$, C_{max}, and $C_{min,168}$ in adult candidemia or invasive candidiasis patients was approximately 30%, 18%, and 36% lower compared to healthy adults.

Characteristic	Drug Information
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Table 7. Geometric Mean (CV%) for REZ Pharmacokinetic Parameter Estimates Adults With Candidemia or Invasive Candidiasis Following a 400 mg REZ Loading Dose Then 200 mg REZ Once Weekly (Infused Over 1 Hour)** **Geometric Mean (%GCV)** **Day** | $AUC_{0\text{-}168}$ (µg·h/mL) | C_{max} (µg/mL) | $C_{min,168}$ (µg/mL) Day 1 | 791 (32) | 17.4 (35) | 2.22 (43) Day 8 | 648 (34) | 11 (33) | 2.08 (46) Day 15 (steady-state) | 639 (33) | 10.9 (33) | 2.08 (46) Source: FDA reviewer analysis using final popPK model with the phase 2 and 3 patients' PK data. See reviewer's independent analysis in Section 14.5 Abbreviations: %GCV, geometric coefficient of variation expressed as a %; $AUC_{0\text{-}168}$, area under the concentration-time curve from time 0 to 168 hours after drug administration; C_{max}, maximum plasma concentration of drug after administration; $C_{min,\ 168}$, minimum plasma concentration of drug at pre-dose or 168 hours after administration
Range of effective dose(s) or exposure	Effective dosage: The pivotal phase 3 study evaluated only one REZ dosing regimen, i.e., a loading dose of 400 mg REZ then 200 mg once weekly. Effective exposure range: The relationships between REZ exposure ($AUC_{0\text{-}168}$, C_{max}, $C_{min,\ 168}$, $AUC_{0\text{-}168}$/MIC) and secondary efficacy endpoint global cure and exploratory time to negative blood culture in the phase 3 or phase 2 and 3 studies, respectively, were flat over the range of exposures achieved following a loading dose of 400 mg REZ then 200 mg once weekly (phase 2 and 3) to 400 mg once weekly (phase 2 only).
Maximally tolerated dose (MTD) or exposure	An MTD was not determined. The highest evaluated single dose in humans was 1400 mg REZ infused over 3.5 hr. The highest evaluated multiple dose in humans was 400 mg REZ infused over 1 hr weekly for 3 weeks.
Dose proportionality	REZ AUC_{inf} and C_{max} increased in a dose proportional manner over the dose range of 50 mg to 400 mg.
Accumulation	At the proposed REZ dosage, C_{max} and $AUC_{0\text{-}168}$ ratios following first dose and third dose were 1.33-fold and 1.55-fold, respectively.
Time to achieve steady-state	Steady-State is achieved after the third dose (week 3) following the proposed REZ dosage.
Distribution	
Volume of distribution	The mean (CV%) is 67 L (41.8) in patients with candidemia/IC
Plasma protein binding	REZ is highly protein bound and plasma protein binding (PPB) estimates varied during in vitro and in vivo assessments from 87.5% to >98.7%. PPB estimates were independent of concentrations.
Drug as substrate of transporters	REZ is not a substrate of major drug transporters.
Elimination	
Mass balance results	Following a single 400 mg radiolabeled (~200 µCi) REZ dose, 88.3% of the dose was expected to be recovered through Day 60 postdose. Cumulative excretion data indicate that elimination is primarily nonrenal. Ratios of blood to plasma total radioactivity ranged between 0.86 to 1.02 and REZ was the most abundant circulating component (77% of total radiocarbon AUC) in plasma.
Clearance	The mean (CV%) is 0.35 L/hr (37%)) in patients with candidemia/IC

Characteristic	Drug Information
Half-life	REZ has demonstrated a multiphasic pharmacokinetic profile. Based on the terminal/elimination phase, the estimated mean (CV%) steady-state half-life in adults with candidemia and invasive candidiasis is 152 (19%) hours. Also see Accumulation information above.
Metabolic pathway(s)	REZ is minimally metabolized. REZ is not predicted to be a substrate of cytochrome P450 (CYP) enzymes. Primary metabolism of REZ was mediated by hydroxylation and, to a lesser extent, oxidation, and oxidative O-dealkylation.
Primary excretion pathways (% dose)	Following a single 400 mg radiolabeled (~200 µCi) REZ dose, 25.7% of the dose was recovered in urine, <1% of which was recovered as unchanged REZ, and 74.3% of the dose was recovered in feces, 94% of which was recovered as unchanged REZ.
Intrinsic Factors and Specific Populations	
Body weight	Population pharmacokinetic (PK) analyses indicate that the magnitude of predicted change in REZ ($AUC_{0\text{-}168}$) over a body surface area (BSA) range of 1.2 to 2.7 m^2 is not clinically relevant. For bodyweight, a highly correlated covariate to BSA, a similar finding was observed over a body weight range of 34 to 154.5 kg. No dosage adjustments are recommended based on BSA or bodyweight.
Age	A population PK analysis based on the PK data from phase 1, phase 2, and phase 3 studies, show that age (range: 20 to 89 years) is not a significant covariate of REZ PK in adults. Of the total number of REZ treated adults, 41 (15%) were 65 to 74 years and 25 (9%) were 75 to 89 years of age. The available PK information suggests no dosage adjustments are required in elderly patients aged 65 years or more.
Renal impairment	A population PK analysis based on the PK data from phase 1, phase 2 and phase 3 studies, show that measures of renal function, serum creatinine and creatinine clearance (9.3 mL/min to >120 mL/min), are not significant covariates of REZ PK. No dosage adjustments are recommended for subjects with renal impairment.
Hepatic impairment	In a PK study in subjects with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment, the mean exposure of REZ (C_{max} and $AUC_{0\text{-}168}$) was reduced by approximately 30% in subjects with hepatic impairment relative to matched control subjects with normal hepatic function. Based on a relatively flat $AUC_{0\text{-}168}$, $AUC_{0\text{-}168}$/MIC-, or C_{max}-efficacy response relationship, a 30% reduction in AUC is not anticipated to be clinically meaningful (see Section 14.5.6). In addition, Bayesian estimates of rezafungin Day 1 C_{max} and $AUC_{0\text{-}168}$ did not indicate a difference between candidemia and IC patients with moderate hepatic impairment (n=5 [phase 2 and 3] with Child-Pugh score 7 to 9) and those without hepatic impairment. Collectively, the total (bound+unbound) REZ $AUC_{0\text{-}168}$ reduction in hepatically impaired subjects is not considered to be clinically meaningful. No dosage adjustment is recommended for patients with hepatic impairment.
Drug Interaction Liability (as Perpetrator)	
Inhibition/induction of metabolism	REZ is not a clinically significant inhibitor or inducer of the common drug metabolizing CYP enzymes
Inhibition/induction of transporter systems	REZ is not a clinically significant inhibitor or inducer of the common drug transporters

Source: FDA reviewer's assessment
Abbreviations: $AUC_{0\text{-}168}$, area under the plasma concentration-time curve from time zero to 168 hours; $AUC_{0\text{-}168}$/MIC, area under the rezafungin plasma concentration-time curve from time 0 to 168 hours relative to MIC; AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity; C_{max}, maximum plasma concentration of drug; $C_{min,\ 168}$, minimum plasma concentration of drug at pre-dose or 168 hours after administration; HPLC-MS/MS, high pressure liquid chromatography with tandem mass spectrometry; IRT-QT, Interdisciplinary review team QT; IV, intravenous; MIC, minimum inhibitory concentration; QTc, QT corrected for heart rate interval; QTcF, corrected QT interval by Fridericia; REZ, rezafungin

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant's proposed REZ dosing regimen, a 400 mg loading dose followed by 200 mg once weekly, was evaluated in the pivotal phase 3 study (ReSTORE) and supportive phase 2 study (STRIVE). The Applicant also conducted PTA analyses based on nonclinical PK-PD targets and clinical efficacy exposure-response (E-R) analyses to support the adequacy of the proposed regimen throughout drug development phases.

Nonclinical PK-PD Data and PTA

Through Monte Carlo simulation and Week 1 PTA, the Applicant integrated the nonclinical REZ PK-PD information (see Section 5.1) with clinical REZ PK information to support selection of the proposed dosing regimen (400 mg loading dose followed by 200 mg once weekly) throughout clinical drug development.

For the STRIVE study, guided by PK information from phase 1 healthy adults, two REZ dosing regimens with the same loading dose of 400 mg followed by 400 mg once weekly (high weekly dose) or 200 mg once weekly (low weekly dose) were selected. These regimens were predicted to achieve the nonclinical PK-PD targets (stasis and 1-$\log_{10}$ kill from baseline), at the end of Week 1, in greater than 90% of candidemia and IC patients infected with the two most common *Candida* species at their MIC_{90} values (REZ MIC_{90} of 0.06 mcg/mL against *C. albicans* and *C. glabrata,*).

For the ReSTORE study, PK information was further updated with the STRIVE study data and Week 1 PTA conclusions noted above remained supportive of the 400 mg REZ loading dose followed by 200 mg REZ once weekly that was evaluated in the ReSTORE study.

It is noteworthy that uncertainties were observed with REZ protein binding in human plasma (see Section 14.1.1). Therefore, the review team performed independent sensitivity analyses and the findings also showed PTA ≥90% for Week 1 and Week 3 at the MIC_{90} values against *C. albicans* and *C. glabrata* (the two most common *Candida* species in patients with candidemia and IC). For more details see PTA analyses and E-R analyses (Section 6.3.2, Section 14.5.6, and Figure 16).

Clinical Phase 2 Study, CD101.IV.2.03 (STRIVE)

STRIVE evaluated two REZ dosing regimens with the same loading dose of 400 mg followed by 400 mg once weekly (high weekly dose) or 200 mg once weekly (low weekly dose) in patients with candidemia and IC. The primary endpoint for STRIVE was overall success at Day 14, with success defined as resolution of signs of candidemia/IC and mycological eradication. At Day 14, the proportion of subjects assessed as having an overall response of success in the low weekly REZ dose arm was higher than in the high weekly REZ dose arm or caspofungin arm. At Day 5,

when the REZ dose received for Week 1 was identical between the two REZ arms, the low weekly REZ dose arm achieved a numerically higher proportion of subjects with mycological eradication of 82.6% versus 71.7% for the high weekly REZ dose arm. Since both REZ arms had received the same Week 1 REZ dose, no difference would be expected to be seen at this timepoint and could be due to chance. Based on the clinical and nonclinical data, the Applicant considered a favorable benefit-risk profile for the REZ dosing regimen with the low weekly dose (i.e., 200 mg) and selected this dosing regimen for the phase 3 ReSTORE study. For more details see the phase 2 efficacy Section 6.2.1 and pooled safety Section 7.5

Phase 3 Study, CD101.IV.3.05 (ReSTORE)

ReSTORE evaluated the proposed REZ dosing regimen, a 400 mg loading dose followed by 200 mg once weekly. The primary endpoint for ReSTORE was all-cause mortality at Day 30 (if survival could not be confirmed, the outcome was considered deceased). The primary efficacy results for all-cause mortality at Day 30 demonstrated noninferiority of REZ (compared to caspofungin) using a 20% noninferiority margin. The all-cause mortality rate at Day 30 was 23.7% in the REZ arm and 21.3% in the caspofungin arm, which led to an estimated difference in mortality rates of 2.4% [95% CI: -9.7% to 14.4%]. In general, the REZ dosing regimen was well tolerated. For more details see the phase 3 efficacy Section 6.2.2 and pooled safety Section 7.5.1.

Pooled Clinical REZ Exposure-Efficacy and Safety Response (E-R) Analyses

REZ E-R analyses were performed by the Applicant using pooled data from the STRIVE and ReSTORE studies. Flat E-R relationships were observed between Bayesian estimated REZ exposures at the doses evaluated in the STRIVE and ReSTORE studies and (1) the secondary efficacy endpoints global assessment of cure on Day 5 or Day 14, (2) exploratory efficacy endpoint time to negative blood culture, (3) gastrointestinal adverse events (AEs), and (4) serious AEs (Section 14.5.5). No change in responses was observed across the rezafungin exposures in subjects from the STRIVE and ReSTORE studies, potentially suggesting that exposures are on the plateau of the response curve. For more details see Section 14.5.5.

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. Phase 2 Study CD101.IV.2.03 (STRIVE)

6.2.1.1. Design, Phase 2 Study

The phase 2 study (STRIVE) was a dose-ranging, exploratory study, providing supportive evidence of efficacy. It was a multicenter, randomized, double-blind study to evaluate the safety, tolerability, and efficacy of two rezafungin dose groups and a caspofungin control group for the treatment of candidemia and/or IC. Please refer to Section 15.1 for a description of the dosing regimens and how they were modified in different study parts.

6.2.1.2. Eligibility Criteria, Phase 2 Study

Eligible subjects were ≥18 years of age with ≥1 systemic sign attributable to candidemia and/or IC. Diagnosis was based on a recent (≤96 hours before randomization) sample and required ≥1 blood culture positive for yeast or *Candida* or positive test for *Candida* from a rapid in vitro diagnostic (IVD) or positive Gram stain for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site.

6.2.1.3. Statistical Analysis Plan, Phase 2 Study

This was an exploratory study and, therefore, it was not powered for inferential statistical analyses.

Efficacy Endpoints

Efficacy was assessed using the outcome measures of overall response, mycological response, and investigator's assessment of clinical response.

The primary efficacy outcome was overall response at Day 14 with success defined as resolution of signs of candidemia/IC and mycological eradication. Signs of candidemia/IC were fever, hypothermia, tachycardia, tachypnea, or hypotension. Resolution of signs of infection was determined programmatically. See Section 15.1 for definitions of the secondary endpoints.

Efficacy Analysis

All efficacy analyses were conducted in the mITT population for Part A, Part B, and Parts A and B combined, unless otherwise specified.

Analysis Populations

Intent-to-treat (ITT): all subjects randomized to treatment.

Safety: all subjects randomized to treatment and who receive any amount of study drug.

Modified ITT: A subset of the safety population with documented *Candida* infection based on a central laboratory evaluation of an isolate from a blood culture obtained within 96 hours of randomization or from a specimen obtained from a normally sterile site.

Analyses

Analyses were conducted in subjects in Part A, Part B, Part A + Part B, and by treatment arm. Descriptive statistics were provided by treatment arm for each part of the study (Part A and Part B). All data were summarized separately by cohort and study drug. An exact 2-sided 95% CI for the point estimates of overall success in each treatment group was determined using the Clopper-Pearson method. Additional analysis of the primary efficacy outcome at different time points was conducted.

Two efficacy interim analyses were performed: an unblinded review of selected efficacy and safety data for 70 subjects in Part A; and an unblinded review of all parameters for all 107 subjects in Part A. An independent unblinded statistician performed the analysis on the interim and final unblinded Part A data.

Multiplicity was not considered given the descriptive nature of the study.

6.2.1.4. Results of Analyses, Phase 2 Study

In Part A, a total of 115 subjects were screened and 107 were randomized. In Part B, a total of 104 subjects were screened and 100 were randomized.

Table 8. Data Sets Analyzed, Phase 2 Study

Population	Rezafungin 400 mg/400 mg	Rezafungin 400 mg/200 mg[a]	Caspofungin	Total
Part A				
Total number of subjects screened	-	-	-	115
Screen failures[b]	-	-	-	8 (7.0)
Randomized (ITT population)[b]	35 (30.4)	36 (31.3)	36 (31.3)	107 (93.0)
Received at least 1 dose (safety population)[c]	35 (100.0)	36 (100.0)	33 (91.7)	104 (97.2)
Modified intent-to-treat (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 at least 1 dose of study drug	0	0	3 (8.3)	3 (2.8)
Part B				
Total number of subjects screened	-	-	-	104
Screen failures[b]	-	-	-	4 (3.8)
Randomized (ITT population)[b]	46 (44.2)	21 (20.2)	33 (31.7)	100 (96.2)
Received at least 1 dose (safety population)[c]	46 (100.0)	19 (90.5)	33 (100.0)	98 (98.0)
Modified intent-to-treat (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[d]	3 (6.5)	5 (23.8)	0	8 (8.0)
Did not receive at least 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
[a] The number of subjects in the Safety Population are presented based on the randomized treatment group.
[b] Percentages are based on the number of subjects screened overall.
[c] Percentage and all subsequent percentages are based on the number of subjects randomized.
[d] Documented *Candida* infection is based on a culture obtained within 96 hours of randomization or from a specimen obtained from a normally sterile site.
Note: mITT = subject received any amount of study drug and had *Candida* infection based on a blood culture obtained within 96 hours of randomization.
Abbreviations: ITT, intent-to-treat; n, number of subjects in the specified category

Efficacy Results

In this section, overall response, mycological response, clinical response, and all-cause mortality results are presented. Results for other efficacy endpoints are included in Section 16.

Overall Response at Day 5 and Day 14

The primary efficacy endpoint was overall response at Day 14. 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 9). There were more indeterminate responses for the 400/400 mg arm than the other treatment arms, but there were still numerically more actual failures in this arm. 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 9. 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	n (%)	24 (31.6)	10 (21.7)	24 (39.3)
	Indeterminate	n (%)	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 10). However, there was no statistically significant difference between this arm and the caspofungin arm at either visit. Note that at Day 5, the two rezafungin arms received the same single dose, but the 400/200 mg arm showed a numerically better result.

Table 10. 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

Clinical Response

Clinical response was not assessed by the investigator at Day 5. At Day 14, the 400/200 mg rezafungin arm achieved the highest rate of clinical cure in investigator assessment of clinical response.

Table 11. Investigator's Assessment of Clinical Response by Visit, mITT Population, Phase 2 Study

Visit	Clinical Response	Rezafungin 400/400 mg N=76 n (%)	Rezafungin 400/200 mg N=46 n (%)	Caspofungin N=61 n (%)
Day 14	Success	53 (69.7)	37 (80.4)	43/61 (70.5)
	Failure/Indeterminate	23 (30.3)	9 (19.5)	18/61 (29.5)
	Failure	18 (23.7)	6 (13)	17/61 (27.9)
	Indeterminate	5 (6.6)	3 (6.5)	1/61 (1.6)
Follow-up	Success	42 (55.3)	32 (69.6)	38/61 (62.3)
	Failure/Indeterminate	34 (44.7)	14 (30.4)	23/61 (37.7)
	Failure	25 (32.9)	10 (21.7)	21/61 (34.4)
	Indeterminate	9 (11.8)	4 (8.7)	2/61 (3.3)

Source: Table 30 of Study Report & Statistical Reviewer's Analysis
Abbreviations: 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]).

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)
Death at Day 30	n (%)	12 (15.8)	2 (4.3)	8 (13.1)
	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

An 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 analysis (Table 13).

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

Parameter	Rezafungin 400/400 mg N=76 n (%)	Rezafungin 400/200 mg N=46 n (%)	Caspofungin N=61 n (%)
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

The following table (Table 14) shows mortality by part in the phase 2 study and the Applicant's combined analysis. Decreasing mortality was observed in the 400/200 mg arm from Part A to Part B2.

Table 14. All-Cause Mortality at Day 30 (Known + Unknown) by Part, mITT Population, Phase 2 Studyl

Part	Rezafungin 400/400 mg N=76 n (%)	Rezafungin 400/200 mg N=46 n (%)	Caspofungin N=61 n (%)
Part A	(5+3)/33 (24.2)	(1+2)/31 (9.7)	(3+2)/28 (17.9)
Part B1	(7+3)/43 (23.3)		(3+0)/23 (13.0)
Part B2		(1+0)/15 (6.7)	(2+0)/10 (20)
Combined	(12+6)/76 (23.7)	(2+2)/46 (8.7)	(8+2)/61 (16.4)
Difference vs. caspofungin (95% CI)	6.7% (-7.1, 20.5)	-7.0% (-21.2, 7.3)	

Source: Applicant's AC briefing package (Table 20) and Statistics Reviewer's analysis of results by part.
Abbreviation: mITT, modified intent-to-treat

It is noted that a Fisher's exact test for the difference between two rezafungin arms had a p-value of 0.0509 for the combined data. The lower ACM rate observed for the low-dose arm is not explainable from a clinical perspective.

Phase 2 Study Conclusion

In conclusion, the phase 2 study provided initial evidence suggesting efficacy to allow for further study of rezafungin in a pivotal study.

However, caution is needed when interpreting the results from this exploratory study given the lack of inferential testing, the multiple amendments and interim analyses with no multiplicity adjustment, and the differences observed between the two rezafungin arms at Day 5 when both had received the same dose.

6.2.2. Phase 3 Study CD101.IV.3.05 (ReSTORE)

6.2.2.1. Design, Phase 3 Study

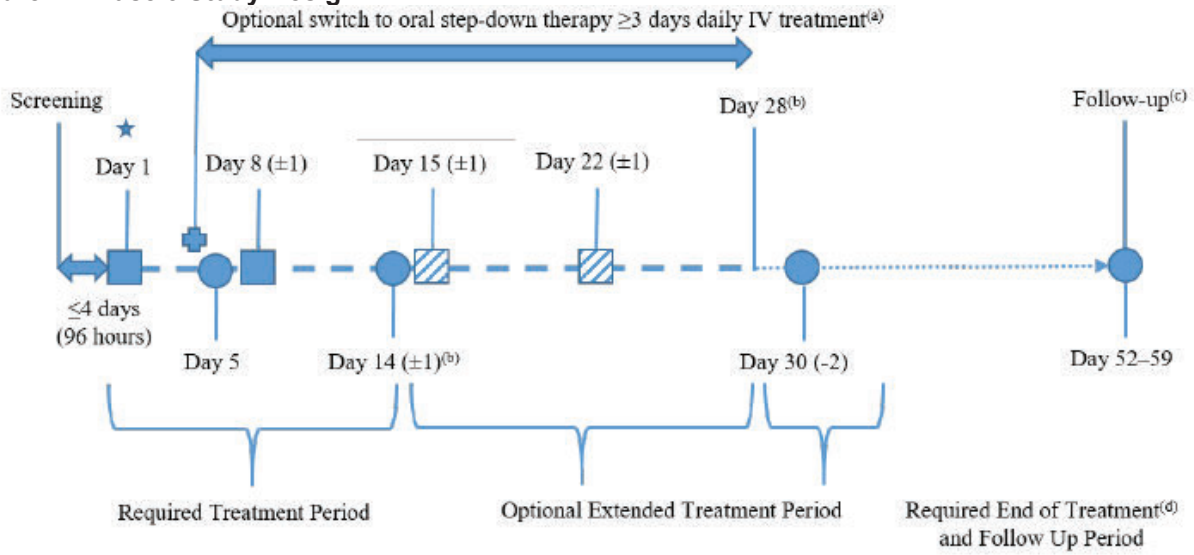
Results from the ReSTORE study serve as the main basis of the efficacy assessment. The Agency reviewed key statistical and clinical aspects of the study design (noninferiority design, the choice of control, and the primary and key secondary endpoints, inclusion/exclusion criteria) prior to protocol implementation and found them acceptable.

ReSTORE was a phase 3, multicenter, randomized, double-blind, double dummy study to compare the efficacy, safety, and tolerability of rezafungin with caspofungin for the treatment of candidemia and invasive candidiasis in adult patients.

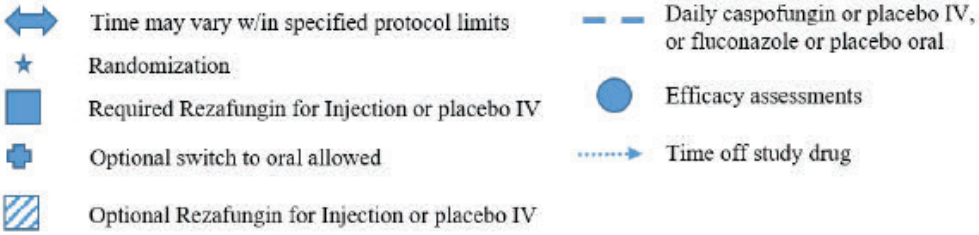
Subjects were randomized (1:1) to receive either rezafungin or caspofungin. Randomization was stratified based on diagnosis (candidemia only; invasive candidiasis) and by Acute Physiology and Chronic Health Evaluation (APACHE II) score/absolute neutrophil count (ANC) (APACHE II score ≥20 or ANC <500 cells/µL; APACHE II score <20 and ANC ≥500 cells/µL) at screening. If a subject had a positive result for both blood culture/rapid IVD and culture specimen obtained from a normally sterile site, the subject was randomized within the invasive candidiasis stratum.

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 2 to 4 doses. Subjects in the caspofungin arm were to receive a total treatment 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 ≤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 days and up 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, page 38
Abbreviations: IV, intravenous

6.2.2.2. Eligibility Criteria, Phase 3 Study

Main Inclusion Criteria

Subjects had to meet all of the inclusion criteria described in Section 15.2 to qualify for the study. The main inclusion criteria were:

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

a. ≥1 blood culture positive for yeast or *Candida* OR
b. Positive test for *Candida* from a Sponsor-approved rapid in vitro diagnostic OR
c. Positive gram stain (or other method of direct microscopy) for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site.

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

Main Exclusion Criteria

Subjects must NOT have met any of the exclusion criteria described in Section 15.2 to qualify for the study. The main exclusion criteria were:

(1) Any of the following forms of invasive candidiasis at baseline:

a. Septic arthritis in a prosthetic joint (septic arthritis in a native joint was allowed)
b. Osteomyelitis
c. Endocarditis or myocarditis
d. Meningitis, endophthalmitis, chorioretinitis, or any central nervous system infection
e. Chronic disseminated candidiasis
f. Urinary tract candidiasis due to ascending *Candida* infection secondary to obstruction or surgical instrumentation of the urinary tract

(2) Received systemic treatment with an antifungal agent at approved doses for treatment of candidemia for >48 hours (e.g., >2 doses of a once daily antifungal agent or >4 doses of a twice daily antifungal agent) ≤4 days (96 hours) before randomization.

– Exception: Receipt of antifungal therapy to which any *Candida* spp. isolated in culture was not susceptible

6.2.2.3. Statistical Analysis Plan, Phase 3 Study

The Applicant and the review division agreed on the statistical analysis plan prior to the study completion.

Analysis Populations

Two 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 ≥1 dose of study drug.

Efficacy Endpoints

Primary Efficacy Endpoints

All-cause mortality at Day 30 (-2 days) for FDA: All attempts were to be made to determine the survival status of all subjects at Day 30. If it was unknown, the subject was considered deceased for the primary efficacy analysis.

Secondary Efficacy Endpoints

- **Global response:** Global response at Day 14 was the primary efficacy outcome recommended by the European Medicines Agency to support a marketing authorization. A cure of global response was defined as clinical cure as assessed by the investigator, radiological cure [for qualifying invasive candidiasis subjects], and mycological eradication/resumed eradication confirmed by an independent data review committee at the specified time points.
- Mycological response
- Investigator's assessment of clinical response
- Radiological response (for IC only)

Details of these secondary efficacy endpoints are included in Section 15.2.

Efficacy Analysis

Unless otherwise stated, all efficacy analyses were conducted using the mITT population.

For the primary efficacy endpoint for FDA (ACM at Day 30), the NI test was based on the upper limit of the two-sided 95% CI for the observed difference in primary efficacy endpoint rates (rezafungin minus caspofungin), which was calculated for the mITT Population using the unadjusted Miettinen and Nurminen method. If the upper limit of the 95% CI for the difference was lower than 20%, then the null hypothesis was rejected and noninferiority of rezafungin versus caspofungin was declared (see Section 6.3.1).

To control the overall alpha level, superiority of rezafungin for injection for ACM at Day 30 was planned to test if noninferiority was established and the observed mortality was lower in the rezafungin arm. Analysis for superiority was not conducted, as the observed mortality was higher in the rezafungin arm.

The analysis of global response at Day 14 was also based on the mITT population using the Mantel-Haenszel method adjusted for randomization strata.

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.

6.2.2.4. Results of Analyses, Phase 3 Study

Patient Disposition

A total of 222 subjects were screened for enrollment (Table 15). Twenty-three subjects were screening failures. A total of 199 (100 in the rezafungin arm and 99 in the control arm) and 187 subjects (93 in the rezafungin arm and 94 in the caspofungin arm) were included in the ITT and mITT populations, respectively (Table 16). The most common reason for exclusion from the mITT population was not having documented *Candida* infection within 96 hours prior to randomization. There were some subjects who did not satisfy all inclusion and exclusion criteria for the ITT and mITT populations (major protocol deviation). This will be addressed in the protocol deviation and sensitivity analysis section. Approximately 60% of patients completed the study. The main reasons for discontinuation from the study were death and withdrawal by subject. Approximately 69% of patients completed study treatment. The main reasons for premature discontinuation of treatment were death and adverse events. It was noted that significantly more subjects discontinued treatment due to "other" reasons in the rezafungin arm than in the caspofungin arm (Fisher's exact test p-value=0.018). A sensitivity analysis was conducted to see the impact of this imbalance (see Section 16.2.6.1).

Table 15. Patient Screening and Enrollment, Phase 3 Study

Disposition	N n (%)
Patients screened	222
Screening failures	23 (10.4%)
Patients enrolled	199 (89.6%)
Patients randomized	199 (89.6%)

Source: Figure 5 of Study Report and Statistics Reviewer's Analysis

Table 16. Disposition of Patients, 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 at least one dose of study drug	1 (1.0)	1 (1.0)	2 (1.0)
Did not receive at least one dose of study drug and did not have documented *Candida* infection within 96 hours prior to randomization	1 (1.0)	0	1 (<1)

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
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 types 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 Characteristics and Clinical Characteristics

The following table (Table 17) shows baseline demographic and clinical characteristics in the ITT population. Overall, the demographic and baseline clinical characteristics were reasonably balanced between the two treatment arms. The mean age was 61 years old. About 41% of subjects were 65 years of age or older. The majority of subjects (61%) were white. About 61% of 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-square p-value=0.17).

Table 17. 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 (15.8)	62.0 (14.6)	60.7 (15.2)
Median	59.0	62.0	61.0
IQR	48.5, 71.0	53.0, 73.0	50.0, 72.0
Min, max	19.0, 89.0	20.0, 91.0	19.0, 91.0
Age categories, n (%)			
<65	60 (60.0)	58 (58.6)	118 (59.3)
≥65	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)

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
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 (23.3)	69.8 (22.6)	71.7 (23.0)
Median	68.0	66.2	67.9
IQR	55.0, 84.0	56.0, 80.0	56.0, 82.0
Min, max	37.2, 149.9	33.0, 153.6	33.0, 153.6
Missing	5	8	13
Height at baseline (cm)			
Mean (SD)	169.5 (10.0)	167.3 (11.4)	168.4 (10.7)
Median	170.0	168.0	168.0
IQR	160.0, 177.0	160.0, 176.0	160.0, 176.8
Min, max	137.0, 190.0	115.0, 192.0	115.0, 192.0
Missing	6	9	15
BMI, kg/m^2			
Mean (SD)	25.4 (7.0)	24.5 (6.5)	25.0 (6.8)
Median	23.6	24.1	24.0
IQR	20.8, 28.4	20.7, 26.7	20.8, 27.7
Min, max	13.7, 51.9	12.9, 47.6	12.9, 51.9
Missing	6	11	17
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 (%)			
AUS	8 (8.0)	5 (5.1)	13 (6.5)
BEL	5 (5.0)	7 (7.1)	12 (6.0)
BGR	6 (6.0)	4 (4.0)	10 (5.0)
CHN	6 (6.0)	5 (5.1)	11 (5.5)
COL	1 (1.0)	0	1 (<1)
ESP	12 (12.0)	12 (12.1)	24 (12.1)
FRA	5 (5.0)	1 (1.0)	6 (3.0)
GRC	6 (6.0)	11 (11.1)	17 (8.5)
ISR	3 (3.0)	2 (2.0)	5 (2.5)
ITA	2 (2.0)	3 (3.0)	5 (2.5)
KOR	6 (6.0)	6 (6.1)	12 (6.0)
SGP	3 (3.0)	0	3 (1.5)
THA	8 (8.0)	17 (17.2)	25 (12.6)
TWN	3 (3.0)	1 (1.0)	4 (2.0)
USA	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)
United States	26 (26.0)	25 (25.3)	51 (25.6)

Source: Statistical Reviewer Analysis; adsl.xpt
Abbreviations: AUS, Australia; BEL, Belgium; BGR, Bulgaria; CHN, China; COL, Colombia; ESP, Spain; FRA, France; GRC, Greece; ISR, Israel; ITA, Italy; ITT, intention-to-treat population; IQR, interquartile range; KOR, South Korea; SD, standard deviation; SGP, Singapore; THA, Thailand; TWN, Taiwan; USA, United States of America

Baseline clinical characteristics are summarized in the following table (Table 18). Most subjects had a final diagnosis of candidemia only (69.3%). These baseline clinical characteristics were well balanced between the two treatment arms.

Table 18. 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)
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
Min, max	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 to 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 (cells/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, 11100	4380, 10915
Min, max	0, 41174	0, 37220	0, 41174
Missing	3	0	3
ANC at randomization (cells/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 cells/µL	51 (51.0)	53 (53.5)	104 (52.3)

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
Candidemia only, APACHE II score ≥20 or ANC <500 cells/µL	19 (19.0)	17 (17.2)	36 (18.1)
Invasive candidiasis, APACHE II score <20 and ANC ≥500 cells/µL	25 (25.0)	24 (24.2)	49 (24.6)
Invasive candidiasis, APACHE II score ≥20 or ANC <500 cells/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
Min, max	9.4, 949.6	0.4, 314.0	0.4, 949.6
Missing	6	11	17
Child-Pugh score group, n (%)			
<7	5 (5.0)	5 (5.1)	10 (5.0)
7 to 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 21 of the Study Report and Statistical 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: ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation II; eCrCl, estimated creatinine clearance; IQR, interquartile range; ITT, Intention-to-treat population; max, maximum; min, minimum; SD, standard deviation

Primary and Key Secondary Efficacy Results

Primary Endpoint

The Applicant's primary efficacy results for all-cause mortality at Day 30 were confirmed by the statistical review team, and the results demonstrated noninferiority using a 20% noninferiority margin, as summarized in the following table (Table 19). Mortality rates were 23.7% (22/93) in the rezafungin arm and 21.3% (20/94) in the caspofungin arm, which lead to an estimated difference in mortality rates of 2.4% [95% CI: -9.7% to 14.4%]. It is noted that the study did not meet a 10% noninferiority margin, as indicated by the upper limit of the 95% CI. At the protocol development stage, FDA agreed that 20% could be used but would result in a limited use indication. A 10% margin would be needed for a full approval.

Table 19. 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 & Statistics Reviewer's analysis.
The Statistics Reviewer's analysis showed a similar 95% CI [-9.6, 14.3], using the same method as the Applicant.
Abbreviations: mITT, modified intent-to-treat

Secondary Endpoints

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

The proportion of subjects with Day 14 global 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%) (Table 20).

Table 20. Global Response as Assessed by Data Review Committee at Day 14 (±1 Day), mITT Population, 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 in clinical response were death and new or prolonged therapy. For indeterminate outcome, the numbers between the two treatment arms were comparable. See Section 16 for a summary of reasons for failure or indeterminate outcome.

Global Response by Visit

Global response by visit as assessed by the Data Review Committee is presented in the following table (Table 21). 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 21. 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)	

Visit	DRC Global Response, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
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 to 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 & Reviewer's analysis.
Notes: Two-sided 95% confidence intervals (CIs) for the observed differences in cure rates (rezafungin for injection treatment arm minus caspofungin treatment arm) were calculated using the unadjusted methodology of Miettinen and Nurminen, different from the adjusted analysis method in the previous table.
Abbreviations: CI, confidence interval; DRC, Data Review Committee; EOT, end of treatment; mITT, modified intent-to-treat

Mycological Response by Visit

Mycological response by visit in the mITT population is summarized in the following table (Table 22). There was no notable difference between the two treatment arms. The rezafungin arm had the numerically highest eradication percentage at Day 5 among all visits. However, this difference decreased at the later time points.

Table 22. 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)	

Visit	Mycological Response, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
Day 30 (-2 day)	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 to 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 & Statistics Reviewer's analysis
Two-sided 95% confidence intervals (CIs) for the observed differences in eradication rates (rezafungin for injection treatment arm minus caspofungin treatment arm) were calculated using the unadjusted methodology of Miettinen and Nurminen.
Abbreviations: CI, confidence interval; EOT, end of treatment; mITT, modified intent-to-treat

Investigator's Assessment of Clinical Response by Visit

Investigator's assessment of clinical response by visit is summarized in the following table (Table 23). There were no notable differences in cure percentages between the two treatment arms. 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 approximately 67%. The cure proportion decreased to 55% at Day 30, and to about 48% at the follow-up visit. Of note, for clinical response at Day 5, rezafungin had a numerically lower clinical cure rate than caspofungin, which is the opposite trend from that seen for mycological response at Day 5.

Table 23. Investigator's 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)	

Visit	Clinical Response, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
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)	
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 to 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 of the Study Report and Statistics Reviewer's analysis
Two-sided 95% confidence intervals (CIs) for the observed differences in eradication rates (rezafungin for injection treatment arm minus caspofungin treatment arm) were calculated using the unadjusted methodology of Miettinen and Nurminen.
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 24. Because there was a limited number of subjects with IC in each arm, it is not possible to reach a reliable conclusion regarding treatment effects for this endpoint.

Table 24. 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 the potential for differences in the treatment effect for various demographic groups. Subgroup analysis results by age, race, and country in the mITT population are shown in the following table (Table 25).

For each age group, there was no statistically significant treatment effect between the two treatment arms. However, the Breslow-Day test for homogeneity of odds ratio by age group was

nominally statistically significant with a p-value of 0.03, indicating potentially different treatment effects of rezafungin compared to caspofungin in the two age groups.

For sex, APACHE II and ANC, or geographic region, the treatment effects were consistent between groups of each variable.

For subjects on mechanical ventilation, an increased mortality rate was observed in the rezafungin arm compared to caspofungin.

Of note, the sample sizes for some subgroups were small, which limits the ability to identify trends with certainty and interpretability of the subgroup analyses. In addition, conducting multiple subgroup analyses without multiplicity adjustment could result in spurious findings due to chance.

Table 25. Subgroup Analyses of All-Cause Mortality at Day 30, mITT Population, Phase 3 Study

Variable, n (%)	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)
Age and Sex			
<65, male	12/35 (34.3)	4/33 (12.1)	22.2 (2.0, 41.2)
≥65, male	6/27 (22.2)	7/23 (30.4)	-8.2 (-32.9, 16.3)
<65, female	3/20 (15)	4/23 (17.4)	-2.4 (25.5, 22.0)
≥65, female	1/11 (9.1)	5/15 (33.3)	-24.2 (-52.5, 10.7)
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	

Variable, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Difference (%) (95% CI)
APACHE II			
≥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 to 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	
Mechanical ventilation			
Yes	11/16 (68.8)	11/28 (39.3)	29.5 (-1.6, 54.7)[a]
No	11/77 (14.3)	9/66 (13.6)	0.7 (-11.5, 12.3)

Source: Table 14.2.1.3 to Table 14.2.1.10 of the Study Report and Statistics Reviewer's analysis
[a] From the default method in SAS, it was (0.4, 58.5); a Chi-square test p-value was 0.0601.
Confidence intervals were from Miettinen-Nurminen method.
Abbreviations: ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation II; mITT, modified intent-to-treat

Phase 3 Study Conclusion

The phase 3 study demonstrated noninferiority of rezafungin to caspofungin with respect to Day 30 all-cause mortality, using a 20% noninferiority margin. It provided evidence for efficacy to support a candidiasis/IC treatment indication with a limited use statement.

6.3. Key Efficacy Review Issues

6.3.1. Evaluation of Efficacy Data Supporting the NI Assessment of Rezafungin Versus Caspofungin Comparator for the Primary Endpoint of Day 30 ACM

Issue

Can an integrated analysis of the pooled phase 2 and phase 3 studies form the basis of approval of rezafungin for the treatment of candidemia and invasive candidiasis without a limited use statement?

Background

The rezafungin clinical development program consisted of a phase 2 dose-finding study and a single phase 3 study. During drug development, the Agency agreed that a single adequate well-controlled study showing NI of rezafungin compared to an echinocandin-based regimen with respect to Day 30 ACM could 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. The Division assessed whether this could be justified because the upper limit of the 95% CI for the difference in the Day 30 ACM analysis of the pooled phase 2 and phase 3 studies conducted for the integrated summary of efficacy was <10%.

Assessment

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 6.2.1). 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” (November 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 pharmacological and clinical perspectives.

According to International Council for Harmonization 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.

Conclusion

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.

6.3.2. Assessment of Rezafungin’s Antimicrobial Activity Relative to FDA-Approved Echinocandins

Issue

Does rezafungin have better activity against isolates of *Candida* species that are less susceptible to FDA-approved echinocandins?

Background

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 these genes 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. (Garcia-Effron et al. 2011). 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-PD analyses comparing rezafungin's antimicrobial activity to FDA-approved echinocandins are summarized below.

Assessment

Clinical Microbiological Analyses

In Vitro Activity Compared to Other FDA-Approved Echinocandins

In the NDA submission, the Applicant provided in vitro data for rezafungin and the FDA-approved echinocandins against *Candida* spp. The in vitro MIC data from 2018 to 2020 surveillance (NC-188, NC-194, and NC-214) and Centers for Disease Control data for *C. auris* (NC-142) are summarized in Table 26. Overall, rezafungin's in vitro activity appears comparable to the other echinocandins against *Candida* spp.

Table 26. In Vitro MIC_{90} of Rezafungin and Comparator Echinocandins Against *Candida* spp.

	MIC_{90} Values (µg/mL) of *Candida* spp. Isolates					
	Surveillance Studies (2018 to 2020)					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 Vitro Activity Against *Candida* spp. Isolates With *fks* Mutations

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* spp. with *fks* mutations in the *fks1* or *fks2* gene. Overall, rezafungin had in vitro activity similar to anidulafungin but better than caspofungin against these mutant isolates (Table 27).

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

	MIC Values (µg/mL)									
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 inh bitory concentration

In Vitro Activity Against Azole-Susceptible and -Nonsusceptible *Candida* spp. Isolates

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 28). 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 28. 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

Spontaneous Mutation Frequency of Rezafungin

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 29).

Table 29. 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.

Fungicidal Activity of Rezafungin

The in vitro fungicidal activity of rezafungin, or the ≥99.9% or 3-$\log_{10}$-unit decrease in colony forming unit (CFU)/mL compared to starting inoculum, was demonstrated in a time-kill kinetic study (Ernst et al. 2002; Canton et al. 2009). Rezafungin shows a concentration-dependent 3-$\log_{10}$ kill of the starting inoculum at 4-fold the MIC or higher maintained at 24 to 48 hours, similar to other FDA-approved echinocandin drugs.

Clinical microbiology reviewer's comment: Although rezafungin demonstrated in vitro fungicidal activity, the clinical significance of this activity is unknown. We recommend inclusion of this finding in the Prescribing Information under section 12.4 Microbiology, subsection 'Mechanism of Action' to add further clarification that the clinical significance of the in vitro fungicidal activity of rezafungin is unknown.

In Vivo Activity of Rezafungin

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 an 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 30.

Table 30. 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 hr and 48 hr. 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 hr. Significant effect was observed for ANF at 24 hr and 48 hr but not at 72 hr.
NC-128	*C. albicans* SC5314 (ATCC MYA-2876)/ RZF MIC 0.015; MCF MIC ≤0.015	MCF, IP: 5 mg/kg (administered postinfection 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 postinfection 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, and 60 mg/kg	Against wild-type *C. albicans*, rezafungin was significantly more active than MCF at all doses at 24 hr and at 60 mg/kg at 48 hr. For *fks/*FKS mutant *C. albicans*, rezafungin was significantly more active than MCF at all dose levels at 48 hr but not 24 hr.
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, and 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 hr and 48 hr. Against Fks1 S645P *C. albicans* 24 hr kidney burdens were not significantly different in treatment groups, but survival at 48 hr 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 hr but, rezafungin doses reduced kidney burden by ~1 log at 48 hr, significantly better than MCF. In mice infected with the highly resistant *fks* mutant, no treatment was effective at either time point, but at 48 hr rezafungin at 60 mg/kg had the lowest fungal kidney counts.

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

Clinical microbiology reviewer's comments: 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 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 (i.e., 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). The selected PK-PD index was $fAUC_{0\text{-}168h}$/MIC (free-drug) ratio and free fraction calculation for murine data were based on a 0.8% unbound fraction. For human predictions, the $fAUC_{0\text{-}168h}$/MIC target was based on a 2.6% unbound fraction. Of note, uncertainty exists on the adequacy of utilizing a PK-PD target associated with a net-stasis fungal burden endpoint compared to 1-$\log_{10}$ or 2-$\log_{10}$ fungal kill endpoint, given the seriousness of candidemia and invasive candidiasis.

PTA Analyses

PTA analyses relied on the 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.

It is noteworthy that the FDA-approved echinocandins do not always achieve 90% PTA at their FDA-recognized breakpoints (BPs). These BPs 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. 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 MICs 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 31) to allow the determination of concordance between PTA findings and clinical outcome. In addition, there is limited experience with establishing reliable correlation between antifungal nonclinical PK-PD information 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 31. 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

	MIC µg/mL	
***Candida* Species**	**Rezafungin Arm (Total N=137)**	**Caspofungin Arm (Total N=157)**
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

In addition, the plasma protein binding (PPB) estimate is a pertinent consideration when comparing rezafungin's activity with FDA-approved echinocandins based on PK-PD assessments. Like other echinocandins, rezafungin has high PPB, however, estimates varied from 87.5% to >98.7%. A sensitivity analysis that estimated PTA (PK-PD target associated with 1-$\log_{10}$ kill) using 1% rezafungin unbound fraction (to plasma proteins) only supports coverage of *C. albicans* MIC up to 0.12 µg/mL (compared to 0.25 µg/mL with 2.6% unbound fraction) for Week 1 and 0.06 µg/mL (compared to 0.25 µg/mL with 2.6% unbound fraction) for Week 3 with PTA of 90% as the decision threshold (see Sections 14.1.1 and 14.5.6).

Conclusion

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.

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

Issue

The Applicant references a nonclinical murine intra-abdominal candidiasis study to suggest rezafungin may achieve better tissue penetration than approved echinocandins and therefore might fulfill a shortcoming of current FDA-approved echinocandins.

Background

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.

Assessment

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 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 between 5 mg/kg and 20 mg/kg doses. Importantly, no substantial differences were detected in 24-hour tissue infection-site exposure nor in liver fungal burden between micafungin and rezafungin at the same dose (5 mg/kg). Rezafungin (5 mg/kg) systemic exposures (steady-state C_{max} and $AUC_{0\text{-}24hr}$) and micafungin (5 mg/kg) systemic exposures (steady-state C_{max} and $AUC_{0\text{-}24hr}$) in mice reported in different nonclinical studies (Andes et al. 2008; NIH 2022) are approximately 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 (see Sections 14.2.1 and 14.5.5) (Andes et al. 2008; NIH 2022). However, given that the murine intra-abdominal candidiasis study did not measure systemic rezafungin PK, it is not possible to evaluate associations between rezafungin plasma concentrations, infection-site exposures, and liver fungal burdens. It is the reviewer's opinion that such assessments (i.e., associations between infection-site exposures and fungal burdens under humanized systemic exposures) are needed to inform the extent of tissue distribution within different tissues as well as comparing tissue penetration between drugs.

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, and lung to that of total [bound+unbound] 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, because each of these echinocandins exhibits high plasma-protein binding (87.5 to >99%), technical differences (e.g., methodological and/or interlaboratory differences) and measurement variability can strongly influence calculated estimates and thereby have a cascading impact on reliable determination of the unbound drug fraction, PTA analysis findings, and interpretations of REZ activity, sequentially.

The above data do not suggest that the 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. Importantly, the above tissue penetration data are limited to eliminating organs. Whether rezafungin would demonstrate any differences 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 tissue penetration 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 25).

Conclusion

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 present, the clinical relevance of any potential differences in infection-site echinocandin drug concentrations is unclear due to the lack of both nonclinical and clinical target-site specific PK and PD data.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of rezafungin has been extensively explored from single- and repeat-dose studies in mice, rats, dogs, and monkeys up to 6 months duration; in vitro and in vivo genotoxicity studies; reproductive and developmental toxicity studies including fertility studies

in male and female rats; embryo fetal development studies in rats and rabbits; peri- and post-natal developmental toxicity study in rats; and pharmacokinetic and toxicokinetic studies to support rezafungin development and to compare pharmacokinetics in animals and humans. The target organs of toxicity that may be relevant to human risks are highlighted below.

Safety Pharmacology/Pharmacokinetics-Related Functional Effects

Besides the histamine-related signs discussed below, including impaired equilibrium and flattened bodies, increased respiration rate, and dilated pupils, there were no adverse safety pharmacology findings. Secondary pharmacology data showed that rezafungin inhibited binding at several receptor types including a dopamine transporter and beta-adrenergic receptor. Because the beta blocker propranolol is approved by the FDA to treat essential tremors and loss of dopamine-producing cells in the substantia nigra is associated with neurological effects such as tremors, rezafungin interactions at these two binding sites could theoretically contribute to the observed tremors. In monkeys, the greatest exposure to rezafungin was observed in the spinal nerve dorsal root ganglia. Also in monkeys, rezafungin elimination from the spinal nerve was very slow, with a tissue $t_{1/2}$ value of 874 hours.

Injection Site Reactions

In the 26-week monkey study of weekly rezafungin, several animals showed swelling reactions at the cephalic vein/forearm injection site and an increase in difficulty placing catheters into the cephalic vein at Week 4. Local vascular injury at injection sites was also observed in some rat studies.

Histamine Release

In rats, drug-related clinical findings were observed which are likely related to the well documented, echinocandin-related histamine release. Signs included low carriage, decreased activity, swollen forelimb, hindlimb, cranium, muzzle, increased respiration rate, labored breathing, incoordination, blue, discolored skin on forelimb, forepaw, hindlimb, hind paw, pinna, and urogenital areas. Most of these signs were reduced by Day 64, but low carriage and decreased activity persisted during the dosing period. The ERAXIS (anidulafungin) labeling notes that “Possible histamine-mediated symptoms have been reported with ERAXIS, including rash, urticaria, flushing, pruritus, dyspnea, and hypotension. These events are infrequent when the rate of ERAXIS infusion does not exceed 1.1 mg/minute.”

Tremors

Beginning as early as Day 22, tremors, including intention tremors, were observed in monkeys dosed with rezafungin, every three days. After the end of 13 weeks of every three day dosing in monkeys, tremors persisted for as many as 44 days into the recovery period. Moderate, severe, whole body, locomotor and hindlimb tremors were increased (compared to concurrent controls) in rezafungin-treated monkeys dosed weekly for 6 months, at doses similar to human exposures. In the 6-month study of weekly rezafungin, most monkeys showed no tremors after the cessation of dosing, but one animal showed tremors on the last day of the 52-week reversibility period.

Axonal Degeneration

Neurotoxicity, including axonal degeneration, has been observed in rat and monkey studies of rezafungin. For example, minimal axonal degeneration was noted in the medial plantar nerve of one 30 mg/kg group male monkey, in the sural nerve of a single 5 mg/kg female, and the medial plantar nerve of a single 30 mg/kg female in monkeys dosed weekly for 26 weeks with rezafungin. In a 26-week study of weekly rezafungin in rats, nerve fiber/axonal degeneration increased in incidence and severity at 25 and 45 mg/kg and persisted at the end of the 26-week recovery period.

Testes

In rats dosed with rezafungin every 3 days for 4 weeks premating and during mating (total of 21 to 22 doses), hypospermia and decreased sperm motility was noted at ≥30 mg/kg and most animals at 45 mg/kg had no detectable motile sperm. Also in rats, rezafungin doses ≥30 mg/kg were associated with increased incidences of sperm with abnormal morphology as well as degeneration of the seminiferous tubules. Despite these observed changes, fertility was unaffected in male rats dosed for 4 weeks premating. Adverse effects in the testes and sperm do not always affect fertility. There were no adverse histopathology findings in the testes in rats dosed weekly for 26 weeks with a 26-week recovery period. Sperm concentration, production rate, morphology and motility were unaffected in monkeys dosed weekly with rezafungin for 11 or 22 weeks and during the recovery period.

Phototoxicity

Rezafungin demonstrated phototoxic potential in a neutral red uptake phototoxicity assay of rezafungin in BALB/c 3T3 mice. Rezafungin was also associated with a dose-related minimal phototoxic response (increased incidence of erythema and edema in pigmented and nonpigmented skin reactions), at C_{max} plasma concentrations ≥6.9-fold above those achieved clinically following a 400-mg dose.

Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Echinocandins are generally well tolerated. Common symptoms include gastrointestinal symptoms such as vomiting, diarrhea, and nausea. 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 studies was headache. Tremor was reported as an adverse reaction occurring in <5% of patients participating in an open-label noncomparative clinical study 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 in these studies.

7.2. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Rezafungin is not currently approved in the U.S. market or in any foreign market. Safety information can be extrapolated from other members of the echinocandin class.

7.3. FDA Approach to the Safety Review

Please see the discussion in Section 3.2 regarding adequacy of the safety database. No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. There were no major identified issues with respect to recording, coding, and categorizing AEs; the clinical review team performed a group query analysis to evaluate potential splitting of similar AEs. Safety evaluations included recording of AEs, vital signs (including electrocardiogram results), and collection of laboratory parameters. For the phase 2 and phase 3 studies, AEs were collected continuously beginning with the signing of informed consent until the final follow-up visit (or at least 30 days after the last dose of study drug for those subjects who discontinued prior to Day 22). The Medical Dictionary for Regulatory Activities version 23.0 was used for both the phase 2 and phase 3 studies (earlier Medical Dictionary for Regulatory Activities versions were used for almost all of the phase 1 studies). The investigator-assessed severity for each AE and serious adverse event (SAE) reported during the study, using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 for the phase 3 ReSTORE study. All phase 1 studies and the phase 2 STRIVE study used a 3-point grading scale (mild, moderate, and severe). For the pooled analysis in the integrated summary of safety, Common Terminology Criteria for Adverse Events grades were mapped to the 3-point scale. For all studies, AEs included any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE (also referred to as an adverse experience) could be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and did not imply any judgment about causality. An AE could arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

7.4. Adequacy of the Clinical Safety Database

The Applicant conducted eight phase 1 studies, seven in healthy adults and one in subjects with hepatic impairment. These studies enrolled 179 subjects who received rezafungin (Table 32). 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.

Table 32. 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: Sponsor Summary of Clinical Safety (Table 4)
Abbreviations: DDI, drug-drug interaction; ECG, electrocardiogram; F, female; HI, hepatic impairment; M, male; NCT, National Clinical Trial

The ISS dataset was pooled from the phase 2 and 3 studies 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 (4 weekly doses; Table 33). These subjects form the basis of the safety data for the proposed indication.

Table 33. 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: Caspo, caspofungin; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; Reza, rezafungin; 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 duration of treatment ranged from 2 to 115 weeks in these subjects, and in some cases is expected to be indefinite. 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.

The Applicant is currently conducting two clinical studies of rezafungin: an extension of the phase 3 candidemia/IC study enrolling subjects in China only (required as part of regulatory approval there) and a phase 3 prophylaxis study enrolling subjects to receive 13 weeks of rezafungin or standard comparator for the prevention of invasive fungal diseases in the allogeneic blood/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).

Although generally a minimum safety database of 300 subjects is expected at the proposed dose and duration in the intended indication, a smaller database may be acceptable provided the drug product is expected to fulfill an unmet need/limited use indication and provided much is already known regarding safety of the drug class. Rezafungin appears to fill an unmet need (namely as an option for candidemia/IC in patients unable to transition to oral azole therapy due to intolerance/DDIs/infection with an azole-resistant pathogen or for such patients in need of prolonged intravenous therapy but with contraindications to central line placement), is part of a known drug class (the first echinocandin was approved in 2001), and safety signals to date have generally been manageable relative to the potential benefit of the drug (see discussions below). Thus, the safety database is considered adequate.

7.5. Safety Results

7.5.1. Safety Results, Pooled Analyses, ISS

7.5.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, ISS

In the ISS dataset, treatment-emergent adverse events (TEAEs), including SAEs, were common in both treatment arms. This is expected in this population of seriously ill subjects with many underlying comorbidities. TEAEs and SAEs occurred at slightly higher frequencies in the rezafungin arm, and SAEs with a fatal outcome occurred in roughly a quarter of subjects in both arms. Treatment discontinuations due to TEAEs occurred at similar rates in the two arms.

Table 34. Overview of TEAEs, Safety Population, ISS

Parameter	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.
[a] 95% CI excludes zero.
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.
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; TEAE, treatment-emergent adverse event

7.5.1.2. Deaths, Pooled Analyses, ISS

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 of 151 (23.2%) deaths in the rezafungin arm and 40 of 166 (24.1%) in the caspofungin arm (Table 35). 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 35. 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)
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)

	Pooled		
Preferred Term	Reza (400/200 mg) N=151 n (%)	Caspo N=166 n (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
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; NOS, not associated with more specific term; Reza, rezafungin

7.5.1.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, ISS

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 of 151 subjects (55%) and 81 of 166 subjects (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 36).

Table 36. Subjects With SAEs 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. 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)
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)

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)
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)
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)

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)
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)
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)

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)
Neoplasms benign, malignant and unspecified (including 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)
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)

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)
Vascular disorders (SOC)	7 (4.6)	1 (0.6)	4.0 (0.5, 7.6)[a]
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.
[a] indicates rows where the 95% confidence interval excludes zero
*67-year-old male described as having increased right-sided weakness, dysarthria due to new cerebral/cerebellar infarcts.
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; NOS, not associated with more specific term; 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 the 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 was started.

7.5.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, ISS

AEs leading to treatment discontinuation occurred in similar proportions of subjects in the rezafungin and caspofungin treatment arms (14 [9.3%] and 15 [9.0%] subjects, respectively) in the ISS (Table 37). Infusion-related reaction is the only TEAE in the rezafungin arm that resulted in discontinuation in more than one subject.

Table 37. 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)
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)	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)

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)
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

7.5.1.5. Treatment-Emergent Adverse Events, Pooled Analyses, Studies, ISS

TEAEs occurred in 138 of 151 subjects (91.4%) in the rezafungin 400 mg/200 mg treatment arm and in 138 of 166 subjects (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 ≥5% in the caspofungin arm were pyrexia and vomiting. Table 38 summarizes other common TEAEs that occurred at a ≥2% rate in the rezafungin arm, including erythema and tremor.

Table 38. Common AEs Occurring at ≥2% Frequency in the Rezafungin Arm and a ≥2% Risk Difference Compared to the Caspofungin Arm, Safety Population, ISS

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)
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)

	Pooled		
Preferred Term	Reza (400/200 mg) N=151 n (%)	Caspo N=166 n (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
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.
[a] 95% CI excludes zero.
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.
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

Table 39. Patients in Pooled Rezafungin Arm With Common Adverse Events Occurring at ≥2% Frequency, 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]
Hypophosphatasemia	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)
Abdominal pain	11 (7.3)	9 (5.4)	1.9 (-3.5, 7.3)
Sepsis	10 (6.6)	8 (4.8)	1.8 (-3.3, 6.9)
Hypocalcemia	6 (4.0)	4 (2.4)	1.6 (-2.3, 5.5)
Hyponatremia	6 (4.0)	4 (2.4)	1.6 (-2.3, 5.5)
Hypernatremia	5 (3.3)	3 (1.8)	1.5 (-2.0, 5.0)
Cardiac failure	4 (2.6)	2 (1.2)	1.4 (-1.6, 4.5)
Cardiac arrest	3 (2.0)	1 (0.6)	1.4 (-1.1, 3.9)
Leukocytosis	3 (2.0)	1 (0.6)	1.4 (-1.1, 3.9)
Non-cardiac chest pain	3 (2.0)	1 (0.6)	1.4 (-1.1, 3.9)
Phlebitis	3 (2.0)	1 (0.6)	1.4 (-1.1, 3.9)
Pneumonia bacterial	3 (2.0)	1 (0.6)	1.4 (-1.1, 3.9)
Pulmonary embolism	3 (2.0)	1 (0.6)	1.4 (-1.1, 3.9)
Upper gastrointestinal hemorrhage	3 (2.0)	1 (0.6)	1.4 (-1.1, 3.9)

	Pooled		
Preferred Term	Reza (400/200 mg) N=151 n (%)	Caspo N=166 n (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
Bacteremia	7 (4.6)	6 (3.6)	1.0 (-3.4, 5.4)
Diarrhea	17 (11.3)	17 (10.2)	1.0 (-5.8, 7.9)
Decubitus ulcer	6 (4.0)	5 (3.0)	1.0 (-3.1, 5.0)
Hypertension	6 (4.0)	5 (3.0)	1.0 (-3.1, 5.0)
Clostridium difficile infection	5 (3.3)	4 (2.4)	0.9 (-2.8, 4.6)
Multiple organ dysfunction syndrome	5 (3.3)	4 (2.4)	0.9 (-2.8, 4.6)
Edema peripheral	5 (3.3)	4 (2.4)	0.9 (-2.8, 4.6)
Tachycardia	5 (3.3)	4 (2.4)	0.9 (-2.8, 4.6)
Abdominal pain upper	4 (2.6)	3 (1.8)	0.8 (-2.4, 4.1)
Pneumonia aspiration	4 (2.6)	3 (1.8)	0.8 (-2.4, 4.1)
Cytomegalovirus infection	3 (2.0)	2 (1.2)	0.8 (-2.0, 3.6)
Dizziness	3 (2.0)	2 (1.2)	0.8 (-2.0, 3.6)
Constipation	8 (5.3)	8 (4.8)	0.5 (-4.4, 5.3)
Headache	4 (2.6)	4 (2.4)	0.2 (-3.2, 3.7)
Cholestasis	3 (2.0)	3 (1.8)	0.2 (-2.8, 3.2)
Hypoalbuminemia	3 (2.0)	3 (1.8)	0.2 (-2.8, 3.2)
Pain	3 (2.0)	3 (1.8)	0.2 (-2.8, 3.2)
Thrombocytopenia	3 (2.0)	3 (1.8)	0.2 (-2.8, 3.2)
Septic shock	11 (7.3)	12 (7.2)	0.1 (-5.7, 5.8)
Hypoglycemia	4 (2.6)	5 (3.0)	-0.4 (-4.0, 3.3)
Delirium	3 (2.0)	4 (2.4)	-0.4 (-3.6, 2.8)
Acute respiratory failure	3 (2.0)	5 (3.0)	-1.0 (-4.4, 2.4)
Hematuria	3 (2.0)	5 (3.0)	-1.0 (-4.4, 2.4)
Hypotension	7 (4.6)	10 (6.0)	-1.4 (-6.3, 3.5)
Atrial fibrillation	3 (2.0)	6 (3.6)	-1.6 (-5.2, 2.0)
Cough	3 (2.0)	6 (3.6)	-1.6 (-5.2, 2.0)
Urinary tract infection	5 (3.3)	9 (5.4)	-2.1 (-6.6, 2.4)
Acute kidney injury	6 (4.0)	11 (6.6)	-2.7 (-7.6, 2.2)
Hyperkalemia	3 (2.0)	9 (5.4)	-3.4 (-7.5, 0.7)
Pleural effusion	3 (2.0)	10 (6.0)	-4.0 (-8.3, 0.2)

Source: adae.xpt; Software: R
[a] Indicates rows where the 95% confidence interval excludes zero.
Treatment-emergent adverse events are defined as an adverse event that occurred during or after study drug administration and up through the follow-up visit.
Duration is 28 days.
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator; sorted by decreasing risk difference
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

Identification of Adverse Reactions for Proposed Labeling

In its proposed labeling, the Applicant included a table in section 6 *Adverse Reactions* highlighting all AEs that were assessed as possibly/likely an adverse reaction that occurred in the pooled rezafungin arm at an incidence rate ≥5%. This included diarrhea, nausea, vomiting, abdominal pain, constipation, hypokalemia, hypomagnesemia, hypophosphatemia, pyrexia, and anemia. The review team agrees with the inclusion of these events given their high incidence and given that a relationship to rezafungin cannot be reasonably excluded.

In addition, the review team has proposed including most of the terms from Table 38 in the labeling's list of adverse reactions that occurred in <5% of patients receiving rezafungin because this analysis includes AEs occurring in the pooled rezafungin arm at an incidence ≥2% and ≥2% risk difference from the caspofungin arm. Dehydration, malnutrition, and staphylococcal bacteremia were the only AEs not included from this table as they were considered by the clinical review team as unlikely to be related to rezafungin given the mechanism of action of the drug, duration of treatment, etc.

TEAEs occurring in the pooled rezafungin arm at ≥2% frequency (Table 39) were also evaluated to identify any additional events plausibly associated with rezafungin treatment based on the nature of the event, the safety signals identified in the nonclinical development program, the occurrence of similar events in phase 1 rezafungin studies, and the safety profile of other drugs in the echinocandin class. Acute kidney injury was proposed for inclusion in labeling given its incidence of >2% in the ISS as well as the current warning in the micafungin labeling for "renal effects." Two AEs occurring at >2% in the ISS, headache and dizziness, were proposed for inclusion in labeling given their frequency of occurrence in phase 1 studies with healthy volunteers. The TEAE infusion-related reaction occurred at an incidence of 2% in the pooled rezafungin arm and had been included by the Applicant in the labeling list of adverse reactions that occurred in <5% of patients; the review team agrees with the inclusion of this event given its frequency of occurrence in phase 1 studies and its reported occurrence with other echinocandins.

Finally, two events evaluated as grouped query terms, "abnormal liver tests" and "peripheral neuropathy" were proposed for inclusion in labeling given the history of hepatotoxicity in the echinocandin drug class as well as nonclinical/clinical findings with rezafungin concerning neurotoxicity. Grouped queries were used to analyze similar adverse event terms under a single umbrella term in order to ensure that "splitting" of AEs into multiple similar event terms was not impacting the ability to use event incidence to identify potential adverse reactions (by making each individual AE appear to have a low incidence). The grouped query "abnormal liver tests" included the AE terms drug-induced liver injury, hepatic function abnormal, hepatocellular injury, hyperbilirubinemia, hypertransaminasemia, alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, hepatic enzyme increased, liver function test abnormal, liver function test increased, transaminases increased and increased gamma-glutamyltransferase; the incidence of this group query in the pooled rezafungin arm was 4.6% and 9.0% in the caspofungin arm. The grouped query "peripheral neuropathy" included the AE terms neuropathy peripheral, polyneuropathy, and peroneal nerve palsy; the incidence of this group query in the pooled rezafungin arm was 0.7% and 1.8% in the caspofungin arm.

TEAEs considered by the investigator to be related to the pooled rezafungin arm are listed in the table below (Table 40). Only infusion-related reaction and nausea occurred in more than one subject in the rezafungin arm. Both of these events were included by the Applicant as adverse reactions in the proposed labeling.

Table 40. Patients With Adverse Events in the Pooled Rezafungin Arm Assessed by Investigator as Treatment-Related, Safety Population, Study 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)
Infusion related reaction	3 (2.0)	0	2.0 (-0.2, 4.2)
Nausea	2 (1.3)	0	1.3 (-0.5, 3.1)
Abdominal pain upper	1 (0.7)	0	0.7 (-0.6, 2.0)
Adverse drug reaction	1 (0.7)	0	0.7 (-0.6, 2.0)
Atrioventricular block first degree	1 (0.7)	0	0.7 (-0.6, 2.0)
Cholestasis	1 (0.7)	0	0.7 (-0.6, 2.0)
Eosinophil count increased	1 (0.7)	0	0.7 (-0.6, 2.0)
Erythema	1 (0.7)	0	0.7 (-0.6, 2.0)
Hyperbilirubinemia	1 (0.7)	0	0.7 (-0.6, 2.0)
Hyperphosphatasemia	1 (0.7)	0	0.7 (-0.6, 2.0)
Hypomagnesemia	1 (0.7)	0	0.7 (-0.6, 2.0)
Hyponatremia	1 (0.7)	0	0.7 (-0.6, 2.0)
Muscle spasms	1 (0.7)	0	0.7 (-0.6, 2.0)
Pneumonia	1 (0.7)	0	0.7 (-0.6, 2.0)
Sepsis	1 (0.7)	0	0.7 (-0.6, 2.0)
Sinus tachycardia	1 (0.7)	0	0.7 (-0.6, 2.0)
Tremor	1 (0.7)	0	0.7 (-0.6, 2.0)
Urticaria	1 (0.7)	0	0.7 (-0.6, 2.0)
Wheezing	1 (0.7)	0	0.7 (-0.6, 2.0)
Blood alkaline phosphatase increased	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Blood bilirubin increased	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Electrocardiogram QT prolonged	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Hepatic enzyme increased	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Vomiting	1 (0.7)	1 (0.6)	0.1 (-1.7, 1.8)
Diarrhea	1 (0.7)	4 (2.4)	-1.7 (-4.4, 0.9)

Source: adae.xpt; Software: R
Treatment-emergent adverse events are defined as an adverse event that occurred during or after study drug administration and up through the follow-up visit.
Duration is 28 days.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator; sorted by risk decreasing risk difference
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

Other 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; neurotoxicity is discussed in further detail in Section 7.6.1).

Phototoxicity

Nonclinical studies (both in vitro [NC-103] and in vivo [NC-113]) suggested that rezafungin had phototoxic potential, and this was explored further in a phase 1 study (CD101.IV.1.07 - A Phase 1, Multiple-dose, Assessor-Blinded Study to Determine the Photosensitivity of CD101 for Injection [Rezafungin for Injection] in Healthy Subjects). 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 were 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.

As noted in the section on SAEs, a rezafungin-treated subject in the phase 3 study developed a generalized urticarial rash during infusion and the treatment was stopped; the rash fully resolved the same day.

7.5.1.6. Laboratory Findings, Pooled Analyses, ISS

For this review, laboratory findings were primarily evaluated up to Day 14 ; the median duration of treatment was 14 days, which would have meant two weekly injections of rezafungin. Several parameters were evaluated using multiple metrics and are listed below.

Chemistry Clinical Safety Laboratory Test Results

Sodium: The mean change from baseline to Day 14 was not clinically significant and similar to changes in the caspofungin arm. The incidence of two grade increases and decreases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the rates of such changes did not differ between the two arms by ≥5%.

Potassium: The mean change from baseline to Day 14 was not clinically significant and similar to changes in the caspofungin arm. The incidence of two grade decreases from baseline at any postbaseline visit was ≥10% (11%) of the pooled rezafungin population but the pooled rezafungin rate did not differ by ≥5% from the pooled caspofungin arm rate. The incidence of two grade increases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the pooled rezafungin rate did not differ by ≥5% from the pooled caspofungin arm rate. “Hypokalemia” is proposed by the Applicant as a common adverse reaction in labeling (reported as an adverse event in ≥5% of the pooled rezafungin population).

Chloride: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm.

Bicarbonate: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm. The incidence of two grade increases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the pooled rezafungin rate did not differ by ≥5% from the pooled caspofungin arm rate.

Glucose: The mean change from baseline to Day 14 was not clinically significant and only modestly differed from changes in the caspofungin arm. The incidence of two grade decreases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the pooled rezafungin rate did not differ by ≥5% difference from the pooled caspofungin arm rate. The incidence of two grade increases from baseline at any postbaseline visit was ≥10% (13.8%) of the pooled rezafungin population but the pooled rezafungin rate did not differ by ≥5% from the pooled caspofungin arm rate. There was only one case of “hyperglycemia” as a TEAE in the pooled rezafungin arm and three cases in the pooled caspofungin arm.

Calcium: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm. The incidence of two grade increases and decreases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the pooled rezafungin rates did not differ by ≥5% from the pooled caspofungin arm rates.

Magnesium: The mean change from baseline to Day 8 was not clinically significant and was similar to changes in the caspofungin arm. However, “hypomagnesemia” appears in proposed labeling as an adverse reaction because this adverse event had an incidence >5% in the pooled rezafungin population.

Phosphate: Serum phosphate was not part of the protocol-based laboratory safety monitoring for either the phase 2 or phase 3 studies. However, the Applicant noted the AE "hypophosphatemia" was reported in the pooled rezafungin arm at an incidence ≥5%. The Applicant noted that serum phosphate could have been measured as part of routine local inpatient/outpatient clinical care and low levels requiring treatment were reported as adverse events.

Serum Protein: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm.

Urea Nitrogen: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm. The incidence of two grade increases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the pooled rezafungin rate did not differ by ≥5% from the pooled caspofungin arm rate.

Creatinine: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm. The incidence of two grade increases from baseline at any postbaseline visit was ≥10% of the pooled rezafungin population and the pooled rezafungin rate (13.1%) was ≥5% difference from the pooled caspofungin arm rate (19.8%). The incidence of grouped query terms for "renal impairment" (included blood creatinine increased, acute kidney injury, renal failure, and renal impairment) was 6% in the pooled rezafungin arm and 10.8% in the pooled caspofungin arm.

Hematology Clinical Safety Laboratory Test Results

White Blood Cells: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm. The incidence of two grade decreases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the pooled rezafungin rate did not differ by ≥5% from the pooled caspofungin arm rate. The incidence of two grade increases from baseline at any postbaseline visit was ≥10% of the pooled rezafungin population and the pooled rezafungin rate (12.8%) was ≥5% difference from the pooled caspofungin arm rate (19.8%).

Hemoglobin: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm. The incidence of two grade decreases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the pooled rezafungin rate did not differ by ≥5%from the pooled caspofungin arm rate. It should be noted that "anemia" is listed in proposed labeling as a common adverse reaction since the incidence of this AE is >5% in the pooled rezafungin population.

Platelets: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm. The incidence of two grade decreases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the pooled rezafungin rate did not differ by ≥5% from the pooled caspofungin arm rate.

Eosinophils: The mean change from baseline to Day 8 was not clinically significant and was similar to the caspofungin arm (measured in phase 2 study only).

Neutrophils: The mean change from baseline to Day 14 was not clinically significant and was similar to changes in the caspofungin arm. The incidence of two grade decreases from baseline at any postbaseline visit was <10% of the pooled rezafungin population and the pooled rezafungin rate did not differ by ≥5%from the pooled caspofungin arm rate.

Taken together, general laboratory findings did not raise safety concerns; however, rezafungin effects on increasing glucose, creatinine, and white blood cell levels cannot be excluded. While leukocytosis and hyperglycemia appear as adverse reactions in the anidulafungin labeling, AEs related to leukocytosis and hyperglycemia were reported at a low incidence in the pooled rezafungin arm (possibly due to alternate etiologies explaining abnormal results such as infection); thus, such terms are not proposed for inclusion as adverse reactions in rezafungin labeling at this time. As noted earlier, "renal effects" appears as a warning in micafungin labeling and "acute kidney injury" is already being proposed as an adverse reaction that should be included in rezafungin labeling.

7.5.1.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, ISS

Hepatotoxicity is a known safety concern of the echinocandin drug class and, currently, warnings related to such adverse reactions are present in the labeling of each approved echinocandin. Thus, it is imperative that rezafungin's propensity for drug-induced liver injury be adequately explored and represented, if necessary, in labeling.

The following liver function parameters were evaluated for their mean change from baseline to Day 14:

- Alanine aminotransferase (ALT): There were minimal mean changes from baseline to Day 14 for both arms in the pooled analysis (there was a general trend toward a decrease for the rezafungin arm).
- Aspartate aminotransferase (AST): There were minimal mean changes from baseline to Day 14 for both arms in the pooled analysis
- Alkaline phosphatase: There were clinically insignificant mean changes from baseline to Day 14 for both arms in the pooled analysis
- Total Bilirubin: There were clinically insignificant mean changes from baseline to Day 14 for both arms in the pooled analysis
- Direct bilirubin: There were clinically insignificant changes from baseline to Day 14 for both arms in the pooled analysis

For most liver function parameters, significant elevations occurred at a similar or lesser level in the pooled rezafungin arm relative to the pooled caspofungin arm (see Table 41). There is also not a clear dose-dependent toxicity seen when comparing the 400 mg/400 mg and 400 mg/200 mg arms of the phase 2 study.

Table 41. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Study ISS

	STRIVE					ReSTORE			Pooled		
Laboratory Parameter	Reza (400/200 mg) N=53 n/N_w (%)	Reza (400/400 mg) N=81 n/N_w (%)	Caspo N=68 n/N_w (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)	Reza (400/400 mg) vs. Caspo Risk Difference (%) (95% CI)	Reza (400/200 mg) N=98 n/N_w (%)	Caspo N=98 n/N_w (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)	Reza (400/200 mg) N=151 n/N_w (%)	Caspo N=166 n/N_w (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
ALP, high (U/L)											
Level 1	23/50 (46.0)	27/76 (35.5)	25/65	7.5	-2.9	44/96 (45.8)	35/96	9.4	67/146 (45.9)	60/161	8.6
(>1.5X ULN)			(38.5)	(-10.6, 25.7)	(-18.9, 13.1)		(36.5)	(-4.5, 23.2)		(37.3)	(-2.4, 19.6)
Level 2	14/50 (28.0)	17/76 (22.4)	20/65	-2.8	-8.4	32/96 (33.3)	27/96	5.2	46/146 (31.5)	47/161	2.3
(>2X ULN)			(30.8)	(-19.5, 14.0)	(-23.0, 6.2)		(28.1)	(-7.8, 18.2)		(29.2)	(-8.0, 12.6)
Level 3	4/50 (8.0)	9/76 (11.8)	14/65	-13.5	-9.7	16/96 (16.7)	14/96	2.1	20/146 (13.7)	28/161	-3.7
(>3X ULN)			(21.5)	(-26.0, -1.0)	(-22.1, 2.7)		(14.6)	(-8.2, 12.4)		(17.4)	(-11.8, 4.4)
ALT, high (U/L)											
Level 1	2/52 (3.8)	2/77 (2.6)	10/67	-11.1	-12.3	11/97 (11.3)	14/97	-3.1	13/149 (8.7)	24/164	-5.9
(>3X ULN)			(14.9)	(-21.1, -1.1)	(-21.6, -3.1)		(14.4)	(-12.5, 6.3)		(14.6)	(-13.0, 1.1)
Level 2	0/52 (0)	1/77 (1.3)	3/67	-4.5	-3.2	2/97 (2.1)	7/97	-5.2	2/149 (1.3)	10/164	-4.8
(>5X ULN)			(4.5)	(-9.4, 0.5)	(-8.7, 2.4)		(7.2)	(-11.0, 0.7)		(6.1)	(-8.9, -0.7)
Level 3	0/52 (0)	0/77 (0)	0/67 (0)	0 (0, 0)	0 (0, 0)	1/97 (1.0)	3/97	-2.1	1/149 (0.7)	3/164	-1.2
(>10X ULN)							(3.1)	(-6.1, 1.9)		(1.8)	(-3.6, 1.3)
AST, high (U/L)											
Level 1	2/52 (3.8)	6/76 (7.9)	10/67	-11.1	-7.0	16/97 (16.5)	18/97	-2.1	18/149 (12.1)	28/164	-5.0
(>3X ULN)			(14.9)	(-21.1, -1.1)	(-17.5 3.4)		(18.6)	(-12.8, 8.6)		(17.1)	(-12.8, 2.8)
Level 2	1/52 (1.9)	0/76 (0)	1/67	0.4	-1.5	5/97 (5.2)	10/97	-5.2	6/149 (4.0)	11/164	-2.7
(>5X ULN)			(1.5)	(-4.3, 5.2)	(-4.4, 1.4)		(10.3)	(-12.6, 2.3)		(6.7)	(-7.6, 2.3)
Level 3	0/52 (0)	0/76 (0)	1/67	-1.5	-1.5	1/97 (1.0)	4/97	-3.1	1/149 (0.7)	5/164	-2.4
(>10X ULN)			(1.5)	(-4.4, 1.4)	(-4.4, 1.4)		(4.1)	(-7.5, 1.3)		(3.0)	(-5.3, 0.6)

	STRIVE					ReSTORE			Pooled		
Laboratory Parameter	Reza (400/200 mg) N=53 n/N_w (%)	Reza (400/400 mg) N=81 n/N_w (%)	Caspo N=68 n/N_w (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)	Reza (400/400 mg) vs. Caspo Risk Difference (%) (95% CI)	Reza (400/200 mg) N=98 n/N_w (%)	Caspo N=98 n/N_w (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)	Reza (400/200 mg) N=151 n/N_w (%)	Caspo N=166 n/N_w (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
Bilirubin, total, high (mg/dL)											
Level 1	6/52 (11.5)	10/77 (13.0)	14/67	-9.4	-7.9	20/97 (20.6)	23/97	-3.1	26/149 (17.4)	37/164	-5.1
(>1.5X ULN)			(20.9)	(-22.4, 3.7)	(-20.2, 4.4)		(23.7)	(-14.8, 8.6)		(22.6)	(-13.9, 3.7)
Level 2	5/52 (9.6)	8/77 (10.4)	10/67	-5.3	-4.5	15/97 (15.5)	15/97	0	20/149 (13.4)	25/164	-1.8
(>2X ULN)			(14.9)	(-17.0, 6.4)	(-15.5, 6.4)		(15.5)	(-10.2, 10.2)		(15.2)	(-9.6, 5.9)
Level 3	1/52 (1.9)	5/77 (6.5)	5/67	-5.5	-1.0	12/97 (12.4)	10/97	2.1	13/149 (8.7)	15/164	-0.4
(>3X ULN)			(7.5)	(-12.9, 1.8)	(-9.3, 7.4)		(10.3)	(-6.9, 11.0)		(9.1)	(-6.7, 5.9)

Source: ad b.xpt; Software: R
Duration is 28 days.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Caspo, caspofungin; CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; Reza, rezafungin; ULN, upper limit of normal

Similarly, most hepatotoxicity-related adverse events occurred with similar or decreased frequency in the pooled rezafungin arm relative to the pooled caspofungin arm (Table 42). The reviewer found similar findings when evaluating an "abnormal liver function test (LFT)" grouped query created by combining several related terms in the ISS including drug-induced liver injury, hepatic function abnormal, hepatocellular injury, hyperbilirubinemia, hypertransaminasemia, alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increase, blood alkaline phosphatase increased, blood bilirubin increased, gamma-glutamyl transferase increase, hepatic enzyme increased, liver function test abnormal, liver function test increased, and transaminases increased (7/151 [4.6%] in the rezafungin arm versus 15/166 [9.0%] in the caspofungin arm).

Table 42. Potential Drug-Induced Liver Injury Adverse Events – Safety Population

	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
Standardized MedDRA Query (SMQ) Preferred Term, n (%)	**Rezafungin for Injection (Group 1: 400/400 mg) N=81**	**Rezafungin for Injection (Group 2: 400/200 mg) N=53**	**Caspofungin (70/50 mg) N=68**	**Rezafungin for Injection (400/200 mg) N=98**	**Caspofungin (70/50 mg) N=98**	**Rezafungin for Injection (400/200 mg) N=151**	**Caspofungin (70/50 mg) N=166**
Number of subjects with at least one drug-induced liver injury adverse event	9 (11.1)	8 (15.1)	13 (19.1)	13 (13.3)	16 (16.3)	21 (13.9)	29 (17.5)
Cholestasis and jaundice of hepatic origin (SMQ, broad)	4 (4.9)	2 (3.8)	0	2 (2.0)	4 (4.1)	4 (2.6)	4 (2.4)
Cholestasis	2 (2.5)	2 (3.8)	0	1 (1.0)	3 (3.1)	3 (2.0)	3 (1.8)
Hyperbilirubinemia	1 (1.2)	0	0	1 (1.0)	2 (2.0)	1 (0.7)	2 (1.2)
Drug-induced liver injury[a]	1 (1.2)	0	0	0	0	0	0
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ, broad)	2 (2.5)	0	4 (5.9)	2 (2.0)	2 (2.0)	2 (1.3)	6 (3.6)
Hepatic steatosis	0	0	1 (1.5)	1 (1.0)	0	1 (0.7)	1 (0.6)
Hepatic lesion	0	0	0	1 (1.0)	0	1 (0.7)	0
Ascites	0	0	2 (2.9)	0	0	0	2 (1.2)
Hepatocellular injury	0	0	1 (1.5)	0	1 (1.0)	0	2 (1.2)
Liver injury	0	0	0	0	1 (1.0)	0	1 (0.6)
Drug-induced liver injury	1 (1.2)	0	0	0	0	0	0
Liver disorder	1 (1.2)	0	0	0	0	0	0
Hepatitis, noninfectious (SMQ, broad)	0	0	0	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.6)
Hepatitis	0	0	0	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.6)
Liver related investigations, signs and symptoms (SMQ, broad)	6 (7.4)	6 (11.3)	11 (16.2)	9 (9.2)	10 (10.2)	15 (9.9)	21 (12.7)
Hypoalbuminemia	1 (1.2)	4 (7.5)	1 (1.5)	2 (2.0)	2 (2.0)	6 (4.0)	3 (1.8)
Gamma-glutamyl transferase increased	0	0	1 (1.5)	2 (2.0)	2 (2.0)	2 (1.3)	3 (1.8)
Hypertransaminasemia	0	0	0	2 (2.0)	2 (2.0)	2 (1.3)	2 (1.2)
Blood alkaline phosphatase increased	1 (1.2)	0	0	2 (2.0)	1 (1.0)	2 (1.3)	1 (0.6)
Blood bilirubin increased	0	0	1 (1.5)	1 (1.0)	2 (2.0)	1 (0.7)	3 (1.8)
Hepatic enzyme increased	1 (1.2)	0	3 (4.4)	1 (1.0)	0	1 (0.7)	3 (1.8)
Hyperbilirubinemia	1 (1.2)	0	0	1 (1.0)	2 (2.0)	1 (0.7)	2 (1.2)
Hepatic function abnormal	1 (1.2)	0	0	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.6)
Liver function test increased	0	1 (1.9)	1 (1.5)	0	0	1 (0.7)	1 (0.6)
Bilirubin conjugated increased	0	0	0	1 (1.0)	0	1 (0.7)	0
Hyperammonemia	0	1 (1.9)	0	0	0	1 (0.7)	0
Ascites	0	0	2 (2.9)	0	0	0	2 (1.2)

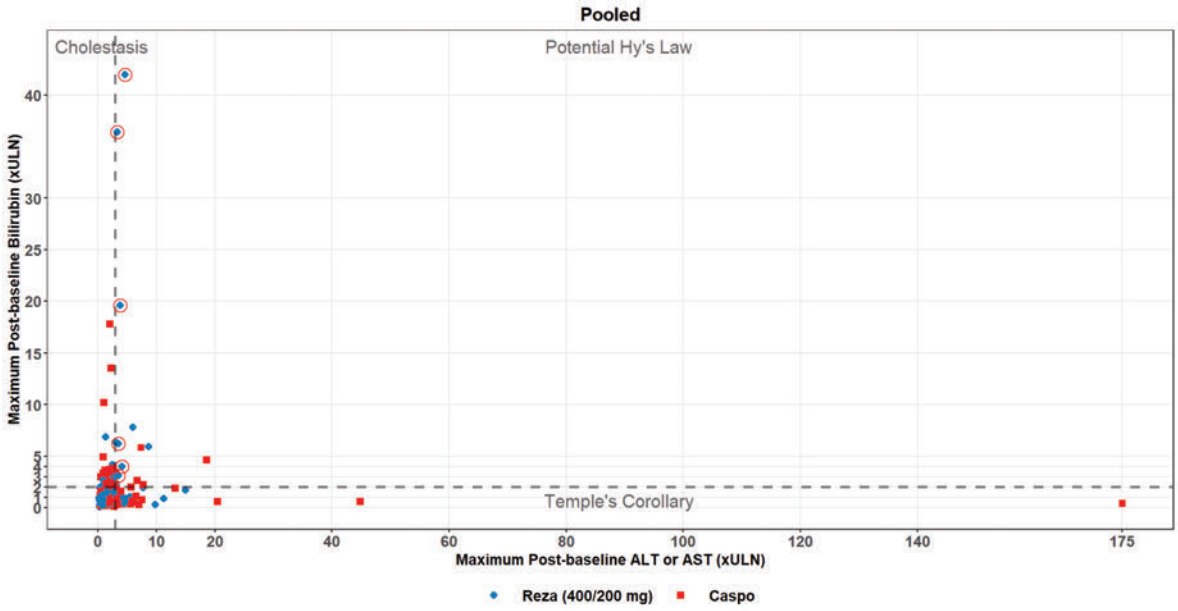
Standardized MedDRA Query (SMQ) Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) N=81	Rezafungin for Injection (Group 2: 400/200 mg) N=53	Caspofungin (70/50 mg) N=68	Rezafungin for Injection (400/200 mg) N=98	Caspofungin (70/50 mg) N=98	Rezafungin for Injection (400/200 mg) N=151	Caspofungin (70/50 mg) N=166
Alanine aminotransferase increased	0	0	0	0	1 (1.0)	0	1 (0.6)
Aspartate aminotransferase increased	0	0	0	0	1 (1.0)	0	1 (0.6)
Hemorrhagic ascites	0	0	1 (1.5)	0	0	0	1 (0.6)
Hepatomegaly	0	0	1 (1.5)	0	0	0	1 (0.6)
Liver function test abnormal	1 (1.2)	0	1 (1.5)	0	0	0	1 (0.6)
Transaminases increased	0	0	1 (1.5)	0	0	0	1 (0.6)
Liver-related coagulation and bleeding disturbances (SMQ, broad)	0	0	0	0	2 (2.0)	0	2 (1.2)
Hypofibrinogenemia	0	0	0	0	1 (1.0)	0	1 (0.6)
International normalized ratio increased	0	0	0	0	1 (1.0)	0	1 (0.6)

Source: ISS Table 2.12
[a] Drug-induced liver injury in a Phase 2 STRIVE Group 1 subject was reported as hepatic toxicity to fluconazole. The subject received only a single dose of study drug before withdrawing. The event was reported as an SAE upon starting treatment with open-label fluconazole.
Note: A subject with multiple adverse events within an SMQ or PT was counted only once. SMQs were presented alphabetically; PTs were sorted within SMQ by descending frequency in the pooled rezafungin for injection column. Percentages were calculated using the total number of subjects in each treatment group (N) as the denominator.
MedDRA Version 23.0 was used for reporting adverse events.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects in the category; PT, Preferred Term; SAE, serious adverse event

To note, six subjects met Hy's Law numerical criteria in the pooled rezafungin arm and one subject met such criteria in the 400/400 mg rezafungin arm of the phase 2 study, however, all seven subjects had alternative plausible etiologies for the abnormal liver tests (see Figure 2). No cases met Hy's Law numerical criteria for the pooled caspofungin arm. Additional information on the seven rezafungin subjects follows:

- Subject #1 ([(b) (6)]; phase 3) – alternative etiologies present including sickle cell crisis, improvement while still on rezafungin treatment; no LFT AE reported
- Subject #2 ([(b) (6)]; phase 3) – alternative etiologies present including penetrating liver trauma from gunshot wound; improvement in LFTs while still on rezafungin treatment; no LFT AE reported
- Subject #3 ([(b) (6)]; phase 3) – confounded by bacterial septic shock and death on Day 13; ALT levels actually decreased from baseline
- Subject #4 ([(b) (6)]; phase 3) – confounded by potential baseline cirrhosis and death on Day 4 from sepsis. Only screening and Day 2 transaminase levels reported; Day 2 level AST/ALT decreased from screening
- Subject #5 ([(b) (6)]; phase 3) – confounded by autoimmune hemolytic anemia and death from sepsis on day 17
- Subject #6 ([(b) (6)]; phase 3) – only LFT elevations at Day 14 (not prior) and confounded by multiple comorbidities including heart failure, death from bacterial septic shock/multiple organ dysfunction syndrome on Day 18
- Subject #7 ([(b) (6)] phase 2) – AST was 247 U/L and bilirubin 3.5 X upper limit of normal at baseline but ALT was normal. Severe motorcycle accident with associated rhabdomyolysis 12 days prior to screening. AST and bilirubin levels actually improved during course of therapy and normalized by end-of-trial (ALT levels remained normal).

Figure 2. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses, ISS



Source: ad b.xpt; Software: R
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled).
All patients with at least one post-baseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Caspo, caspofungin; Reza, rezafungin; ULN, upper limit of normal

In conclusion, hepatotoxicity is a known safety concern of the echinocandin drug class. Though there is potentially a slightly decreased risk of hepatotoxicity for rezafungin relative to caspofungin, the small safety database limits the interpretability of the findings noted to date. Moreover, the anidulafungin labeling (Pfizer 2020), from which rezafungin is derived, and the labeling for the other FDA-approved echinocandins [caspofungin (Merck 2021) and micafungin (Astellas 2005)] contain language related to hepatotoxicity in their respective *Warnings and Precautions* sections. Taken together, the clinical team recommends including hepatotoxicity in the *Warnings and Precautions* section of the rezafungin labeling.

7.5.1.8. Vital Signs, Pooled Analyses, ISS

Heart Rate

Both tachycardia (defined as a heart rate ≥120 bpm and an increase from baseline to any point postbaseline of ≥15 bpm) and bradycardia (defined as ≤50 bpm and a decrease from baseline to any point postbaseline of ≥15 bpm) occurred with less frequency in the pooled rezafungin arm versus the caspofungin arm. For tachycardia, the frequency was 31/151 (20.9%) and 46/166 (28.4%), respectively, and for bradycardia the frequency was 10/151 (6.8%) and 22/166 (13.6%), respectively. The median heart rate for both treatment arms from Day 1 to Day 14 was similar and stayed in the 90s bpm range.

Temperature

Significant increases in body temperature (defined as >38°C and an increase of ≥1°C from baseline) and significant decreases in body temperature (defined as <36°C and a decrease of ≥1°C from baseline) occurred at similar frequencies between the pooled rezafungin and caspofungin arms. For temperature increases, the frequency was 29/151 (19.6%) and 31/166 (19.1%), respectively. For temperature decreases, the frequency was 52/151 (35.1%) and 59/166 (36.4%), respectively. The mean highest daily body temperature from Day 1 to Day 14 for both arms was 37°C. As noted earlier, "pyrexia" occurred as a TEAE in >10% of patients in the pooled rezafungin arm.

Respiratory Rate

The mean highest daily respiratory rate for both arms from Day 1 to Day 14 was similar for both arms (20 to 23 breaths/minute).

Systolic Blood Pressure

The Applicant defined a significant increase in systolic blood pressure as ≥180 mm Hg and an increase of ≥20 mm Hg from baseline. This occurred at a similar frequency between the pooled rezafungin (29/151; 19.6%) and caspofungin arms (28/161; 17.4%). The Applicant defined a significant decrease in systolic blood pressure as ≤90 mm Hg and a decrease of ≥20 mm Hg from baseline. This also occurred with similar frequencies in the pooled rezafungin (38/151; 25.7%) and caspofungin (41/166; 25.5%) arms. The highest daily mean systolic blood pressure from Day 1 to Day 14 was similar in both arms.

Diastolic Blood Pressure

The Applicant defined a significant increase in diastolic blood pressure as ≥105 mm Hg and an increase of ≥15 mm Hg from baseline. This occurred with a similar frequency in the pooled rezafungin (19/151; 12.8%) and caspofungin (19/166; 11.8%) arms. The Applicant defined a significant decrease in diastolic blood pressure as ≤50 mm Hg and a decrease of ≥15 mm Hg from baseline. This also occurred with similar frequencies between the pooled rezafungin (42/151; 28.4%) and caspofungin (42/166;26.1%) arms. The highest daily mean diastolic blood pressure from Day 1 to Day 14 was similar in both arms.

Electrocardiogram Results

A thorough QT phase 1 study (CD101.IV.1.06) was performed by the Applicant and found to be negative (please see the clinical pharmacology discussion in Section 5.2). Because electrocardiograms were conducted at different timepoints in the phase 2 and phase 3 studies, no pooled analysis was performed. For the phase 3 study, no significant mean or median changes in PR interval, QRS duration, or QT interval were noted (and were generally similar for both arms) from baseline to the Day 1 postinfusion timepoint. Similarly, in the phase 2 study, no significant mean or median changes were noted in PR interval, QRS duration, or QT interval (and were generally similar for both arms) from baseline to end of therapy.

7.5.1.9. Subgroups, Pooled Analyses, ISS

Given the small safety dataset, it is difficult to interpret subgroup analyses with any certainty. The following analyses of SAEs by subgroup are presented as exploratory only, Notably, within the pooled rezafungin arm, SAEs occurred relatively equally among the various age, sex, race, and ethnicity subgroups.

Table 43. SAEs by Specified Subgroups, ISS

Characteristic	Pooled Rezafungin (400/200 mg) N=151 n/N_s (%)	Pooled Caspofungin N=166 n/N_s (%)	Pooled Rezafungin (400/200 mg) vs. Pooled Caspofungin Risk Difference (%) (95% CI)
Sex, n (%)			
F	30/53 (56.6)	34/73 (46.6)	10.0 (-7.5, 27.6)
M	53/98 (54.1)	47/93 (50.5)	3.5 (-10.6, 17.7)
Age group, years, n (%)			
≥65	37/64 (57.8)	38/68 (55.9)	1.9 (-15.0, 18.8)
18 to <65	46/87 (52.9)	43/98 (43.9)	9.0 (-5.4, 23.4)
≥75	14/26 (53.8)	20/33 (60.6)	-6.8 (-32.2, 18.6)
Race, n (%)			
American Indian or Alaska Native	0/1 (0)	0/1 (0)	0 (0, 0)
Asian	17/27 (63.0)	18/34 (52.9)	10.0 (-14.7, 34.8)
Black or African American	8/12 (66.7)	6/8 (75.0)	-8.3 (-48.5, 31.8)
Not Reported	3/5 (60.0)	1/1 (100)	-40.0 (-82.9, 2.9)
Other	2/3 (66.7)	2/2 (100)	-33.3 (-86.7, 20.0)
White	51/100 (51.0)	52/117 (44.4)	6.6 (-6.8, 19.9)
Missing	2/3 (66.7)	2/3 (66.7)	0 (-75.4, 75.4)
Ethnicity, n (%)			
Hispanic or Latino	9/15 (60.0)	6/12 (50.0)	10.0 (-27.6, 47.6)
Not Hispanic or Latino	73/131 (55.7)	74/150 (49.3)	6.4 (-5.3, 18.1)
Not Reported	1/5 (20.0)	1/4 (25.0)	-5.0 (-60.0, 50.0)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm; SAE, serious adverse event

7.6. Key Safety Review Issues

7.6.1. Assessment of Neurotoxicity Safety Signal From Nonhuman Primate Studies of Rezafungin

Issue

Neurotoxicity, including tremors and neurodegeneration were observed in subchronic nonclinical studies of rezafungin.

Background

Although 4-week studies of rezafungin in nonhuman primates did not show clear evidence of neurotoxicity, a subchronic 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 and axonal degeneration.

Assessment

Analyses of Nonclinical Data

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 three to five 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 that 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 arms but with higher incidence and severity in the 60/45 mg/kg arm. Other histopathological findings observed in this study included intracytoplasmic inclusions (minimal to marked) in the peripheral nerves at all dose

levels, with the highest in the 30 and 60/45 mg/kg 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. Only females were included in this study, 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 three days 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 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 male and female (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 4,355 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). 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 at the screening visit and at the end-of-treatment visit (within two 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 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.

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 (three 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 five 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, and 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 the 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, gastroesophageal reflux disease, 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 (i.e., rezafungin usage led to hypokalemia, which led to tremor). The neurologist noted that spironolactone was used to address the hypokalemia and both the 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 was a long duration between last study drug administration and tremor development and plausible alternative etiologies (e.g., indirect toxicity as a result of the hypokalemia) exist.

Subject (b) (6) A 28-year-old Asian 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 (four days after her second rezafungin infusion), she was noted to have spontaneous mild tremor of the hands and feet. The tremor resolved two 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 to 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.

Peripheral Neuropathy

Peripheral neuropathy is also a potential risk given the neurotoxicity findings in the nonhuman primate studies with rezafungin. 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 (0.7%; preferred term, peroneal neuropathy) was seen in the pooled 400 mg/200 mg rezafungin arm and three cases (1.8%) 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 intensive care unit-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, including the 400 mg/400 mg arm.

Conclusion

Given the totality of evidence, it is reasonable to conclude that rezafungin does pose a neurotoxicity risk. Neurotoxicity (tremors beginning 35 to 43 days after the beginning of dosing, axonal degeneration, demyelination and increased cellularity/hyperplasia of Schwann cells) was noted in multiple nonclinical studies in nonhuman primates in a dose-dependent manner and neurotoxicity (axonal/nerve fiber degeneration) was also observed in rats dosed with rezafungin weekly for 26 weeks. In clinical studies, tremor (which was reversible) was noted at an incidence higher than the comparator. It is notable that more significant findings of neurotoxicity were observed in nonclinical studies with prolonged exposure at the doses evaluated in nonhuman primates (approximately 6 to 9 times clinical exposure) and rats (approximately 2 to 4 times clinical exposure).

Though the severity of tremor/neurotoxicity findings was mild in clinical studies where patients were treated with up to four weekly doses of rezafungin, the potential for more severe findings with prolonged exposure remains a possibility and the safety and tolerability of longer duration rezafungin dosing is under evaluation in the ongoing phase 3 prophylaxis study. The review team proposes revising the *Dosage and Administration* section of the rezafungin labeling to recommend a maximum total of four weekly doses since this is the maximum duration of dosing evaluated in the clinical safety database of this submission. Tremors and peripheral neuropathy will be added to the *Adverse Reaction* section of the labeling in the list of less common adverse reactions occurring in <5% of rezafungin-treated patients; tremors are described in further detail in this section as well. The neurotoxicity findings from the 3- to 6-month duration nonhuman primate studies and 6-month duration rat studies will be described in the *Animal Toxicology* and/or *Pharmacology* section of the rezafungin labeling.

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

Issue

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, post-surgical 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.

Background

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.

Assessment

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's 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).

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 (January 2020a; January 2020b). Results of clinical DDI studies (CD101.IV.1.09 and CD101.IV.1.17) are listed in Table 44. 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 44. 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	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; 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%)

Rezafungin is not anticipated to be an inducer of CYP3A4 enzyme and/or P-glycoprotein (P-gp) transporter at the Applicant-proposed dosing regimen (i.e., a 400 mg loading dose, then 200 mg weekly) based on in vitro and in vivo DDI assessments. As shown in Table 44, 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), or 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 123 and Table 124) and compared. 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. For FDA-approved echinocandins, an alternative dosing regimen is recommended only for caspofungin when administered concomitantly with drugs that are CYP enzyme inducers.

Conclusion

The comparison of rezafungin's DDI potential with the abovementioned antifungals (Table 123 and Table 124) show:

- Rezafungin has a lower DDI potential than azole antifungal drug products
- For echinocandins, rezafungin may have a favorable DDI profile compared to caspofungin; however, rezafungin appears to have a similar DDI profile to anidulafungin and micafungin. See Section 14.2.9.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

Renal impairment is not likely to significantly impact rezafungin PK. No dose adjustment is warranted for patients with renal impairment.

Renal elimination does not play a significant role in rezafungin total body clearance (<1%). A population PK analysis based on PK data from phase 1, 2, and 3 clinical studies demonstrated that renal function, measured based on creatinine clearance (CL_{cr}) was not a significant covariate on rezafungin PK. Rezafungin $AUC_{0\text{-}168}$ ranged between 95% to 123% in subjects with various degrees of renal impairment (CL_{cr}: 9.3 mL/min to 89 mL/min) compared to subjects with normal renal function (CL_{cr} ≥90 mL/min) (see Sections 14.2.4, 14.2.6, and 14.5).

Because of rezafungin's molecular weight (1,226.4 g/mol) and extensive binding to plasma proteins (from 87.5% to >99%), FDA reviewers agree with the Applicant that rezafungin is not anticipated to be dialyzable. Rezafungin may be administered without regard to the timing of hemodialysis.

Hepatic Impairment

Rezafungin undergoes minimal metabolism and is primarily biliary excreted based on a radiolabeled mass balance study of rezafungin (see Section 14.2). The observed influence (~30% reduction in rezafungin exposure) of hepatic impairment on rezafungin PK is not clinically meaningful and no dose adjustment is recommended for patients with hepatic impairment (Child-Pugh Class A, B, or C).

In a dedicated hepatic impairment PK study, following administration of a single 400 mg dose of rezafungin, the C_{max} and $AUC_{0\text{-}168h}$ estimates were decreased by approximately 30% in subjects with moderate (Child Pugh Class B) and severe (Child Pugh Class C) hepatic impairment as compared to subjects with normal hepatic function. Considering the range of rezafungin $AUC_{0\text{-}168h}$ [287 to 2,040 µg·h/mL] and C_{max} [5 to 45 µg/mL] observed in candidemia and IC

subjects and a relatively flat exposure to response relationship for efficacy, a 30% reduction in AUC and C_{max} is not anticipated to be clinically meaningful (see Section 14.5.6).

Furthermore, Bayesian estimates of the rezafungin Day 1 C_{max} and AUC_{0-168} did not indicate a difference between candidemia and IC subjects with moderate hepatic impairment (n=5 phase 2 and phase 3 subjects with Child-Pugh score 7 to 9) and those with normal hepatic function (see Section 14.2.10).

Other Intrinsic Factors

The population PK analysis indicated that sex (60.6% male), race (76.5% Caucasian, 9.7% Black/African American, 10.1% Asian, and 3.6% other or unknown), age (20 to 89 years), or body size (e.g., body surface area [1.2, 2.7 m^2], body weight [34 kg to 154.5 kg]) do not have a clinically meaningful impact on rezafungin PK (see Section 14.5).

8.2. Extrinsic Factors

Drug-Drug Interactions

Clinical Studies

Drug-drug interaction studies in healthy subjects show no clinically significant effect of rezafungin treatment (initial 400 mg loading dose, followed by a 200 mg dose once weekly) on the pharmacokinetics of substrates of CYP enzymes and/or drug transporters (repaglinide [CYP2C8], cyclosporine [CYP3A and P-gp], tacrolimus [CYP3A and P-gp], caffeine [CYP1A2], midazolam [CYP3A]), metformin [OCT-1 and OCT-2 and MATE-1 and MATE-2], pitavastatin [OATP], rosuvastatin [BCRP and OATP], digoxin [P-gp]). These studies also show no clinically significant effect of rezafungin treatment (initial 400 mg loading dose, followed by a 200 mg dose once weekly) on the PK of other drugs likely to be coadministered (Ibrutinib, venetoclax, efavirenz, mycophenolate mofetil). For more details see Section 14.2.7.

In Vitro Studies

Rezafungin is not a substrate of CYP enzymes or drug transporters. Rezafungin is not an inhibitor or inducer of common drug metabolizing CYP enzymes or transporters. For more details see Sections 14.1.3 and 14.1.4.

8.3. Plans for Pediatric Drug Development

The Applicant was granted an Orphan Designation for the indication of IC/candidemia in February 2016. As such, the Applicant is requesting a full waiver of pediatric assessments for rezafungin related to the treatment indication. (b) (4)

(b) (4)

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The following nonclinical information was used in support of the drug's labeling. Additional details are available in Section 13.1.

Table 45. Nonclinical Data Supporting Labeling on Pregnancy and Lactation

Parameter	Nonclinical Data
Pregnancy	Maternal toxicity (hypoactivity, ataxia, flushed extremities, dilated pupils and/or swollen facial area) were observed in female rats in the 15, 30, and 45 mg/kg dose groups. No adverse, rezafungin-related embryofetal effects were observed in a rat embryofetal development study when rezafungin was administered intravenously to pregnant rats during the period of organogenesis at 45 mg/kg, 5 times the clinical exposure, based on AUC comparisons. In rabbits, reduced bodyweight gains were observed at 15 and 35 mg/kg but no adverse outcomes were observed when rezafungin was dosed intravenously once every three days to pregnant rabbits during the period of organogenesis (GD 7 to 19) at doses up to 35 mg/kg (approximately 3 times the clinical exposure. In a pre- and postnatal study, there were no adverse effects on offspring growth, maturation, or measures of neurobehavioral or reproductive function in rats administered rezafungin intravenously once every three days from one week prior to mating through LD 20, at doses up to 45 mg/kg day (about 5 times the recommended human dose based on AUC comparisons).
Lactation	In a pre- and postnatal study in rats, rezafungin was detected in the fetal plasma and maternal milk at 5, 15 and 45 mg/kg.
Males of reproductive potential	Rezafungin did not affect mating or fertility in male and female rats following IV administration once every three days at doses up to 45 mg/kg (9 times the clinical exposure, based on AUC determined in a separate rat study). Decreased sperm motility was noted at ≥30 mg/kg and most males at 45 mg/kg showed mild hypospermia and had no detectable motile sperm. At rezafungin doses ≥30 mg/kg, there were increased incidences of sperm with abnormal morphology as well as mild to moderate degeneration of the seminiferous tubules. In a 3-month study of every three days IV rezafungin in rats, males dosed at 45 mg/kg showed minimal tubular degeneration/atrophy in the testes and cellular debris in the epididymides at the end of 3 months. The incidence of this finding reduced by the end of a 4-week reversibility period. In contrast, sperm concentration, production rate, morphology, and motility were unaffected in adult monkeys dosed weekly with rezafungin, up to 30 mg/kg (about 6 times the clinical dose based on AUC comparisons) for 11 or 22 weeks or after a 52-week recovery period.

Source: Reviewer generated table.
Abbreviations: AUC, area under the concentration-time curve; GD, gestation day; IV, intravenous; LD, lactation day

Table 46. Reproductive Toxicity Safety Margins

Study	NOAEL	Nonclinical Exposure (µg*h/mL)	Safety Margins (Multiples)
Fertility rat	45 mg/kg	4704	6
EFD rat	30 mg/kg	3036	4
EFD rabbit	35 mg/kg	2730	4
PPND rat	45 mg/kg	3547	5

Source: Reviewer generated table.
Abbreviations: EFD, embryo-fetal development; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development

9. Product Quality

Approval With a Postmarketing Commitment

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 217417 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. That includes an assessment of all manufacturing and testing facilities listed in the NDA, which have been found acceptable. Therefore, OPQ recommends approval of this NDA from a quality perspective.

The proposed drug product, rezafungin for injection, is a sterile (b) (4) solid (cake or powder) supplied in a single-dose vial, which needs to be reconstituted and further diluted for intravenous infusion. As such, the drug product needs to comply with applicable guidances and regulations to ensure that the excess solid in a vial is sufficient to allow for withdrawal and administration of the net container content of the drug product. Therefore, during the NDA review, the drug product specification was amended with two additional tests such as assay/gross content and assay of the drug product reconstituted solution. It was agreed that qualification and validation data for these additional tests would be provided via a postmarketing commitment (PMC). The following CMC PMC between OPQ and the Applicant should be included in the action letter.

PMC

Complete necessary qualification and validation studies of the current assay high-performance liquid chromatography (HPLC) analytical procedure to be used for the gross content and assay of reconstituted solution tests in the drug product specification. Update the relevant sections of Module 3 accordingly.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Three clinical study sites, as well as the Applicant, Cidara Therapeutics, Inc., were inspected in support of NDA 217417 covering two clinical studies, Protocols CD101.IV.2.03 (the STRIVE Study) and CD101.IV.3.05 (the ReSTORE Study). Overall, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

11. Advisory Committee Summary

A meeting of the Antimicrobial Drugs Advisory Committee was convened on January 24, 2023 to discuss this NDA. The committee was asked to vote on whether the overall benefit-risk assessment is favorable for the use of rezafungin for treatment of candidemia/IC in adults with limited or no alternative treatment options. There were 14 "yes" votes, 1 "no" vote, and 0 abstentions.

Additionally, the committee members were asked if voting "yes", to comment on the clinical scenario(s) in which rezafungin fulfills an unmet need and if voting "no", to comment on the additional information that would be needed for the benefit-risk assessment to be favorable for the use of rezafungin in these populations.

The committee members who voted "yes" indicated that rezafungin was a member of an established drug class (echinocandins) for which there is extensive clinical experience, and as the first in the class to allow weekly dosing, rezafungin would provide advantages for patients requiring extended echinocandin therapy, particularly in the outpatient setting. They noted that daily IV therapy often requires inpatient treatment and the need for a central venous catheter or a peripherally inserted central catheter. They identified the patient population most likely to require extended echinocandin therapy as those who have experienced drug toxicity related to azoles or who require drugs for treatment of comorbidities that have unfavorable DDIs with azoles. They felt the benefit may be greatest in patients requiring even longer durations of echinocandin therapy than were studied in the phase 3 study. The committee members stated that additional data would be needed to support the Applicant's claims of improved efficacy in other proposed populations with unmet needs, such as patients infected with *Candida* spp. with reduced susceptibility to other echinocandins or those with deep tissue infections. They also recommended that FDA consider noting in the rezafungin labeling that patient populations with higher risk of neurological complications were excluded from the phase 3 study.

The committee member who voted “no” commented that the strength of the evidence of rezafungin’s efficacy was inadequate given the severity of the outcome (mortality) and while the available data were promising, the committee member did not feel that the regulatory standards to support approval were met.

III. Additional Analyses and Information

12. Summary of Regulatory History

During the process of its development, rezafungin (REZ) was known as CD101 and Biafungin.

A Type-B, pre-IND Meeting Request for PIND 124401 was submitted by Cidara Therapeutics, Inc. (Cidara) on October 30, 2014. The purpose of the meeting was to discuss the overall development program for CD101 (for injection) with the proposed indication of treatment of candidemia and invasive candidiasis (IC) in adults caused by susceptible *Candida* spp., including azole-resistant and echinocandin-resistant isolates. A guidance meeting was held on December 19, 2014. On March 10, 2015, Cidara submitted a request for Qualified Infectious Disease Product (QIDP) and Fast Track designations, for CD101 (biafungin) injection product for intravenous (IV) use, indicated for treatment of candidemia and invasive candidiasis. On May 8, 2015, the same product was granted both QIDP and Fast Track designations for the requested indications.

On June 10, 2015, IND 124401 for CD101 injection, was submitted by Cidara to the Division. The IND was indicated for the treatment of candidemia and invasive candidiasis in adults. The Division of Anti-Infectives (DAI) determined that the IND was safe to proceed.

In 2016, rezafungin was granted orphan drug designation for the treatment of candidemia and invasive candidiasis caused by susceptible *Candida* species.

On April 19, 2016, a Type B, end-of-phase 1 meeting was held to discuss the design of a new phase 2 study.

On May 5, 2017, and June 8, 2017, Cidara submitted requests for QIDP and Fast Track designations for CD101 for injection (b) (4) dosage form), indicated for the treatment of candidemia and the treatment of invasive candidiasis. On June 27, 2017, the same product was granted both QIDP and Fast Track designations for the requested indications.

On May 30, 2018, a Type A meeting was held between DAI and Cidara to discuss 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 and the addition of new safety measures in the phase 3 protocol for treatment of candidemia/IC. Given that the neurologic AEs in the monkey study were observed with longer periods of dosing, DAI 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 Cidara was informed that studies using longer rezafungin dosing regimens in their prophylaxis development program could not be initiated under the IND until additional nonclinical data were available for review.

On July 13, 2018, Cidara submitted requests for QIDP and Fast Track designations for rezafungin for injection, indicated for the prevention of invasive fungal infections in adults undergoing allogenic hematopoietic stem cell transplantation. On September 10, 2018, the same product was granted both QIDP and Fast Track designations for the requested indication.

On July 24, 2018, a Type B, end-of-phase 2 meeting was held between DAI and Cidara to discuss the development plan for rezafungin for injection for the treatment of candidemia and invasive candidiasis. A separate, end of phase 2 meeting to discuss the chemistry, manufacturing, and controls (CMC) development plan for rezafungin for injection was held on same day.

On May 1, 2020, a Type A meeting was held to discuss design of the 6-month chronic toxicology study in monkeys and rats and conducting the phase 3 prophylaxis study concurrent with the 6-month chronic toxicology studies. DAI did not agree with initiation of the phase 3 clinical prophylaxis study concurrently given questions regarding the reversibility of tremors and occurrence of axonal degeneration but did note they were willing to consider evaluating safety data (preliminary clinical observations and histology of brain and peripheral nerves) at the end of the 6-month monkey study in addition to any clinical data available at that time.

On July 29, 2020, DAI discussed the rezafungin development program with the CDER medical policy and program review council (MPPRC). The MPPRC agreed with DAI that the risks to the proposed prophylaxis study subjects were not well-characterized for this vulnerable patient population, and thus results from the in-life portion of the 6-month nonhuman primate (NHP) study should be submitted for review prior to initiation of the prophylaxis study under the IND. The outcome of the MPPRC meeting was communicated to Cidara on July 31, 2020.

On April 12, 2021, Cidara requested a Type A meeting to discuss the safety profile of rezafungin following 26 weeks of intravenous administration in chronic toxicology study (NC-190) in monkeys, interim clinical safety data, including neurologic assessments, following 13 weeks of intravenous administration from the phase 3 prophylaxis study (CD101.IV.3.08) conducted ex-U.S., and additional clinical neurologic safety data from expanded access patients. DAI agreed that it was acceptable to initiate the prophylaxis study under the IND concurrent with the ongoing recovery phase from the 6-month toxicology study in monkeys and provided responses to all Cidara's questions in a Meeting Preliminary Responses document on May 7, 2021. Based on these responses, the teleconference was subsequently cancelled at the request of Cidara.

On May 24, 2021, the Division of Medication Error Prevention and Analysis conditionally approved Cidara's proposed proprietary name Rezzayo, for rezafungin acetate (b) (4) powder.

On November 9, 2021, a Type A meeting was held to discuss several issues related to the upcoming NDA filing. The issues discussed included the approach to achieve a 300-patient safety database at the proposed dose and duration for an initial NDA for the treatment of candidemia and IC, (b) (4) The Division did not agree (b) (4)

On January 3, 2022, Cidara requested a pre-NDA meeting to discuss clinical, nonclinical, and regulatory topics related to the upcoming NDA submission. The pre-NDA meeting request included the top-line results from the phase 3 ReSTORE study reporting that the study met the pre-specified 20% noninferiority (NI) margin. FDA provided responses to all Cidara's questions in a Meeting Preliminary Responses document on February 25, 2022. Since preliminary comments adequately addressed all the questions submitted by Cidara and no further feedback was needed from the Division, the teleconference was cancelled at the request of Cidara. On January 28, 2022, Cidara requested a pre-NDA meeting to discuss CMC topics related to the upcoming NDA submission. Based on CMC preliminary responses, provided March 22, 2022, the meeting was cancelled at the request of Cidara.

Cidara Therapeutics, Inc., submitted NDA 217417 for rezafungin acetate for injection, indicated for the treatment of candidemia and invasive candidiasis in adult patients, on July 22, 2022. Cidara requested priority NDA review. The NDA was filed on September 19, 2022, as a new molecular entity. Due to the new molecular entity status and QIDP designation, this NDA is being reviewed under a priority review clock.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Secondary Pharmacology Studies

Study NC-046: In Vitro Pharmacology Study of CD101 (Biafungin) in binding enzyme and uptake assays.

Rezafungin was evaluated in vitro in a panel of 44 receptor-ligand binding and enzyme inhibition assays at 10 μM (NC-046). The panel consisted of 6 enzymes, 29 receptors, 3 neuronal membrane transport proteins, and 6 ion channels. Rezafungin had significant effects on binding (inhibition or stimulation) for the targets shown in the table below (Table 47).

Table 47. Percent Inhibition of Control Specific Binding by Rezafungin and IC_{50} for Uptake Assays

Receptor/Neurotransmitter Uptake Assay	% Inhibition/IC_{50}
5-HT (h) transporter antagonist [3H]imipramine	59%
5-HT2B (h) agonist [125I]2,5-dimethoxy-4-iodoamphetamine	59%
α1A (h) antagonist [3H]prazosin	86%
β1 agonist (h) [3H](-)CGP 12177	84%
CCK1 (CCKA) (h) agonist [125I]CCK-8s	81%
D1 (h) antagonist [3H]SCH 23390	67%
Dopamine transporter (h) antagonist [3H]N-[1-(2-benzo(b)thiophenyl) cyclohexyl]piperidine	80%
H2 (h) antagonist [125I]aminopotentidine	52%
GR (h) agonist [3H]dexamethasone	99%
hERG (membrane preparation) antagonist [3H]astemizole	87%
κ (KOP) (r) agonist [3H]U 69593	52%
M2 (h) antagonist [3H]AF-DX 384	59%
M3 (h) antagonist [3H]4-diphenyl-acetoxy-N-methyl-piperidine	76%
μ (MOP) (h) agonist [3H][D-Ala2, N-MePhe4,Gly-ol]-enkephalin)	95%
Norepinephrine transporter (h) antagonist [3H]nisoxetine	81%
DAT Rat Dopamine Transporter Functional Antagonist Uptake Assay – Dopamine Uptake	IC_{50}=2.93 μM
NET Rat Norepinephrine Transporter Functional Antagonist Uptake Assay – Norepinephrine Uptake	IC_{50}=31.9 μM

Source: Reviewer generated table.
Abbreviation: IC_{50}, half maximal inh bitory concentration

13.1.2. Safety Pharmacology Studies

Table 48. Safety Pharmacology Study Number NC-025: Central Nervous System

Study Features and Methods	Details
Applicant Study number	NC-025
Contract Lab Study Number	(b) (4)-148510
Study title	A 4-Week Once Every 3 Days (9 Doses) Intravenous (Slow Bolus Push) Toxicity and Toxicokinetic Study of CD101 in Sprague Dawley Rats with a 4-Week Recovery Period
Species/Strain	Rats, Sprague Dawley
Number/sex/dose group	15, 10, 10, 15 (males only)
Doses	0, 5, 15, 30, and 45 mg/kg
Route of administration	Intravenous (slow bolus push [3 to 4 minutes])
Dosing frequency	Once every 3 days
Findings	There were no effects on neurobehavioral assessments (modified Irwin screen) and body temperatures conducted in males compared to the control group following administration of 5, 15, or 45 mg/kg/dose rezafungin. Histamine-related signs included impaired equilibrium, blue extremities, increased respiration rate, flattened body, dilated pupil and swollen/purple tongue, swollen ears, facial area, forelimb, hind limbs, reddened ears. These histamine-related clinical signs generally resolved by 2 to 4 hours after dosing, decreased in incidence after the second and third doses, and were typically absent after the fourth dose.

Source: Reviewer generated table.

Table 49. Safety Pharmacology Study Number NC-059: Cardiovascular and Respiratory System

Study Features and Methods	Details
Applicant study number	NC-059
Contract lab study number	(b) (4)-148506
Study title:	CD101: Cardiovascular and Respiratory Assessment following 20-Minute Intravenous Infusion Administrations to Conscious, Radiotelemetry-Instrumented Cynomolgus Monkeys
Species/strain	Macaca fascicularis (Cynomolgus monkeys)
Number/sex/dose group	15, 10, 10, 15
Doses	0, 5, 15, 30, and 45 mg/kg
Route of administration	Rezafungin was administered as a single dose by 20-minute intravenous infusion to 7 groups (Groups 1, 2, 2A, 3, 3A, 4, and 4A) of male cynomolgus monkeys at 0, 1, 0, 3, 0, 10, or 0 mg/kg, respectively. The same 6 monkeys were administered vehicle in Group 1, followed by a washout period of 7 days before the second dose of either rezafungin (Group 2) or vehicle (Group 2A). Following a 21-day washout period between the remaining doses, the same 6 animals were either administered rezafungin in a dose escalating manner (Groups 3 and 4) or vehicle (Groups 3A and 4A). Heart rate, arterial blood pressure (systolic, diastolic, and mean arterial pressure), pulse pressure, body temperature, ECG waveforms (from which the ECG intervals PR, QRS, QT, and heart rate-corrected QT [QTcB] were derived), and respiratory parameters (respiratory frequency [BPM], tidal volume [TV], and minute volume [MV]) were collected.
Dosing frequency	Once every 3 days
Findings	Rezafungin administration was associated with a minimal (-14%), transient (0 to 4 hours) reduction in heart rate, but this finding was not evident 4 hours later. There were no other biologically significant rezafungin-related effects on arterial or pulse pressure parameters, body temperature, ECG waveform morphology, duration of PR, QRS, QT, and QTcB intervals, respiratory parameters, or the clinical condition of the animals.

Source: Reviewer generated table.
Abbreviation: ECG, electrocardiogram

13.1.3. Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics

The absorption, distribution, metabolism, and excretion profile of rezafungin and related compounds was studied in vitro and in vivo in mice, rats, monkeys, rabbits, dogs, and chimpanzees. The information was obtained to validate nonclinical safety studies that provide human risk assessment assistance prior to and during clinical studies.

Absorption

Rezafungin consistently exhibited very low clearance (0.1 to 0.6 mL/min/kg), modest volume of distribution, and long half-life. Exposure to rezafungin was generally dose-proportional with no apparent sex differences. Minimal to moderate accumulation was noted after repeated administrations.

Table 50. Single Dose Pharmacokinetics of Rezafungin

	Mouse	Rat	Monkey	Rabbit
Study	**NC-007**	**NC-006**	**NC-017**	**NC-082**
Doses (mg/kg)	1	5, 15,45	3,10,30	5,15,45,80
Cl (mL/min/kg)	0.1	0.4	0.1-0.2	0.4-0.6
V_{ss} (mL/kg)	254	1160-1570	532-645	719-1970
$T_{1/2}$ (h)	28	35-45	49-58	29-81

Source: Reviewer generated table.
Abbreviations: Cl, clearance; $T_{1/2}$, half-life; V_{ss}, volume of distribution

Table 51. Mean $AUC_{(0-t)}$ (µg*h/mL) Following Single Intravenous Administration of Rezafungin in Rat, Rabbit, and Monkey

	Rat	Monkey	Rabbit
Dose	**NC-006**	**NC-017**	**NC-082**
3		413	
5	183		235
10		1025	
15	499		540
30		3135	
45	1550		958
80			3010

Source: Reviewer generated table
Abbreviation: $AUC_{(0-t)}$, area under the concentration-time curve from zero to time t

Distribution

The steady-state volume of distribution of rezafungin showed a wide range from 254 L/kg in mouse, 532 to 645 L/kg in monkeys, 1,160 to 1,570 in rats, and 719 to 1,970 L/kg in rabbits. The values are up to 2-fold total body water in a rat (approximately 700 mL/kg) suggesting good distribution beyond the plasma compartment. Protein binding of rezafungin was high across different animal species and humans, and ranged between 98% (rat, human) and 99% (mouse, monkey).

Rezafungin concentrations in most tissues were higher than, or similar to, those in blood. The maximum plasma concentration (C_{max}) in blood was observed at 4 hours postdose and concentrations were quantifiable through 1,440 hr postdose. The C_{max} of radioactivity in most tissues was observed either at 4 or 24 hours postdose. Relatively high tissue concentrations were found in the spinal nerve (dorsal root ganglia), adrenal gland (outer medulla), adrenal gland (cortex), stomach (gastric mucosa), liver, adrenal gland (entire), and kidney medulla. Relatively low tissues concentrations were observed in brain tissues, spinal cord, bone, eye (lens), and preputial gland. Many tissues had quantifiable concentrations of radioactivity at 1,440 hours, with highest concentrations being observed in the spinal nerve dorsal root ganglia, spinal nerve, and liver.

Table 52. Tissue Radioactivity PK Parameters in Male Cynomolgus Monkeys Given a Single IV Dose of Rezafungin

Parameters	C_{max} (µg equiv/g)	$T_{1/2}$ (h)	AUC (h*µg equiv/g)
Spinal nerve dorsal root ganglia	114	270	44605
Liver	64	375	39575
Adrenal gland	70	382	23820
Thyroid	32	490	18153
Pituitary gland	54	304	13552
Mesenteric lymph node	47	246	13028
Spleen	50	287	11491
Spinal nerve	12	873	11189
Kidney	48	378	8500
Thymus	38	323	7740
Blood	21	289	3182

Source: Reviewer generated table.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; IV, intravenous; PK, pharmacokinetic; $T_{1/2}$, half-life

Rezafungin concentrations were measurable in milk from lactating F0 females, and in plasma of F1 fetuses. Both plasma and milk concentrations increased with dose.

Table 53. Maternal Plasma, Milk, and Fetal Plasma Rezafungin Concentrations: NC172: An Intravenous (Slow Bolus Push) Study of the Effects of CDIOI Administered Once Every 3 Days on Pre- and Postnatal Development, Including Maternal Function in Rats

Maternal Dose (mg/kg)	5	15	45
F0 maternal plasma GD18 to GD20 (µg/mL)	8.5	20	72
F1 fetal plasma GD18 to GD 20 (µg/mL)	0.2	0.7	2.2
F0 maternal plasma LD8 to LD (10 µg/mL)	6.8	19	58
F0 maternal milk LD8 to LD10 (µg/mL)	1.7	4.1	13

Source: Reviewer generated table.
Abbreviations: GD, gestation day; LD, lactation day

Metabolism

Rezafungin undergoes minimal biotransformation. In vitro metabolism studies showed that rezafungin was stable in liver microsomes from all species tested. A separate cross-species study determined that rezafungin was stable after incubation with intestinal microsomes from rats, dogs, monkeys, and humans. Subsequent [^{14}C] rezafungin studies in the rat and monkey revealed the presence of a few low-level metabolites, namely, hydroxylation of the terphenyl, pentyl ether group of rezafungin, and loss of the pentyl group via O-dealkylation. Parent drug is the primary circulating and major form excreted in feces/bile, and the majority of the low overall urinary excretion was primarily hydroxylated metabolites.

Excretion

In rat studies, excretion into feces predominated with the mean cumulative amount of rezafungin eliminated into the bile/feces over the course of five days accounting for approximately half of the total dose administered. Excretion in bile was roughly half of the amount of radioactivity excreted in feces of bile-duct cannulated rats, indicating direct intestinal secretion of rezafungin is likely.

Table 54. Recovery (%) of Drug-Related Radioactivity Over 120 Hours (NC-134)

Sample	Recovery (% Dose)
Bile	17
Urine	14
Feces	35
Cage rinse	1
Carcass	30
Total	97

Source: Reviewer generated table.
NC-134: Excretion Mass Balance, Pharmacokinetics, and Tissue Distr bution by Quantitative Whole Body Autoradiography in Rats Following a Single Intravenous Administration of [^{14}C]CD101

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Study Title: A 26-Week Once Weekly Intravenous Infusion Toxicity and Toxicokinetic Study of Rezafungin in Mature Cynomolgus Monkeys With a 52-Week Recovery Period

Key Study Findings

- Moderate, severe, whole body, locomotor, and hindlimb tremors were increased in rezafungin treated monkeys, beginning as early as Day 27, and generally not persisting for more than two weeks after the end of dosing.
- Minimal axonal degeneration was observed in the medial plantar nerve of one 30 mg/kg group male at the end of dosing, and in the sural nerve of a single 5 mg/kg female and the medial plantar nerve of a single 30 mg/kg female at the end of the 52-week recovery period
- Sperm concentration, production rate, morphology, and motility were unaffected in monkeys dosed weekly with rezafungin for 11 or 22 weeks with a 52-week recovery period

Table 55. Study Information for 26-Week Once Weekly Intravenous Infusion Toxicity and Toxicokinetic Study of Rezafungin in Mature Cynomolgus Monkeys With a 52-Week Recovery Period

Study Features and Methods	Details
Study number	NC-190
CRO Study number	00148558
Document location	EDR NDA 217417 SDN 12
Conducting laboratory	(b) (4)
Date of study initiation	March 25, 2020
Date of Initiation of Dosing	16 Jun 2020
GLP compliance	Yes
QA report	Yes
Drug lot #	AB002-012
Purity	98%
Doses	0, 5, 15, and 30 mg/kg
Species	*Macaca fascicularis*; of Chinese origin
Number/sex/group (main study)	4
Ages	Males: 6 to 10 years old; Females: 6 to 8 years old

Study Features and Methods	Details
Weights	Males: 6 to 11 kg; Females: 3 to 6 kg
Route	Intravenous infusion into the cephalic vein (with exceptions noted below)
Formulation	0.5% Tween 80, (b) (4)% mannitol, (b) (4) in sterile water for injection adjusted to pH (b) (4)
Dose Volume	3 mL/kg
Infusion duration	Weeks 1 to 5: 1 hour; Weeks 6 to 26: 20 minutes
Number/sex/group (recovery group)	2
Sampling times for pharmacokinetics	Immediately following the completion of infusion and 1, 2, 4, 8, 24, 48, 96, and 168 hours after dosing on Days 1, 92, and 176

Source: Reviewer generated table.
Abbreviations: CRO, contract research organization; GLP, good laboratory practice; QA, quality assurance

Unique Study Design

Once weekly for 4 weeks starting in Week 6, all pretreatment animals were given sham intravenous infusions in the cephalic vein over 60 minutes. As a result of injection site reactions in rezafungin-treated animals, the infusion duration was reduced to 20 minutes (see below). This was followed by a 2-week nondosing observation period.

The study was blinded with respect to treatment and dose group designations regarding the following observations: mortality observations, clinical observations (cage side, detailed, injection site and unscheduled observations), veterinary neurobehavioral examinations, body weights, food consumption evaluation, dose administration, ophthalmic examinations, electrocardiology collections/measurements, nerve conduction measurements/calculations, testicular volume measurements, sperm collection/analysis, clinical pathology and bioanalytical blood collections, necropsies, and macroscopic examinations.

Methods and Results

Mortality

All animals survived until scheduled main study necropsy. Animals were assessed for mortality at least twice daily.

Clinical Signs

During Weeks 1 through 5, intravenous infusion to the cephalic vein or tail vein (Week 5 only) occurred over 60 minutes using an over-the-needle catheter with extension set and a calibrated syringe pump with an appropriately sized dosing syringe. Several animals showed swelling reactions at the cephalic vein/forearm injection site and an increase in difficulty placing catheters into the cephalic vein at Week 4. The tail vein was subsequently utilized for dosing at Week 5. Several animals developed lesions of the tail, (leading to partial tail amputation in some cases). Beginning at Week 6, the tail vein was removed as a possible injection site and the infusion duration was reduced from 60 minutes to 20 minutes (with a few exceptions). In addition, a postdose flush of 2 mL of vehicle was performed immediately following infusion completion. Following implementation of these procedures, only 3 animals were noted with swelling of the forelimb utilized for dosing following infusion. Despite this improvement in injection site

reactions, there continued to be difficulty dosing/placing a catheter into the cephalic vein throughout the dosing period, with the highest incidence in the 30 mg/kg group. Despite these deviations, pharmacokinetics evaluations on Study Days 1, 92 and 196 demonstrated exposure to rezafungin up to between 5-fold and 6-fold the clinical exposure at 30 mg/kg at all time points.

Tremors were observed in all dose groups. See Neurobehavioral Assessments below. Clinical observations were recorded at least once daily and detailed clinical examinations were conducted once weekly, at the time of the neurobehavioral exams.

Body Weights

Bodyweights were reduced by 12 to 32% in 30 mg/kg male monkeys after Day 126 and 11 to 24% lower in 15 mg/kg and 30 mg/kg females after Day 84. Bodyweights were measured weekly in conjunction with the veterinary physical examination.

Food Consumption

There were no rezafungin-related effects on food consumption. Food intake was recorded daily during the morning viability observations.

Ophthalmic Findings

No drug-related ophthalmic lesions were observed in any of the rezafungin-treated groups at the end of the dosing period. Ophthalmic examinations were conducted by a board-certified veterinary ophthalmologist using an indirect ophthalmoscope and slit lamp biomicroscope once during the pretreatment period and once near the end of the dosing period (Week 24).

Electrocardiology

There were no drug-related effects on electrocardiology and heart rates. Electrocardiograms were evaluated once during the pretreatment period and once near the end of the dosing period (Week 24) within 1 hour following the end of infusion. Electrocardiograms and heart rates were recorded on fasted animals anesthetized with ketamine using multi-lead electrocardiogram equipment.

Neurobehavioral Assessments

Tremors were commonly observed when animals were restrained in the dosing chair during the infusion procedure but also observed when animals were moving. The tremors followed no distinct time course. Tremor was observed each day of dosing, but in no animal was generalized tremor observed at every dose.

Table 56. Summary of Generalized Intermittent Tremors in Monkeys (Study NC-190)

Dose Level (mg/kg)	Sex	Involvement	Total Instances	Mean
0	M	5 of 6	59	12
	F	2 of 6	12	6
5	M	5 of 6	41	8
	F	4 of 6	16	4
15	M	5 of 6	30	6
	F	2 of 6	8	4
30	M	6 of 6	67	11
	F	4 of 6	20	5

Source: Reviewer generated table.
Involvement = number of monkeys within a group displaying the sign at least once during the 26-week dosing period.
Mean = the number of occurrences divided by the number of monkeys for which the sign was recorded.
Abbreviations: F, female; M, male

While minimal tremors were observed in all study groups including controls, moderate, severe, whole body, locomotor, and hindlimb tremors were increased in rezafungin-treated monkeys. Minimal tremors were defined as barely perceptible, with no impact on quality of life, ability to grasp/manipulate food, locomotion, gait, or posture. Moderate tremors were easily perceptible, with no impact on quality of life, grasping and manipulating food normally, with normal locomotion and gait, and exhibiting normal posture. Moderate tremors were observed once in one 5 mg/kg monkey (M9016) on Day 69 and on eight occasions in one 15 mg/kg animal (M9002) between Days 63 and 133. Severe tremors were overtly perceptible, clearly affecting quality of life, impacting ability to grasp or manipulate food, impairing ability to move normally, and/or affecting posture. Severe tremors were observed in one 30 mg/kg animal (M9017), Day 152. Tremors were so severe that he missed his mouth a couple of times with treats.

Tremors identified as 'whole body' (generalized, affecting the whole body) were only observed in rezafungin-treated animals: 1 in a 5 mg/kg male (M9006) on Day 453, 76 instances at 15 mg/kg (M9002, Day 63 to 546), and 27 instances at 30 mg/kg (M9017, Days 33 to 180). Locomotor-associated tremors (occurring only during or immediately following locomotion, typically legs) were observed only in rezafungin-treated animals: 1 instance at 5 mg/kg (M9003, Day 110), 60 instances at 15 mg/kg (40 instances in M9002, between Days 63 to 182 and 20 instances in M9009 between Days 27 to 181), and 14 instances at 30 mg/kg (M9004 and M9022 between Days 91 to 182). Hindlimb tremors were observed at 5 mg/kg in 3 instances (once each in animals M9003, M9008 and F9511 on Days 110, 117 and 195 respectively), 20 instances at 15 mg/kg in animal M9009 (Days 27 to 181), and 14 instances at 30 mg/kg (11 instances in M9022 between Days 91 to 182 and 3 instances in M9004 between Days 145 to 180). Drug-related tremors began as early as Day 27 and generally did not persist for more than two weeks after the end of dosing except for a single 15 mg/kg male that showed whole body tremors at the end of the reversibility period.

Table 57. Summary of Individual Observations of Monkey Tremor Recorded During Veterinary Neurological Evaluations (Study NC-190)

Dose mg/kg	Sex	Animal Number	Tremor Count	Day Range	Location	Typical Description
0	M	9005	5	97 to 181	Chair/cage	Intermittent; both arms, in extension
		9010	20	70 to 182	Chair or cage	Intermittent; both arms, in extension
		9011	14	33 to 181	Chair	Intermittent both arms in extension

Dose mg/kg	Sex	Animal Number	Tremor Count	Day Range	Location	Typical Description
		9011	10	194 to 425	Chair	Intermittent both arms in extension
		9020	5	82 to 180	Chair or cage	Intermittent both arms in extension
		9021	1	154	Chair	Intermittent both arms in extension
	F	9502	4	84 to 182	Chair or cage	Intermittent both arms extension
		9502	7	189 to 329	Chair	Intermittent both arms in extension
		9514	1	286	Chair	Intermittent both arms in extension
		9518	1	89	Chair	Intermittent both arms in extension
5	M	9003	1	110	Chair	Intermittent both feet locomotor after flexor reflex
		9006	1	103	Chair	Intermittent both arms intention
		9006	1	453	Chair	Intermittent whole body at rest
		9008	1	117	Chair	Intermittent both legs at rest
		9013	13	62 to 181	Chair or cage	Intermittent both arms in extension and intention
		9016	22	27 to 181	Chair or cage	Intermittent both arms in extension
	F	9510	9	68 to 152	Chair	Intermittent both arms in extension
		9511	13	76 to 181	Chair	Intermittent both arms in extension
		9511	1	195	Chair	Intermittent both feet at rest
		9513	13	75 to 166	Chair or cage	Intermittent both arms in extension
		9516	4	118 to 167	Chair	Intermittent both arms in extension
		9520	1	98	Cage	Intermittent both arms in extension
15	M	9002	40	63 to 182	Chair/cage/pole	Intermittent; both arms, in extension and intermittent; whole body locomotor and twitches; intermittent; upper arms/shoulders
		9002	36	196 to 546	Pole/chair	Intermittent whole body moving from chair to scale
		9007	19	83 to 181	Chair or cage	Intermittent both arms in extension
		9009	20	27 to 181	Chair or cage	Intermittent both arms in extension and intermittent both feet locomotor after flexor reflex
		9014	8	83 to 181	Chair	Intermittent both arms in extension
		9014	2	209, 300	Chair	Intermittent both arms in extension
		9015	1	118	Chair	Twitches intermittent right arm shoulder at rest
		9023	10	96 to 168	Chair or cage	Intermittent both arms in extension
	F	9501	1	287	Cage	Intermittent both arms in extension
		9509	8	56 to 154	Chair or cage	Intermittent both arms in extension
		9512	11	96 to 152	Chair or cage	Intermittent both arms in extension
		9515	2	112 to 147	Chair	Intermittent both arms in extension
		9521	1	90	Chair	Intermittent both arms in extension
		9523	1	208	Cage	Intermittent both arms in extension

Dose mg/kg	Sex	Animal Number	Tremor Count	Day Range	Location	Typical Description
30	M	9004	3	145 to 180	Chair	Intermittent both feet locomotor
		9012	3	105 to 175	Cage	Intermittent both arms in extension
		9017	27	33 to 180	Chair or cage	Intermittent whole body at rest and intermittent both arms in extension and intention
		9019	8	77 to 182	Chair	Intermittent both arms in extension
		9022	11	91 to 182	Chair/Cage/Pole	Intermittent both feet locomotor
		9024	4	75 to 166	Chair	Intermittent both arms in extension
	F	9504	15	62 to 167	Chair or cage	Intermittent both arms in extension
		9504	10	195 to 314	Chair	Intermittent both arms in extension
		9505	8	55 to 153	Chair or cage	Intermittent both arms in extension and intention
		9506	1	133	Chair	Intermittent arm in extension
		9522	9	82 to 180	Chair	Intermittent both arms in extension
		9524	3	110 to 145	Chair or cage	Intermittent both arms in extension
		9524	1	194	Chair	Intermittent both arms extension

Source: Reviewer generated table.
Abbreviations: F, female; M, male

Blinded cage-side observations were conducted for all animals 1 to 3 hours following the end of infusion and at least once daily on nondosing/recovery days. Blinded detailed clinical observations were recorded weekly by the veterinary staff at the time of the neurobehavioral exams. The absence or presence of findings was recorded for individual animals. Neurobehavioral exams included evaluation of fine motor skills, sensory endpoints, general attitude, behavior, motor function, cranial nerves, proprioception and postural reactions, and spinal nerves.

Nerve Conduction Velocity

Sensory and motor nerve conduction velocity (NCV) were within normal physiological range at baseline, Week 13, Week 25, and Week 53 in all animals. There were no statistically or biologically significant changes in NCV or amplitude in the sural or tibial nerve at the Week 13, 25, or 53 timepoint. Although radial NCV and amplitude remained within normal physiological ranges, two 30 mg/kg males showed minimally slower (≥10 m/s) radial conduction velocity at Week 13 and Week 25. For females, a statistically significant decrease from control in radial sensory nerve conduction was noted at mid-dose (15 mg/kg; Group 3) at Week 25 and 1/6, 4/6, 5/6, and 3/6 females in Groups 1, 2, 3, and 4, respectively, displayed slower NCV at Week 25. Further, Female Nos. 9519 (Group 2), 9509 (Group 3), 9501 (Group 3), and 9523 (Group 3) were noted with a reduction of ≥10 m/s in radial. NCV for females 9501 and 9523 were comparable to controls at Week 53 showing recovery from the effect.

Table 58. Group Mean Nerve Conduction Velocity Data for the Radial Nerve in Female Monkeys (Study NC-190)

	Nerve Conduction Velocity in Radial Nerve (m/s)		
Rezafungin Dose (mg/kg)	Baseline	Week 13	Week 25
0	54.5	53.0	52.2
5	54.7	54.1	49.0
15	54.3	49.2	45.5
30	54.8	53.8	50.3

Source: Reviewer generated table.

NCV measurements were obtained once during the pretreatment period, Week 13, and 25. Measurements were also obtained during the recovery period (Week 53) for recovery animals.

Ophthalmic Examination

No rezafungin-related ophthalmic lesions were observed in any of the rezafungin-treated groups at the end of the dosing period. Blinded ophthalmic examinations were conducted once during the pretreatment period and near the end of the dosing period (Week 24).

Testicular Volume

There were no rezafungin-related effects on testicular volume. Testicular volume was measured in all male main study and recovery animals, once during the pretreatment period (within 2 weeks prior to rezafungin administration), during Weeks 13 and 24, and once near the end of the recovery period.

Sperm Analysis

Sperm concentration, production rate, morphology, and motility were unaffected in monkeys dosed weekly with rezafungin for 11 or 22 weeks and during the recovery period. Sperm collection and analysis were conducted in all male main study and recovery animals once during the pretreatment period (within 2 weeks prior to rezafungin administration), during Weeks 11/12 and 22/23 and once near the end of the recovery period.

Hematology

There were no toxicologically significant rezafungin-related effects on hematology parameters.

Coagulation

There were no toxicologically significant rezafungin-related effects on coagulation parameters.

Clinical Chemistry

Alanine aminotransferase (ALT) was minimally increased in males and females at ≥5 mg/kg (up to 1.88x compared to control) and aspartate aminotransferase (AST) was minimally increased in males at ≥15 mg/kg (up to 2.03x compared to control) and females at 30 mg/kg (1.97x compared to control) at Day 184.

Urinalysis

There were no toxicologically significant rezafungin-related effects on urinalysis.

Hematology, coagulation, clinical chemistry, and urinalysis were evaluated in all animals once during the pretreatment and on the day of scheduled necropsy.

Macroscopic Pathology

There were no rezafungin-related macroscopic observations at the terminal necropsy or in recovery animals.

Organ Weights

Relative adrenal gland weights were higher in females (+11 to 19%) and males (+16 to 78%) at all doses at the end of dosing and remained marginally higher at the end of recovery. Besides an increase in eosinophilic globules, there were no microscopic correlates for this observation in the adrenal glands.

Table 59. Relative Adrenal Weights (%Bodyweight) in Male and Female Monkeys at the End of Dosing and Recovery (Study NC-190)

Rezafungin Dose (mg/kg)	0	5 mg/kg	15 mg/kg	30 mg/kg
Males				
Day 185	7.5	9.6 (+28%)	8.6 (+16%)	13.4 (+78%)
Day 547	6.9	9.3 (+33%)	7.8 (+12%)	7.2 (+3%)
Females				
Day 185	13.1	15.5 (+19%)	12.7 (-3%)	14.5 (+11%)
Day 547	12.8	14.8 (+16%)	16.1 (+26%)	14.6 (+14%)

Source: Reviewer generated table.

Higher relative liver/gall bladder weight (%bodyweight) was noted in 30 mg/kg group males (+27%) at the end of dosing but this change was not observed at the end of the recovery period.

Histopathology

Adequate Battery: yes (√), no ()

Peer review: yes (), no (√)

Table 60. Tissue Weighing, Collection, Processing, and Evaluation Table

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Animal ID	-	X	-	-
Artery, aorta	-	X	X	X
Body cavity, nasal	-	X	-	-
Bone with marrow, sternum	-	X	X	X
Bone marrow smear	-	X[a]	-	-
Bone, femur	-	X (1)	X (1)	X (1)
Bone, sternum	-	X	X	X
Brain[g]	X	X	X	X
Epididymis	X (2)	X (2)[b]	X (2)	X (2)
Esophagus	-	X	X	X
Eye[g]	-	X (2)[b]	X (2)	X (2)
Gallbladder	-[c]	X	X	X
Ganglia, trigeminal[g]	-	X	X	X
Ganglion, dorsal root, cervical[g]	-	X	X	X
Ganglion, dorsal root, lumbar[g]	-	X	X	X
Ganglion, superior mesenteric[g]	-	X	X	X
Ganglion, superior cervical[g]	-	X	X	X
Gland, adrenal	X (2)	X (2)	X (2)	X (2)
Gland, lacrimal	-	X (2)	-	-
Gland, mammary	-	X	X	X
Gland, parathyroid	-[d]	X (2)	X (2)	X (2)
Gland, pituitary	X	X	X	X
Gland, prostate	X[f]	X	X	X
Gland, salivary, submandibular	-	X (2)	X (1)	X (1)
Gland, salivary, sublingual	-	X (2)	-	-
Gland salivary, parotid	-	X (2)	-	-
Gland, seminal vesicle	-	X (2)	X (2)	X (2)
Gland, thyroid	X (2)	X (2)	X (2)	X (2)
Gut-associated lymphoid tissue[e]	-	X	X	X
Heart	X	X	X	X
Joint, femorotibial	-	X (1)	X (1)	X (1)
Kidney	X (2)	X (2)	X (2)	X (2)
Large intestine, cecum	-	X	X	X
Large intestine, colon	-	X	X	X
Large intestine, rectum	-	X	X	X
Liver	X	X	X	X
Lung	-	X	X	X
Lymph node, mandibular	-	X (2)	X (1)	X (1)
Lymph node, mesenteric	-	X	X	X
Muscle, skeletal[g]	-	X (2)	X (1)	X (1)
Nerve, medial plantar[g]	-	X	X	X
Nerve, optic[g]	-	X (2)[b]	X (2)	X (2)
Nerve, sciatic[g]	-	X (2)	X (2)	X (2)
Nerve, sural[g]	-	X (2)	X (2)	X (2)
Nerve, tibial[g]	-	X (2)	X (2)	X (2)
Ovary	X (2)	X (2)	X (2)	X (2)
Oviduct	-	X (2)	-	-
Pancreas	-	X	X	X
Site(s), infusion (final)	-	X	X	X
Skin	-	X	X	X
Small intestine, duodenum	-	X	X	X
Small intestine, ileum	-	X	X	X
Small intestine, jejunum	-	X	X	X
Spinal column[g]	-	X	X	X
Spleen	X	X	X	X
Stomach	-	X	X	X
Testis	X (2)	X (2)[b]	X (2)	X (2)
Thymus	X	X	X	X
Tongue	-	X	X	X
Trachea	-	X	X	X
Ureter	-	X (2)	-	-
Urinary bladder	-	X	X	X
Uterus/Cervix	X	X	X	X
Vagina	-	X	X	X

X = Procedure to be conducted. - = not applicable. (1) = one side. (2) = both sides.
Macroscopic abnormalities (gross lesions) in the organs listed and in other organs will be sampled at necropsy, processed for histology and examined microscopically.
[a] Bone marrow smears will be collected from the 5th to 7th rib at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
[b] Eyes and optic nerves are preserved in Davidson's fixative. Testes and epididymides are preserved in modified Davidson's fixative.
[c] From small intestine: Peyer's patch or solitary lymphoid follicle.
[d] Weigh with gland, thyroid.
[e] Weigh with liver.
[f] Seminal vesicles weighed with prostate and submitted whole.
[g] See protocol sections 14.4. and 15.1. on collection, preservation and histologic processing procedures.

Source: Applicant table

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, and/or trigeminal nerve of 5, 15, and 30 mg/kg groups males and females. Electron microscopy confirmed that these findings were consistent with phospholipidosis, and this was not considered adverse.

At the end of dosing, minimal axonal degeneration was noted in the medial plantar nerve of one 30 mg/kg group male. In recovery animals, minimal axonal degeneration 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. Otherwise, there were no other biologically significant histopathological findings in these monkeys.

Toxicokinetics

Weekly intravenous injections of rezafungin at 5, 15, and 30 mg/kg resulted in approximately dose-related increases in rezafungin area under the concentration-time curve (AUC) and C_{max}. Terminal elimination half-life ranged from 50.9 to 78.8 hours in individual animals. Clearance values ranged from 5.30 to 12.7 mL/h/kg in individual animals and Vz values ranged from 456 to 1,000 mL/kg in individual animals.

Table 61. Mean Rezafungin $AUC_{(0-t)}$ in Monkeys Dosed With Rezafungin Once Weekly for 6 Months

Dose	$AUC_{(0-t)}$ (µg*h/mL)		
(mg/kg)	5	15	30
Day 1	489	1460	3030
Day 92	670	2200	4505
Day 176	671	2210	4355

Source: Reviewer generated table
Abbreviation: $AUC_{(0-t)}$, area under the concentration-time curve from zero to time t

Data for males and females were combined since there were no significant pharmacokinetic differences between male and female monkeys. The AUC was evaluated over 168 hours.

Inspection of Contract Laboratory

The Division of Pharmacology/Toxicology for Infectious Diseases requested that the Office of Study Integrity and Surveillance (OSIS) conduct a remote regulatory assessment of this study conducted at [redacted] (b) (4). OSIS scientists virtually reviewed the study from [redacted] (b) (4) and observed that catheters became dislodged for several animals during the infusion of the test systems from May 26, 2020, through November 10, 2020. Due to the unusually high incidence of tremors, even in control animals, the study director was asked about the availability of historical data for tremors in NHP infusion studies. The study director assessment and the vet staff communications indicated that the tremors were largely shivering behavior because of prolonged restraint and infusion of NHPs for up to 60 minutes with a solution equilibrated to room temperature for 45 minutes prior to administration. Per a study communication, the term "tremors" was being used for documenting instances of animals shivering during infusion which implies a different mechanism and cause than a general "tremor." See Section 22 for more details.

Discussion

Rezafungin dosing in adult monkeys was associated increased incidence of moderate, severe, whole body, locomotor, and hindlimb tremors, beginning as early as Day 27 and generally not persisting for more than two weeks after the end of dosing. There were an unusually high number of 'tremors' in all animals, including control animals, compared to previous studies. The cause of this increase in tremors in control animals may be related to the use of the term 'tremors' to include shivering behaviors. Despite the increase in 'tremors' in all groups, the increased incidence of moderate, severe, whole body, locomotor, and hindlimb tremors was clearly drug-related occurring primarily in rezafungin-treated animals.

Adverse histopathology findings included minimal axonal degeneration in the medial plantar nerve of one 30 mg/kg group male at the end of dosing, and in the sural nerve of a single 5 mg/kg female and the medial plantar nerve of a single 30 mg/kg female at the end of the 52-week recovery period. There were no biologically significant effects on nerve conduction in the sural, radial, or tibial nerves. In contrast to data from rat studies (in which rats were dose every three days), there were no adverse effects on the testes of monkeys dosed weekly for 26 weeks at doses up to 6-fold the clinical exposure.

OSIS conducted a Remote Regulatory Assessment of this study (conducted (b) (4) and found objectionable conditions. Specifically, catheters became dislodged for several animals during the infusion of the test systems from May 26, 2020, through November 10, 2020, which resulted in "Undetermined amount of test article dosed outside of the vein." Despite these deviations, pharmacokinetics evaluations on study Days 1, 92, and 196 demonstrated exposure to rezafungin up to between 5-fold and 6-fold the clinical exposure at 30 mg/kg at all time points.

Study Number/Title: NC-191: A 26-Week Once Weekly Intravenous (Slow Bolus) Toxicity and Toxicokinetic Study of Rezafungin in Rats With a 26-Week Recovery Period

Key Study Findings

- Transient histamine-related clinical signs were recorded shortly after the end of dosing, at all doses (including low carriage, decreased activity, swollen forelimb, hindlimb, cranium, muzzle, increased respiration rate, labored breathing) but these signs were less severe after about two months.
- Nerve fiber/axonal degeneration increased in incidence and severity in the 25 and 45 mg/kg groups and persisted at the end of the recovery period.
- No adverse effects were observed in the testes.

Table 62. Study Information for a 26-Week Once Weekly Intravenous (Slow Bolus) Toxicity and Toxicokinetic Study of Rezafungin in Rats With a 26-Week Recovery Period

Study Features and Methods	Details
Document location	EDR NDA 217417 SDN 12
Conducting laboratory	(b) (4)
Date of study initiation	21 Apr 2020
GLP compliance	Yes
QA report	Yes
Drug, lot #	Q000003397
Purity	86.2%
Doses	0, 10, 25, and 45 mg/kg
Species/strain	*Rattus norvegicus*, Sprague Dawley
Number/sex/group	10
Age	7 weeks old
Weight	147 to 220 g, females; 169 to 285 g, males
Route	Intravenous
Formulation	2.5% Tween® 80, (b) (4)% mannitol, (b) (4) in sterile water, adjusted to pH (b) (4)
Dose volume	5 mL/kg
Infusion rate	Slow bolus: 3 to 5 minutes duration
Number/sex/group recovery group	5

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; QA, quality assurance

Methods and Results

Mortality

There were no rezafungin-related deaths. All main study animals survived to the scheduled terminal necropsy. One 45 mg/kg male died on Day 1 after dosing and one 10 mg/kg male was sacrificed moribund on Day 133. One 10 mg/kg animal was euthanized on Day 299 with a lymphoma and one control female was euthanized on Day 330.

Clinical Signs

Rezafungin-related clinical observations were noted shortly after dosing completion during the dosing period in all groups. Findings included low carriage, decreased activity, swollen forelimb, hindlimb, cranium, muzzle, increased respiration rate, labored breathing, incoordination, blue, discolored skin on forelimb, forepaw, hindlimb, hind paw, pinna, and urogenital areas. Most of these signs were reduced by Day 64, but low carriage and decreased activity persisted for the remainder of the dosing period. No drug-related clinical signs were observed during the recovery period.

Body Weights

There were no toxicologically significant changes in body weight.

Food Consumption

Food consumption was sporadically reduced at several intervals but reduction in food consumption was marginal, up to (-18%).

Ophthalmoscopy

There were no rezafungin-related ophthalmic lesions in any of the rezafungin-treated groups at Week 26 and so a reversibility evaluation was not conducted. Ophthalmoscopy examinations were conducted once during the pretreatment period and once near the end of the dosing period (during Week 25 or 26).

Hematology

Platelet count was increased (+18%) at the end of dosing in the 45 mg/kg females but this effect was not observed at the end of the reversibility period.

Clinical Chemistry

ALT activity was increased (2x) in the 45 mg/kg group males at the end of dosing on Day 183 but this effect was not observed on Day 365 (end of the reversibility period).

Urinalysis

There were no rezafungin-related urinalysis findings in any of the rezafungin-treated groups.

Clinical pathology samples for hematology, clinical chemistry, coagulation, and urinalysis were collected on the day of scheduled necropsy in main study and recovery animals.

Functional Observational Battery

There were no rezafungin-related effects detected in the functional observational battery in males, including, home cage observations, handling observations, open field observations, sensory observations, neuromuscular observations, and physiological observations. Functional observational battery data were collected pretest, and Weeks 13, 26, and 48.

Gross Pathology

There were no rezafungin-related gross changes. One 10 mg/kg male rat (#2001) had a focal raised yellow lesion on the right epididymis (2x3x4 mm) which correlated with a focally extensive sperm granuloma.

Organ Weights

Pituitary gland weight was decreased by 20 to 28% in females (but not males) at the end of dosing in all rezafungin-treated groups. There were no histopathological correlates.

Table 63. Pituitary Gland Weight in Rezafungin-Treated Rats After 26 Weekly Doses (Study NC-191)

	Pituitary Gland Weight (g)			
Rezafungin Dose (mg/kg)	**0**	**10**	**25**	**45**
Female	0.032	0.026	0.023*	0.024*
Male	0.017	0.017	0.017	0.016

Source: Reviewer generated table
[G] - Anova & Dunnett: * = p≤0.05

Table 64. Tissue Weighing, Collection, Processing, and Evaluation Table, Study NC-191

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Animal ID	-	X	-	-
Artery, aorta	-	X	X	X
Body cavity, nasal	-	X	-	-
Bone with marrow, sternum	-	X	X	X
Bone marrow smear	-	X[a]	-	-
Bone, femur	-	X (1)	X (1)	X (1)
Bone, sternum	-	X	X	X
Brain[g]	X	X	X	X
Epididymis	X (2)	X (2)[b]	X (2)	X (2)
Esophagus	-	X	X	X
Eye[g]	-	X (2)[b]	X (2)	X (2)
Ganglion, cervicothoracic[g]	-	X	X	X
Ganglion, dorsal root, cervical[g]	-	X	X	X
Ganglion, dorsal root, lumbar[g]	-	X	X	X
Ganglion, dorsal root, sacral[g]	-	X	X	X
Ganglion, dorsal root, thoracic[g]	-	X	X	X
Ganglion, trigeminal[g]	-	X	X	X
Gland, adrenal	X (2)	X (2)	X (2)	X (2)
Gland, clitoral	-	X (2)	-	-
Gland, lacrimal	-	X (2) (extra-orbital)	-	-
Gland, Harderian	-	X (2)	X (1)	X (1)
Gland, mammary	-	X	X	X
Gland, parathyroid	-[e]	X (2)	X (2)	X (2)
Gland, pituitary	X	X	X	X
Gland, preputial	-	X (2)	-	-
Gland, prostate	X[f]	X	X	X
Gland, salivary, submandibular	-	X (2)	X (1)	X (1)
Gland, salivary, sublingual	-	X (2)	-	-
Gland salivary, parotid	-	X (2)	-	-
Gland, seminal vesicle	-	X (2)	X (2)	X (2)
Gland, thyroid	X (2)	X (2)	X (2)	X (2)
Gland, Zymbal's	-	X (2)	-	-
Gut-associated lymphoid tissue[d]	-	X	X	X
Heart	X	X	X	X
Joint, femorotibial	-	X (1)	X (1)	X (1)
Kidney	X (2)	X (2)	X (2)	X (2)
Large intestine, cecum	-	X	X	X
Large intestine, colon	-	X	X	X
Large intestine, rectum	-	X	X	X
Larynx	-	X	-	-
Liver	X	X	X	X
Lung	-	X	X	X

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Lymph node, mandibular	-	X (2)	X (1)	X (1)
Lymph node, mesenteric	-	X	X	X
Muscle, skeletal[g]	-	X (2)	X (1)	X (1)
Nerve, optic[g]	-	X (2)[b]	X (2)	X (2)
Nerve, sciatic[g]	-	X (2)	X (1)	X (1)
Nerve, sural[g]	-	X (2)	X (1)	X (1)
Nerve, tibial[g]	-	X (2)	X (1)	X (1)
Ovary	X (2)[e]	X (2)	X (2)	X (2)
Oviduct	-	X (2)	-	-
Pancreas	-	X	X	X
Site(s), administration: final injection site	-	X	X	X
Skin[h]	-	X	X	X
Small intestine, duodenum	-	X	X	X
Small intestine, ileum	-	X	X	X
Small intestine, jejunum	-	X	X	X
Spinal column[g]	-	X	X	X
Spleen	X	X	X	X
Stomach	-	X	X	X
Testis	X (2)	X (2)[b]	X (2)	X (2)
Thymus	X	X	X	X
Tongue	-	X	X	X
Trachea	-	X	X	X
Ureter	-	X (2)	-	-
Urinary bladder	-	X	X	X
Uterus/Cervix	X	X	X	X
Vagina	-	X	X	X

X = Procedure to be conducted. - = not applicable. (1) = one sid; (2) = both sides.
Macroscopic abnormalities (gross lesions) in the organs listed and in other organs will be sampled at necropsy, processed for histology and examined microscopically.

[a] Two bone marrow smears will be collected from the sternum at scheduled and unscheduled necropsies (for possible examination) prior to perfusion. Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
[b] Eyes and optic nerves are preserved in Davidson's fixative. Testes and epididymides are preserved in modified Davidson's fixative.
[c] Weigh with gland, thyroid.
[d] From small intestine: Peyer's patch or solitary lymphoid follicle.
[e] Ovary weighed with oviducts.
[f] Seminal vesicles weighed with prostate and submitted whole.
[g] See protocol sections 13.4. and 14.1. on collection, preservation and histologic processing procedures.
[h] To include plantar biopsy (see Attachment C).

Source: Applicant's table from study report

Histopathology

Adequate Battery: yes (√)

Peer review: yes () no (√)

Rezafungin related changes were observed in the peripheral nervous system of high dose rats at the end of dosing, including increased incidence of minimal nerve fiber degeneration and/or axonal degeneration in the ventral nerve root of the cervical spinal cord, dorsal nerve root of the lumbar spine, the ventral nerve root of the sacral spinal cord, dorsal nerve root of the cervical spinal cord, ventral nerve root of the thoracic spinal cord, and the tibial nerve.

The peripheral nervous system effects of rezafungin were not reversible after a 26-week reversibility period since rezafungin-related histopathology findings at the end of the recovery period were observed in both sexes. Findings with increased incidence or severity in high dose animals compared to controls included increased nerve fiber degeneration and/or axonal

degeneration in the dorsal and ventral nerve roots of the cervical spinal cord, dorsal nerve root of the thoracic spinal cord, dorsal nerve root of the lumbar spinal cord, dorsal and ventral nerve roots of the sacral spinal cord as well as the sciatic, tibial, and sural nerves.

Table 65. Incidence and Severity of Rezafungin-Related Microscopic Findings in Peripheral Nervous System Tissues- Males, Study NC-191

	Main Study – Males				Recovery Study – Males			
Dose Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose Level (mg/kg)	0	10	25	45	0	10	25	45
Dorsal Nerve Root, Spinal, Cervical	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber[1]	0*	1	0	1	0	0	5	4
Minimal	-	1	-	1	-	-	5	3
Mild	-	-	-	-	-	-	-	1
Eosinophilic Globules[1]	0	0	10	8	0	0	0	2
Minimal	-	-	10	5	-	-	-	2
Mild	-	-	-	3	-	-	-	-
Inclusion[2]	0	0	5	10	0	0	0	4
Minimal	-	-	3	5	-	-	-	4
Mild	-	-	2	3	-	-	-	-
Moderate	-	-	-	2	-	-	-	-
Ventral Nerve Root, Spinal, Cervical	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal[2]	0	0	0	0	0	0	0	2
Minimal	-	-	-	-	-	-	-	2
Degeneration, Nerve Fiber	0	0	0	1	0	0	0	1
Minimal	-	-	-	1	-	-	-	1

	Main Study – Males				Recovery Study – Males			
Dose Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose Level (mg/kg)	0	10	25	45	0	10	25	45
Inclusion	0	0	0	1	0	0	0	0
Minimal	-	-	-	1	-	-	-	-
Dorsal Nerve Root, Spinal, Thoracic	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber	1	0	1	0	0	0	1	3
Minimal	1	-	1	-	-	-	1	3
Eosinophilic Globules	0	0	10	10	0	0	0	1
Minimal	-	-	8	5	-	-	-	1
Mild	-	-	2	5	-	-	-	-
Ventral Nerve Root, Spinal, Thoracic	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber	0	0	2	0	0	0	1	0
Minimal	-	-	2	-	-	-	1	-
Eosinophilic Globules	0	0	0	3	0	0	0	0
Minimal	-	-	-	3	-	-	-	-
Dorsal Nerve Root, Spinal, Lumbar	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal	0	0	0	1	0	0	0	3
Minimal	-	-	-	1	-	-	-	3
Degeneration, Nerve Fiber	0	1	1	0	1	2	2	4
Minimal	-	1	1	-	1	2	2	4
Eosinophilic Globules[1]	0*	0	9	10	0	0	0	3
Minimal	-	-	8	7	-	-	-	3
Mild	-	-	1	3	-	-	-	-
Inclusion[2]	0	0	5	10	0	0	0	3
Minimal	-	-	4	8	-	-	-	3
Mild	-	-	1	1	-	-	-	-
Moderate	-	-	-	1	-	-	-	-
Ventral Nerve Root, Spinal, Lumbar	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber[1]	0	0	0	1	1	1	1	0
Minimal	-	-	-	1	1	1	1	-
Eosinophilic Globules	0	0	0	2	0	0	0	0
Minimal	-	-	-	2	-	-	-	-
Dorsal Nerve Root, Spinal, Sacral	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber	3	2	0	1	4	3	5	5
Minimal	3	2	-	1	4	2	3	1
Mild	-	-	-	-	-	1	2	4
Eosinophilic Globules	0	0	9	10	0	0	0	2
Minimal	-	-	8	7	-	-	-	2
Mild	-	-	1	3	-	-	-	-
Ventral Nerve Root, Spinal, Sacral	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber	0	0	0	2	1	3	1	4
Minimal	-	-	-	2	1	2	1	3
Mild	-	-	-	-	-	-	-	1
Moderate	-	-	-	-	-	1[3]	-	-
Eosinophilic Globules	0	0	0	1	0	0	0	0
Minimal	-	-	-	1	-	-	-	-
Ganglion, Cervicothoracic	**10**	**7**	**10**	**9**	**3**	**4**	**5**	**5**
Nerve/Eosinophilic Globules	0	0	3	9	0	0	0	0
Minimal	-	-	3	9	-	-	-	-
Degeneration, Nerve Fiber	0	0	0	0	0	0	0	1
Minimal	-	-	-	-	-	-	-	1
Ganglion, Trigeminal	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**

	Main Study – Males				Recovery Study – Males			
Dose Group	1	2	3	4	1	2	3	4
Dose Level (mg/kg)	0	10	25	45	0	10	25	45
Inclusion[2]	0*	0	4	10	0	0	0	0
Minimal	-	-	3	8	-	-	-	-
Mild	-	-	1	1	-	-	-	-
Moderate	-	-	-	1	-	-	-	-
Nerve, Sciatic	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal[2]	1	0	0	0	1	2	1	4
Minimal	1	-	-	-	1	2	1	4
Degeneration, Nerve Fiber[1]	3	1	1	1	4	4	5	4
Minimal	3	1	1	1	4	4	4	1
Mild	-	-	-	-	-	-	1	3
Inclusion	0	0	0	5	0	0	0	2
Minimal	-	-	-	5	-	-	-	2
Nerve/Eosinophilic Globules[1]	0	0	1	6	0	0	0	0
Minimal	-	-	1	6	-	-	-	-
Nerve, Tibial	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal	0	0	0	0	0	1	1	4
Minimal	-	-	-	-	-	1	1	3
Mild	-	-	-	-	-	-	-	1
Degeneration, Nerve Fiber	0	1	1	0	4	3	3	5
Minimal	-	1	1	-	4	3	2	2
Mild	-	-	-	-	-	-	1	3
Inclusion	0	0	0	4	0	0	0	2
Minimal	-	-	-	2	-	-	-	2
Mild	-	-	-	2	-	-	-	-
Nerve/Eosinophilic Globules	0	0	0	4	0	0	0	1
Minimal	-	-	-	4	-	-	-	1
Nerve, Sural	**8**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal	0	0	0	0	0	0	1	1
Minimal	-	-	-	-	-	-	1	1
Degeneration, Nerve Fiber	0	1	0	0	1	2	4	5
Minimal	-	1	-	-	1	2	4	5
Inclusion[2]	0*	0	0	4	0	0	0	1
Minimal	-	-	-	2	-	-	-	1
Mild	-	-	-	2	-	-	-	-
Nerve/Eosinophilic Globules[1]	0	0	1	6	0	0	0	0
Minimal	-	-	1	6	-	-	-	-

*A value of "0" indicates that there were no animals with the diagnosis for the specified dose group. A value of "-" indicates that the grade for the diagnosis was non-applicable.
[1] Diagnosed on paraffin-embedded, H&E-stained sections.
[2] Diagnosed on osmicated, resin-embedded, TB-stained sections.
[3] Due to lymphoma; not rezafungin-related.

Source: Applicant's table from study report

Table 66. Incidence and Severity of Rezafungin-Related Microscopic Findings in Peripheral Nervous System Tissues – Females, Study NC-191

	Main Study – Females				Recovery Study – Females			
Dose Group	1	2	3	4	1	2	3	4
Dose Level (mg/kg)	0	10	25	45	0	10	25	45
Dorsal Nerve Root, Spinal, Cervical	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal[2]	0*	0	0	0	0	0	0	1
Minimal	-	-	-	-	-	-	-	1
Degeneration, Nerve Fiber[1]	0	1	1	3	0	0	1	3
Minimal	-	1	1	3	-	-	1	3
Eosinophilic Globules[1]	0	0	10	10	0	0	0	0
Minimal	-	-	9	7	-	-	-	-
Mild	-	-	1	3	-	-	-	-
Inclusion[2]	1	0	9	10	0	0	0	2
Minimal	1	-	9	5	-	-	-	2
Mild	-	-	-	4	-	-	-	-
Moderate	-	-	-	1	-	-	-	-
Ventral Nerve Root, Spinal, Cervical	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber	0	0	0	1	0	0	0	0
Minimal	-	-	-	1	-	-	-	-
Eosinophilic Globules	0	0	0	4	0	0	0	0
Minimal	-	-	-	4	-	-	-	-
Dorsal Nerve Root, Spinal, Thoracic	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber	0	1	0	1	2	0	0	0
Minimal	-	1	-	1	2	-	-	-
Eosinophilic Globules	0	1	9	10	0	0	0	0
Minimal	-	1	9	6	-	-	-	-
Mild	-	-	-	4	-	-	-	-
Ventral Nerve Root, Spinal, Thoracic	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber	1	0	0	2	1	0	0	0
Minimal	1	-	-	2	-	-	-	-
Mild	-	-	-	-	1	-	-	-
Eosinophilic Globules	0	0	0	4	0	0	0	0
Minimal	-	-	-	4	-	-	-	-
Dorsal Nerve Root, Spinal, Lumbar	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal	0	1	1	0	0	0	0	0
Minimal	-	1	1	-	-	-	-	-
Degeneration, Nerve Fiber	3	1	2	3	2	1	1	2
Minimal	3	1	2	3	2	1	1	2
Eosinophilic Globules[1]	0*	0	9	10	0	0	0	0
Minimal	-	-	9	8	-	-	-	-
Mild	-	-	-	2	-	-	-	-
Inclusion[2]	0	0	8	10	0	0	1	1
Minimal	-	-	7	5	-	-	1	1
Mild	-	-	1	4	-	-	-	-
Moderate	-	-	-	1	-	-	-	-
Ventral Nerve Root, Spinal, Lumbar	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber[1]	3	1	0	2	1	2	1	1
Minimal	3	1	-	2	1	2	1	1
Eosinophilic Globules	0	0	0	3	0	0	0	0

	Main Study – Females				Recovery Study – Females			
Dose Group	1	2	3	4	1	2	3	4
Dose Level (mg/kg)	0	10	25	45	0	10	25	45
Minimal	-	-	-	3	-	-	-	-
Dorsal Nerve Root, Spinal, Sacral	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber	2	3	3	1	2	2	1	5
Minimal	2	3	3	1	1	2	1	2
Mild	-	-	-	-	1	-	-	3
Eosinophilic Globules	0	0	9	10	0	0	0	0
Minimal	-	-	8	9	-	-	-	-
Mild	-	-	1	1	-	-	-	-
Inclusion	0	0	0	1	0	0	0	0
Minimal	-	-	-	1	-	-	-	-
Ventral Nerve Root, Spinal, Sacral	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Nerve Fiber	1	1	2	0	2	0	1	2
Minimal	1	1	2	-	2	-	1	2
Ganglion, Cervicothoracic	**10**	**8**	**9**	**10**	**3**	**5**	**5**	**5**
Nerve/Eosinophilic Globules	0	0	0	8	0	0	0	0
Minimal	-	-	-	8	-	-	-	-
Ganglion, Trigeminal	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Inclusion	0	0	7	9	0	0	0	0
Minimal	-	-	7	7	-	-	-	-
Mild	-	-	-	2	-	-	-	-
Nerve, Sciatic	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal[2]	0	0	0	0	0	0	0	3
Minimal	-	-	-	-	-	-	-	2
Mild	-	-	-	-	-	-	-	1
Degeneration, Nerve Fiber[1]	2	3	5	5	4	2	2	5
Minimal	2	3	5	5	4	2	2	3
Mild	-*	-	-	-	-	-	-	2
Inclusion[2]	0	0	0	4	0	0	0	0
Minimal	-	-	-	4	-	-	-	-
Nerve/Eosinophilic Globules[1]	0	0	1	3	0	0	0	0
Minimal	-	-	1	3	-	-	-	-
Nerve, Tibial	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal[2]	1	0	0	1	0	0	0	2
Minimal	1	-	-	1	-	-	-	1
Mild	-	-	-	-	-	-	-	1
Degeneration, Nerve Fiber	1	1	1	4	2	3	1	4
Minimal	1	1	1	4	2	3	1	1
Mild	-	-	-	-	-	-	-	3
Inclusion	0	0	0	5	0	0	0	0
Minimal	-	-	-	5	-	-	-	-
Nerve/Eosinophilic Globules	0	0	0	8	0	0	0	0
Minimal	-	-	-	8	-	-	-	-
Nerve, Sural	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**
Degeneration, Axonal	0	0	0	0	0	0	0	1
Minimal	-	-	-	-	-	-	-	1
Degeneration, Nerve Fiber	0	0	2	0	1	1	0	3
Minimal	-	-	2	-	1	1	-	1
Mild	-	-	-	-	-	-	-	2
Inclusion	0	0	1	4	0	0	1	0
Minimal	-	-	1	4	-	-	1	-

Source: Applicant's table from study report
A value of "0" indicates that there were no animals with the diagnosis for the specified dose group.
A value of "-" indicates that the grade for the diagnosis was nonapplicable.
[1] Diagnosed on paraffin-embedded, H&E-stained sections.
[2] Diagnosed on osmicated, resin-embedded, TB-stained sections.

Minimal eosinophilic globules, and/or intracytoplasmic inclusions were observed in Schwann cells in spinal nerve roots, other peripheral nerves (sciatic, tibial, and sural), and nerves in other tissues at all doses in both sexes. Eosinophilic globules were small, round, red (binding the eosin stain), intracytoplasmic inclusions in Schwann cells in spinal nerve roots, other peripheral nerves

(sciatic, tibial, and sural), and nerves in other tissues. Inclusions were small, rounded, blue, well-demarcated, intracytoplasmic structures consistent with lysosomes containing lipid/phospholipid. Inclusions appeared to be exclusively within Schwann cells.

There were no rezafungin-related changes in the testes.

Toxicokinetics

Exposure to rezafungin (AUC_{tlast}) increased in an approximately dose proportional manner from 10 to 45 mg/kg on Days 1, 92, and 176.

Table 67. Summary of Toxicokinetic Parameters, Study NC-191

	AUC µg*h/mL			C_{max} µg/mL		
Dose	**Day 1**	**Day 92**	**Day 176**	**Day 1**	**Day 92**	**Day 176**
Males						
10 mg/kg	323	659	726	27	41	45
25 mg/kg	762	1690	1760	66	123	126
45 mg/kg	1470	3360	3560	150	274	290
Females						
10 mg/kg	310	584	661	29	51	55
25 mg/kg	819	1520	1600	93	122	125
45 mg/kg	1480	2830	2940	194	228	251

Source: Reviewer's table
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration

Summary

In rats dosed weekly for 26 weeks, intravenous rezafungin was associated with transient histamine-related clinical signs, shortly after dosing completion, at all doses. These clinical signs improved after 2 months. Histamine-related findings are a known adverse effect of the echinocandin class. Minimal eosinophilic globules, and/or intracytoplasmic inclusions were observed in Schwann cells in spinal nerve roots, other peripheral nerves (sciatic, tibial, and sural), and nerves in other tissues at all doses in both sexes, but these findings were considered to be nonadverse. Neurotoxicity, including axonal and nerve fiber degeneration were observed at 25 and 45 mg/kg (about 2- and 4-fold the clinical dose based on AUC comparison) and these persisted to the end of the 26-week reversibility period. No adverse histopathology effects were observed in the testes. This reviewer disagrees with the Applicant's conclusion that the no observed adverse effect level was 45 mg/kg. If the histamine-related clinical findings are not considered adverse, this reviewer considers the no observed adverse effect level to be 10 mg/kg, which was similar to the human dose based on AUC comparisons.

13.2.1. Reproductive and Developmental Toxicology

13.2.1.1. Fertility and Early Embryonic Development

Study Title/ Number. Study NC-081: An Intravenous (Slow Bolus Push) Fertility and Early Embryonic Development to Implantation Study of CD1O1 Administered Once Every 3 Days in Female Sprague Dawley Rats

Key Study Findings

- In female rats, there were no biologically significant drug-related effects on mating, fertility index, preimplantation loss, postimplantation loss, mean numbers of viable embryos, corpora lutea, and implantation sites.

Table 68. Study Information for Study NC-081: An Intravenous (Slow Bolus Push) Fertility and Early Embryonic Development to Implantation Study of CD1O1 Administered Once Every 3 Days in Female Sprague Dawley Rats

Study Features and Methods	Details
Dose and frequency of dosing:	Rezafungin was dosed at 5, 15, and 45 mg/kg/dose, at a dose volume of 5 mL/kg. The females were dosed every 3 days (study days 0, 3, 6, 9, and 12) prior to cohabitation and until gestation day 7 for a total of 8 to 12 doses
Route of administration:	Intravenous injection (slow bolus push over a 3-4-minute period, once every 3 days)
Formulation/vehicle:	2.5% Tween® 80, (b) (4)% mannitol, and (b) (4) [pH adjusted to (b) (4))
Species/strain:	Crl:CD(SD) rats.
Study design:	**Table 69. Study Design for Study NC-081** Group Number / Treatment / Dosage Level (mg/kg/dose) / Dose Volume (mL/kg) / Number of Males[a] / Number of Females 1 / Vehicle control / 0 / 5 / 25 / 25 2 / CD101 / 5 / 5 / 25 / 25 3 / CD101 / 15 / 5 / 25 / 25 4 / CD101 / 45 / 5 / 25 / 26[b] [a] = Males were not administered the vehicle or test article and were used for breeding purposes only. [b] = An additional female (no. 2528) was assigned to the 45 mg/kg/dose group due to the early euthanasia of another female (no. 2571) in this group on study day 3. Source: Applicant table.
Deviation from study protocol affecting interpretation of results:	No
GLP compliance:	Yes
Conducting laboratory and location:	(b) (4)

Source: Reviewer generated table.
Abbreviation: GLP, good laboratory practices

Table 70. Observations and Results for Study NC-081: An Intravenous (Slow Bolus Push) Fertility and Early Embryonic Development to Implantation Study of CD1O1 Administered Once Every 3 Days in Female Sprague Dawley Rats

Parameters	Major Findings
Mortality	15 mg/kg: 2 Deaths 45 mg/kg: 3 Deaths
Clinical signs	At 15 mg/kg and 45 mg/kg, ataxia, hypoactivity, and/or dilated pupils. were generally noted within a few minutes following dose administration, with some persisting through 1 to 2 hours post-dosing.
Body weights	Drug-related changes were slight and transient
Necropsy findings	There were no biologically significant drug-related effects on mating, fertility index, pre-implantation loss, post-implantation loss, mean numbers of viable embryos, corpora lutea, and implantation sites.

Source: Reviewer generated table

13.2.1.2. Fertility and Early Embryonic Development

Study Title/Number. Study NC-116: An Intravenous (Slow Bolus Push) Fertility Study of CD l 01 Administered Once Every 3 Days in Male Sprague Dawley Rats

Key Study Findings

- No rezafungin-related effects on mating/fertility index after 4 weeks of dosing
- Adverse effects on sperm motility, sperm morphology, with seminiferous tubule degeneration, and increased cellular debris in the epididymis with no detectible motile sperm in many rats at 45 mg/kg

There were no adverse effects on sperm parameters at 15 mg/kg.

Table 71. Study Information for Study NC-116: An Intravenous (Slow Bolus Push) Fertility Study of CD l 01 Administered Once Every 3 Days in Male Sprague Dawley Rats

Study Features and Methods	Details
Dose and frequency of dosing:	Rezafungin was administered to male rats at 15, 30, and 45 mg/kg/dose, at a dose volume of 5 mL/kg, every 3 days beginning 4 weeks prior to the start of mating (for a total of 10 doses) and continuing every 3 days throughout the mating period until 1 day prior to euthanasia for a total of 21 to 22 doses. The females were not dosed.
Route of administration:	Intravenous injection (slow bolus push over a 3 to 4-minute period, once every 3 days)
Formulation/vehicle:	2.5% Tween® 80 (b) (4)% mannitol, and (b) (4) [pH adjusted to (b) (4)])
Species/strain:	Crl:CD(SD) rats.

Study Features and Methods	Details
Study design:	**Table 72. Study Design for Study NC-116**

Group Number	Treatment	Dosage Level (mg/kg/dose)	Dose Volume (mL/kg)	Number of Animals	
				Males	Naïve Females [a]
1	Vehicle	0	5	25	25
2	CD101	15	5	25	25
3	CD101	30	5	25	25
4	CD101	45	5	29[b]	25

[a] Females were not administered vehicle or test article and were used for breeding purposes only.
[b] Additional males (Nos. 4251, 4252, 4268, and 4233) were assigned to the 45 mg/kg/dose group due to the early euthanasia of Male Nos. 4199, 4182, 4258, and 4236 in this group on Study Day 3.

Source: Applicant Table

Deviation from study protocol affecting interpretation of results:	No
GLP compliance:	Yes
Conducting laboratory and location	(b) (4)

Source: Reviewer generated table.
Abbreviation: GLP, good laboratory practices

Table 73. Observations and Results for Study NC-116: An Intravenous (Slow Bolus Push) Fertility Study of CD I 01 Administered Once Every 3 Days in Male Sprague Dawley Rats

Parameters	Major Findings
Mortality	15 mg/kg: 4 Deaths 30 mg/kg: 1 Death 45 mg/kg: 5 Deaths One male in the 45 mg/kg/dose group and three males in the 15 mg/kg/dose group were found dead following the first dose (Study Day 0 or 1). In addition, 1 and 4 males in the 30 and 45 mg/kg/dose groups, were euthanized in extremis on Study Day 3, prior to the second dose, due to the poor condition of their tails (blackened and/or swollen). One of the 15 mg/kg males was euthanized on Day 59 due to the impaired use of the right hindlimb.
Clinical signs	Ataxia, hypoactivity, swollen facial area, swollen forelimbs and hindlimbs, and reddened ears were noted in all test article-treated groups following dose administration
Body weights	Body weight gain was reduced by 11 to 17% in all rezafungin-treated animals between Day 0 to 27.

Parameters	Major Findings
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etic]*	There was no rezafungin-related effect on the mating/fertility index of rats. Decreased sperm motility was noted at ≥30 mg/kg, and most males at 45 mg/kg had no detectable motile sperm. Changes in sperm morphology were observed at ≥30 mg/kg and included increased incidences of sperm with abnormal morphology. Microscopic findings included degeneration of the seminiferous tubules within the testes at 30 mg/kg and in all males at 45 mg/kg. Change was also noted within the epididymides at ≥30 mg/kg. In the testes, retained spermatids were noted at the surface of the germinal epithelium and basement membrane in all animals at 45 mg/kg and in 20/24 animals at 30 mg/kg. In the epididymis, findings of increased cellular debris, hypospermia and/or cribriform changes were noted in all animals at 45 mg/kg and in 21/24 animals at 30 mg/kg.

Source: Reviewer generated table

Table 74. Results of Reproductive Performance in Male Rats

Parameter	Dosage Level (mg/kg/dose)				CRL HC[a] Mean (Range)
	0	15	30	45	
Male Mating Index (%)	100.0	100.0	100.0	100.0	98.9 (92.0-100.0)
Male Fertility Index (%)	100.0	95.5	91.7	91.7	95.3 (84.0-100.0)
Male Copulation Index (%)	100.0	95.5	91.7	91.7	96.7 (88.0-100.0)
Pre-Coital Interval (days)	2.4	2.4	2.8	3.0	2.8 (1.8-4.4)

[a] [redacted] (b) (4) historical control data (version 2017.01)

Source: Applicant table

$$\text{Male mating index (\%)} = \frac{\text{\# of males mating (or females confirmed pregnant)}}{\text{Total \# of males used for mating}} \times 100$$

$$\text{Male fertility index (\%)} = \frac{\text{\# of males siring a litter}}{\text{Total \# of males used for mating}}$$

$$\text{Male copulation index (\%)} = \frac{\text{\# of males siring a litter}}{\text{Total \# of males mating (or females confirmed pregnant)}}$$

Table 75. Rezafungin Effects on Sperm Parameters After IV Rezafungin Every 3 Days in Male Rats

Rezafungin Dose (mg/kg)	0	15	30	45
Male mating index (%)	100	100	100	100
Male fertility index (%)	100	96	92	92
MALE copulation INDEX (%)	100	96	92	92
MEAN PRE-COITAL INTERVALS (days)	2.4	2.4	2.8	3.0
Motility	82	81	72	35
Cauda epid, lt weight (grams)	0.3	0.3	0.3	0.3
Cauda epid, lt concentration (millions/gram)	711	792	654	382[a]
Testis, lt weight (grams)	1.8	1.9	1.8	1.8
Testis, lt concentration (millions/gram)	137	132	138	152
Sperm production rate (millions/gram/day)	23	22	23	25
Normal	99.6	98.7	96.5	89.8*
Normally shaped head Separated from flagellum	0.1	0.5	1.1	2.8

Rezafungin Dose (mg/kg)	0	15	30	45
Head absent with normal flagellum	0.2	0.7	2.3	7.3
Abnormal head	0	0	0	0
Abnormal flagellum	0	0	0	0

Source: Reviewer generated table
[a] Significantly different from control group at 0.01
Abbreviation: IV, intravenous

13.2.1.3. Embryo-Fetal Development

Study Title/ Number: Study NC-105: An Intravenous (Slow Bolus Push) Injection Embryo-Fetal Development Study of CD101 Administered Every 3 Days in Sprague Dawley Rats

Key Study Findings

- Maternal toxicity (hypoactivity, ataxia, flushed extremities, dilated pupils and/or swollen facial area) was observed at all doses.
- At this dose, the $AUC_{0\text{-}168h}$ was estimated at 3547 µg*h/mL, an exposure about 5 times the clinical exposure of 753 µg*h/mL.

Table 76. Study Information for Study NC-105: An Intravenous (Slow Bolus Push) Injection Embryo-Fetal Development Study of CD101 Administered Every 3 Days in Sprague Dawley Rats

Study Features and Methods	Details
Dose and frequency of dosing:	0, 5, 15, 30, and 45 mg/kg, once every 3 days. Dosing in females started 1 week prior to pairing with untreated males and continued through mating to gestation day 17 (total of 9 to 11 doses over approximately 4 to 5 weeks).
Route of administration:	Intravenous injection (slow bolus push over a 3 to 4-minute period) via a tail vein
Formulation/vehicle:	2.5% Tween® 80, (b) (4)% mannitol, and (b) (4) (pH adjusted to (b) (4)),
Species/strain:	Sprague Dawley [Crl:CD(SD)] rats
Number/sex/group:	25 females
Satellite groups:	9 females for toxicokinetics
Study design:	**Table 77. Study Design for Study NC-105**

Group Number	Test Article	Dosage Level (mg/kg/day)[a]	Dose Concentration[a] (mg/mL)	Dose Volume[b] (mL/kg)	Number of Animals/Sex[c] Main	TK
1	Vehicle control	0	0	5	25	9
2	CD101	5	1	5	25	9
3	CD101	15	3	5	25	9
4	CD101	30	6	5	25	9
5	CD101	45	9	5	25	9

a = Test article formulations will be corrected for purity/potency and salt content using a correction factor provided by the Sponsor or supplier and documented in the study records.
b = Dose volume to be delivered by slow bolus push over a 3-4 minute period.
c = Males will not be administered the test or vehicle control article and will be used for breeding only.

Source: Applicant's table from study report

Deviation from study protocol affecting interpretation of results:	No

Study Features and Methods	Details
GLP compliance:	Yes
Conducting laboratory and location:	(b) (4)

Source: Reviewer generated table
Abbreviation: GLP, good laboratory practices

Table 78. Observations and Results for Study NC-105: An Intravenous (Slow Bolus Push) Injection Embryo-Fetal Development Study of CD101 Administered Every 3 Days in Sprague Dawley Rats

Parameters	Major Findings
Toxicokinetics	**Table 79. Toxicokinetic Parameters for CD101 in Rats**

Toxicokinetic Parameters for CD101 in Rats

Gender:	Females			
CD101 Dosage (mg/kg/dose):	5	15	30	45
Parameter (Units)	Study Day Relative to Last Dose (GD 15, 16, or 17)			
AUC0-72 (µg·h/mL)	144	446	1020	1520
DN AUC0-72	28.8	29.8	33.9	33.8
Cmax (µg/mL)	5.81	17.9	38.2	59.0
DN Cmax	1.16	1.20	1.27	1.31
Tmax (h)	1.00	1.00	1.00	1.00

DN = Dose-normalized; units for dose-normalized AUC0-72 and Cmax are (µg·h /mL)/(mg/kg) and (µg/mL)/(mg/kg), respectively

Source: Applicant's table from study report

Mortality	There were no drug-related deaths
Clinical signs	Hypoactivity, ataxia, flushed extremities, dilated pupils and/or swollen facial area were observed in females in the 15, 30, and 45 mg/kg/dose groups. Clinical observations were primarily noted immediately following dosing up to 1 hour following dose administration but swollen facial area persisted through 1 to 2 hours post-dosing.
Body weights	There were not significant differences in body weights between dose groups
Necropsy findings: Cesarean section data [implantation sites, pre- and post-implantation *loss, etc.]*	There were no drug-related adverse effects on implantation sites, pre- or post-implantation loss, live litter size, mean fetal body weights, and fetal sex ratios. Mean numbers of corpora lutea and implantation sites and the mean litter proportions of pre-implantation loss were similar across all groups.
Necropsy findings: Offspring [malformations, variations, etc.]	The incidence of retroesophageal aortic arch at 45 mg/kg (1.0 %) was increased compared to concurrent controls (0.3 %) but was within the range of historical controls (up to 1.1 %)

Source: Reviewer generated table

Table 80. Necropsy Findings

	Incidence: Pups (Litters)				
Dose	**0 (Control)**	**5 mg/kg**	**15 mg/kg**	**30 mg/kg**	**45 mg/kg**
Microphthalmia					2(1)
Situs invertus					1(1)
Retroesophageal aortic arch	1(1)				3(3)
Bent limb bone				1(1)	1(1)

Source: Reviewer generated table

Retroesophageal aortic arch was observed in one pup in one litter (0.3 % per litter) in controls and in one pup in three litters (1.0 %) in the 45 mg/kg group. The incidence of retroesophageal

aortic arch in historical control data provided by the applicant (March 8, 2023 submission) was up to 1.1 % and therefore the incidence in the 45 mg/kg group fell within the range of historical controls. The incidences of microphthalmia (0.6% per litter) were only slightly outside the historical control range (up to 0.58%). The incidence of situs invertus (0.3%) was within the range of historical control (up to 1.1%). The incidence of bent limb bone (0.5%) was within the range of historical controls (up to 1.45%). $AUC_{0\text{-}168h}$ was estimated at 3547 µg*h/mL, an exposure about 5 times the clinical exposure of 753 µg*h/mL.

13.2.1.4. Embryo-Fetal Development

Study Title/ Number: Study NC-106: An Intravenous (Slow Bolus Push) Injection Embryo-Fetal Development Study of CD101 Administered Every 3 Days in Rabbits

Key Study Findings

- Maternal toxicity (reduced bodyweight) gain was observed at 15 and 35 mg/kg.
- There were no test article-related effects up to the 35 mg/kg, about 3 times the clinical dose based on $AUC_{0\text{-}168h}$ comparisons.

Table 81. Study Information for Study NC-106: An Intravenous (Slow Bolus Push) Injection Embryo-Fetal Development Study of CD101 Administered Every 3 Days in Rabbits

Study Features and Methods	Details
Dose and frequency of dosing:	Rezafungin was administered to 3 groups of time-mated female rabbits once every 3 days on gestation days 7, 10, 13, 16, and 19. Dosage levels were 5, 15, and 35 mg/kg/dose administered at a dose volume of 5 mL/kg
Route of administration:	Intravenous injection (slow bolus push over a 3- to 4-minute period) via a marginal ear vein
Formulation/Vehicle:	2.5% Tween® 80, (b) (4)% mannitol, and (b) (4) acid [pH adjusted to (b) (4)
Species/Strain:	New Zealand White [Hra:(NZW) SPF] rabbits
Number/Sex/Group:	22 females
Satellite groups:	For toxicokinetic evaluation, 4 additional rabbits/group were administered the test article and 1 additional rabbit was administered the vehicle
Study design:	**Table 82. Study Design for Study NC-106**

Group Number	Test Article	Dosage Level (mg/kg/dose)	Dose Concentration (mg/mL) [a]	Dose Volume (mL/kg) [b]	Number of Females	
					Main	TK
1	Vehicle control	0	0	5	22	1
2	CD101	5	1	5	22	4
3	CD101	15	3	5	22	4
4	CD101	35	7	5	22	4

a = Test article formulations will be corrected for purity/potency (87.8%) and salt content using a correction factor of 1.14 provided by the Sponsor.
b = Dose volume to be delivered by slow bolus push over a 3-4 minute period.

Source: Applicant's table from study report

Deviation from study protocol affecting interpretation of results:	No

Study Features and Methods	Details
GLP compliance:	Yes
Conducting laboratory and location:	(b) (4)

Source: Reviewer generated table
Abbreviation: GLP, good laboratory practices

Table 83. Observations and Results for Study NC-106: An Intravenous (Slow Bolus Push) Injection Embryo-Fetal Development Study of CD101 Administered Every 3 Days in Rabbits

Parameters	Major findings
Mortality	One 35 mg/kg female was found dead approximately 5 minutes after dosing on Gestation Day 16. This female was noted with clonic convulsions 2 minutes after dosing on the day of death while being restrained. **Table 84. Pharmacokinetics for Study NC-106** Dosage (mg/kg/dose): 5 / 15 / 35 Gestation Day 7 AUC_{0-72} (µg*h/mL): 166 / 495 / 1170 C_{max} (µg/mL): 15.2 / 50.4 / 123 Gestation Day 19 AUC_{0-72} (µg*h/mL): 133 / 468 / 1040 C_{max} (µg/mL): 12.8 / 48.7 / 107 Source: Applicant's table from study report The exposure at the 35 mg/kg dose ($AUC_{(0-168h)}$) was 2730 µg·h/mL, about 4 times the clinical exposure.
Clinical signs	There were no test article-related clinical signs
Body weights	Bodyweight gain was reduced at 35 mg/kg (by 21 to 80%, throughout the dosing period) and at 15 mg/kg (by 18 to 21%, GD 11 to GD 20).
Necropsy findings: Cesarean section data	There were no test article-related macroscopic findings noted at any dose level and no effects on intrauterine growth and survival up to the highest dose tested (35 mg/kg).
Necropsy findings: Offspring	There were no test article-related effects on macroscopic findings and fetal morphology (external, visceral, and skeletal) up to the highest dose tested (35 mg/kg). All findings were within the incidence of historical control.

Source: Reviewer generated table.
Abbreviations: GD, gestation day

13.2.1.5. Prenatal and Postnatal Development

Study Title/ Number: Study NC-172: An Intravenous (Slow Bolus Push) Study of the Effects of CD101 Administered Once Every 3 Days on Pre and Postnatal Development, Including Maternal Function in Rats

Key Study Findings

- Maternal toxicity, including hypoactivity, ataxia, and dilated pupils, were noted in the 15 and 45 mg/kg. Flushed extremities and swollen facial area were seen at ≥5 mg/kg.

- Maternal treatment with rezafungin every three days, up to 45 mg/kg, had no effect on developmental landmarks of offspring, F1 reproductive endpoints or F2 pups

Table 85. Study Information for Study NC-172: an Intravenous (Slow Bolus Push) Study of the Effects of CD101 Administered Once Every 3 Days on Pre and Postnatal Development, Including Maternal Function in Rats

Study Features and Methods	Details
Dose and frequency of dosing:	Female rats were dosed with 0, 5, 15, and 45 mg/kg every 3 days beginning approximately 1 week prior to mating through Lactation Day 20.
Route of administration:	Intravenous injection (slow bolus push)
Formulation/vehicle:	2.5% Tween® 80, (b) (4)% mannitol, and (b) (4) (pH adjusted to (b) (4)
Species/strain:	Crl:CD(SD) rats
Number/sex/group:	25 to 27
Satellite groups:	4 females/group were selected for gestation and lactation exposure assessments
Study design:	**Table 86. Study Design for Study NC-172: Main Study**

Group Number	Test Article	Dose Level[a] (mg/kg/dose)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Females
1	Vehicle	0	0	5	25
2	CD101	5	1	5	25
3	CD101	15	3	5	27
4	CD101	45	9	5	25

[a] Corrected for salt using a correction factor of 1.14.

Source: Applicant's table from study report

Table 87. Study Design for Study NC-172: Exposure Assessment Phase

Group Number	Test Article	Dose Level[a] (mg/kg/dose)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Females[b]
1	Vehicle	0	0	5	8
2	CD101	5	1	5	8
3	CD101	15	3	5	8
4	CD101	45	9	5	9

[a] (b) (4)

[b] 4 females/group were selected for gestation and lactation exposure assessments.

Source: Applicant's table from study report

Deviation from study protocol affecting interpretation of results:	Yes/No
GLP compliance:	Yes
Conducting laboratory and location:	(b) (4)

Source: Reviewer generated table.
Abbreviation: GLP, good laboratory practices

Table 88. Observations and Results for Study NC-172: an Intravenous (Slow Bolus Push) Study of the Effects of CD101 Administered Once Every 3 Days on Pre- and Postnatal Development, Including Maternal Function in Rats

Generation	Major Findings
F0 Dams	Two of the 15 mg/kg F0 females died following the first dose (Day 0). Clinical observations included hypoactivity, ataxia and dilated pupils, in the 15 and 45 mg/kg females. Flushed extremities and increased incidences swollen facial area were noted at ≥5 mg/kg. There were no adverse effects on pregnancy, parturition, and lactation.
PK parameters	**Table 89. Pharmacokinetic Results for Study NC-172**

Parameter	Maternal Dose (mg/kg)		
	5	15	45
F0 Maternal Plasma (GD18 to GD20) (µg/mL)	8.50	19.7	72.1
F1 Fetal Plasma (GD18 to GD20) (µg/mL)	0.165	0.710	2.21
F0 Maternal Plasma, LD8 to LD10 (µg/mL)	6.77	18.9	57.7
F0 Maternal Milk, LD8 to LD10 (µg/mL)	1.73	4.12	13.1

Source: Applicant's table from study report

F1 Generation	There were no adverse effects on the growth, viability, development, learning and memory in the F1 pups and no effects on F1 reproductive performance.
F2 Generation	There were no adverse effects on the F2 pups.

Source: Reviewer generated table.
Abbreviations: Pk, Pharmacokinetics

13.2.2. Genetic Toxicology

13.2.2.1. In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title: Salmonella/E. Coli Mammalian Microsome Reverse Mutation Assay

Table 90. Study Information for Study Number NC-027: Salmonella/E. Coli Mammalian Microsome Reverse Mutation Assay

Study Features and Methods	Details
Study no.:	NC-027
Study report location:	NDA 217417 SDN1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/17/2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	84.5%
Strains:	*Salmonella typhimurium* (TA 1537, TA98, TA100, TA1535), *Escherichia Coli* strain WP2 uvrA
Concentrations in the definitive study:	2.5, 5.0, 10, 25, 50, 100, 250, 500, and 1000 µg/plate
Basis of concentration selection:	Precipitates were not observed in either strain with or without metabolic activation. Cytotoxicity (i.e., reduction in the background lawn and/or mean number of revertant colonies) was observed at ≥100 µg/plate in TA100 and WP2 uvrA

Study Features and Methods	Details
	without metabolic activation and at ≥500 µg/plate in TA100 and WP2 uvrA with metabolic activation.
Negative control:	Dimethylsulfoxide 20 mg/mL
Positive control:	Tests without metabolic activation: TA1537: ICR-191 acridine (0.5 µg/plate) TA98: 2-nitrofluorene (2.5 µg/plate) TA100/TA1535: Sodium azide (1 µg/plate) WP2 uvrA: 4-nitroquinoline-N-oxide (2 µg/plate) Tests with metabolic activation: TA1537, TA98, TA100, TA1535, 2-aminoanthracene (2.5 µg/plate) WP2 uvrA (10 µg/plate)
Formulation/Vehicle:	DMSO

Source: Reviewer generated table
Abbreviations: DMSO, dimethyl sulfoxide; GLP, good laboratory practices; QA, quality assurance

Key Study Findings

- Cytotoxicity was observed at ≥50 µg/plate (in TA1537 without metabolic activation), ≥100 µg/plate (in TA1537 with metabolic activation), ≥250 µg/plate (in TA98, TA1535 and WP2 uvrA without metabolic activation and TA100 with and without metabolic activation), and at ≥500 µg/plate (in TA98, TA1535, and WP2 uvrA with metabolic activation).
- Criteria for a negative response were met for all tester strains with and without metabolic activation, but cytotoxicity prevented the evaluation of high concentrations of rezafungin.

The study was valid. Vehicle and positive controls were consistent with historical control data with and without metabolic activation.

Results

Rezafungin was negative for all tester strains with and without metabolic activation but rezafungin was not adequately tested because cytotoxicity prevented the evaluation of high enough concentrations. Cytotoxicity was observed at ≥50 µg/plate in TA1537 without metabolic activation, ≥100 µg/plate in TA1537 with metabolic activation, ≥250 µg/plate in TA98, TA1535 and WP2 uvrA without metabolic activation, and TA100 with and without metabolic activation, and at ≥500 µg/plate in TA98, TA1535, and WP2 uvrA with metabolic activation.

Table 91. Mutagenicity Assay: Results of Plate Incorporation Experiment for Rezafungin in the Salmonella-E. coli/Mammalian Microsome Reverse Mutation Assay

REVERTANT COLONIES PER PLATE—Mean (SD)[a]

Treatment Group	µg/plate	TA1537		TA98		TA100		TA1535		WP2*uvrA*	
					WITHOUT ACTIVATION						
DMSO	50 µL	9	(4)	17	(6)	65	(11)	8	(4)	14	(5)
ICR	0.5	107	(2)								
2NF	2.5			548	(25)						
SA	1.0					451	(42)	326	(22)		
NQNO	2.0									1587	(305)
	2.5	7	(3)	16	(5)	81	(17)	9	(3)	18	(6)
	5.0	4	(2)	8	(5)	99	(7)	7	(3)	16	(2)
	10	6	(4)	12	(6)	86	(15)	6	(0)	12	(3)
	25	8	(3)	11	(3)	82	(7)	6	(1)	15	(5)
CD101	50	4[d]	(1)	11	(3)	70	(12)	8	(3)	15	(5)
	100	--[c]	--	10	(4)	55	(11)	4	(1)	10	(5)
	250	--[c]	--	1[d]	(1)	--[c]	--	1[b,d]	(1)	3[b,d]	(2)
	500	--[c]	--	0[b,d]	(1)	--[c]	--	--[c]	--	--[c]	--
	1000	--[c]	--	--[c]	--	--[c]	--	--[c]	--	--[c]	--
					WITH ACTIVATION						
DMSO	50 µL	7	(3)	17	(6)	91	(20)	6	(3)	14	(6)
2AA	2.5	56	(18)	1681	(68)	766	(47)	126	(9)		
2AA	10.0									226	(32)
	2.5	7	(4)	15	(7)	74	(5)	7	(4)	18	(4)
	5.0	8	(5)	14	(5)	95	(9)	9	(2)	12	(3)
	10	6	(1)	13	(2)	79	(11)	8	(6)	15	(5)
	25	5	(0)	13	(1)	93	(11)	7	(4)	15	(3)
CD101	50	7	(5)	16	(4)	83	(16)	6	(4)	18	(2)
	100	3[d]	(2)	11	(1)	102	(21)	8	(3)	16	(5)
	250	--[c]	--	17	(6)	37[b,d]	(17)	5	(2)	7	(4)
	500	--[c]	--	1[d]	(1)	--[c]	--	0[b,d]	(1)	2[d]	(0)
	1000	--[c]	--	0[d]	(0)	--[c]	--	--[c]	--	--[c]	--

2AA: 2-Aminoanthracene
2NF: 2-Nitrofluorene
ICR: ICR-191 Acridine
NQNO: 4-nitroquinoline-N-oxide
SA: Sodium azide
SD: standard deviation
DMSO: Dimethylsulfoxide
[a] Calculated from triplicate plates
[b] Slightly reduced background lawn
[c] Cytotoxicity: Reduced background lawn, plates not counted
[d] Cytotoxicity: >50% reduction in mean number of revertant colonies

Source: Applicant's table from study report

13.2.2.2. In Vitro Assays in Mammalian Cells

Study Title: In Vitro Chromosome Aberration Test in Chinese Hamster Ovary (CHO-WBL) Cells

Table 92. Study Information for Study Number NC-028: In Vitro Chromosome Aberration Test in Chinese Hamster Ovary (CHO-WBL) Cells

Study Features and Methods	Details
Study no.:	NC-028
Study report location:	EDR (NDA 217417 SDN 1)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/17/2014

Study Features and Methods	Details
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #	7001888
% purity:	84.5%
Cell line:	CHO-WBL cells were obtained from the (b) (4)
Concentrations in definitive study:	3-hour treatment without metabolic activation: 6.25, 12.5, 25.0, 50.0, 75.0, 100, 125, 150, 175, 200, 225, and 250 µg/mL 20-hour treatment without metabolic activation and the 3-hour treatment with metabolic activation: 6.25, 12.5, 25.0, 37.5, 50.0, 67.5, 75.0, 87.5, 100, 115, 125, 150, and 200 µg/mL Precipitates were observed at ≥50 µg/mL in the 3-hour treatment with metabolic activation and the 20-hour treatment without metabolic activation and at ≥75 µg/mL in the 3-hour treatment without metabolic activation at the end of test article treatment. Changes in cell morphology were observed at the end of test article treatment at ≥25.0 µg/mL in the 20-hour treatment without metabolic activation, ≥67.5 µg/mL in the 3-hour treatment with metabolic activation, and at ≥100 µg/mL in the 3-hour treatment without metabolic activation
Basis of concentration selection:	In the dose range finding study, (0.977, 1.95, 3.91, 7.81, 15.6, 31.3, 62.5, 125, 250, and 500 µg/mL), precipitates were observed at ≥125 µg/mL in the 3-hour treatment with metabolic activation and the 20-hour treatment without metabolic activation and at ≥250 µg/mL in the 3-hour treatment without metabolic activation at the end of test article treatment. Changes in cell morphology were observed at the end of test article treatment at ≥250 µg/mL in the 3-hour treatment without metabolic activation and at ≥125 µg/mL in the 20-hour treatment without metabolic activation.
Negative control:	DMSO 1%
Positive control:	Mitomycin C 0.50 and 0.75 µg/mL (3 hour) or 0.050 and 0.10 µg/mL (20 hour) in cultures without activation. Cyclophosphamide at 5.0 and 7.5 µg/mL in cultures with activation.
Formulation/vehicle:	DMSO
Incubation & sampling time:	Cultures were treated with rezafungin or positive control or vehicle in the presence and absence of metabolic activation for short incubations (3 hours) and in the absence of activation for 20 hours. After 3 hours, the short treatments were washed and returned to the incubator until harvest at 20 hours. Approximately 2 hours prior to harvest, Colcemid® (0.1 µg/mL) was added to each culture to arrest cells in metaphase

Source: Reviewer generated table.
Abbreviations: DMSO, dimethyl sulfoxide; GLP, good laboratory practices; QA, quality assurance

Key Study Findings

- Rezafungin was negative for inducing structural aberrations in CHO-WBL cells with and without metabolic activation

Study Validity

Data from the vehicle and positive controls were comparable to expected historical control ranges and yielded expected results with the following exceptions. The vehicle control for the 20-hour treatment without metabolic activation (2.7%) and the 3-hour treatment with metabolic activation (3.3%) were higher than the historical control range (0 to 2%). Although the vehicle control (3.3%) was slightly higher than the historical control range (0 to 2%), for the 3-hour incubation with metabolic activation, the incidence of percentage cells with aberrations for rezafungin exposed cells (at concentrations without precipitate) was within the historical control range. Although the vehicle control (2.7%) was slightly higher than the historical control range (0 to 2%), for the 20-hour incubation without metabolic activation, the incidence of percentage cells with aberrations was within the historical control range for rezafungin exposed cells at the two highest concentrations tested and there were no statistically significant increases in aberrations at any concentrations under any incubation conditions. This study was considered to be valid.

Results

Table 93. Cytotoxicity and Aberration Summary: 3-Hour Incubation Without Metabolic Activation

Treatment	% Cytotoxicity - RPD	% Cells w/Abs	% Cells w/>1 Abs	% Endo Cells	% Polyploid Cells
DMSO (1%)	0.00	1.7	0.0	0.0	6.3
MMC 0.75 µg/mL	32.80	69.4 *	34.7 *	0.0	5.3
CD101					
25 µg/mL	1.96	4.0	0.0	0.0	2.8
50 µg/mL	6.49	2.7	0.3	0.0	5.3
75 µg/mL [a]	11.99	2.7	0.3	0.0	5.3

Endo - Endoreduplicated cells **DMSO** - Dimethylsulfoxide
Abs - Aberrations **RPD** - Relative Population Doubling
MMC - Mitomycin C
Percent Aberrant cells: * $p \leq 0.01$ using Fisher's Exact Test
[a] Precipitates present at end of treatment
Source: Applicant's table from study report

Table 94. Cytotoxicity and Aberration Summary: 20-Hour Incubation Without Metabolic Activation

Treatment	% Cytotoxicity - RPD	% Cells w/Abs	% Cells w/>1 Abs	% Endo Cells	% Polyploid Cells
DMSO (1%)	0.00	2.7	0.3	0.0	4.5
MMC 0.10 µg/mL	18.25	61.7 *	27.2 *	0.0	5.5
CD101					
6.25 µg/mL	2.94	5.7	0.3	0.0	5.8
12.5 µg/mL	9.60	1.7	0.3	0.0	6.8
25.0 µg/mL	48.39	2.0	0.0	0.0	6.0

Endo - Endoreduplicated cells **DMSO** - Dimethylsulfoxide
Abs - Aberrations **RPD** - Relative Population Doubling
MMC - Mitomycin C
Percent Aberrant cells: * $p \leq 0.01$ using Fisher's Exact Test

Source: Applicant's table from study report

Table 95. Cytotoxicity and Aberration Summary 3-Hour Incubation With Metabolic Activation

Treatment	% Cytotoxicity - RPD	% Cells w/Abs	% Cells w/>1 Abs	% Endo Cells	% Polyploid Cells
DMSO (1%)	0.00	3.3	0.0	7.0	3.3
CP 7.5 µg/mL	27.01	58.1 *	19.8 *	0.5	5.0
CD101					
25.0 µg/mL	0.00	1.3	0.0	7.0	4.5
37.5 µg/mL	0.00	1.0	0.3	4.8	3.3
50.0 µg/mL [a]	2.09	3.0	0.3	5.3	2.8

Endo - Endoreduplicated cells **DMSO** - Dimethylsulfoxide
Abs - Aberrations **RPD** - Relative Population Doubling
CP - Cyclophosphamide
Percent Aberrant cells: * $p \leq 0.01$ using Fisher's Exact Test
[a] Precipitates observed at the end of treatment

Source: Applicant's table from study report

Rezafungin was negative for inducing structural aberrations in CHO-WBL cells with and without metabolic activation.

13.2.2.3. In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study Title: An In Vivo Micronucleus Assay of CDlOl in Sprague Dawley Rats

Table 96. Study Information for Study Number NC-080: An In Vivo Micronucleus Assay of CDlOl in Sprague Dawley Rats

Study Features and Methods	Details
Study no:	NC-080
Study report location:	EDR NDA 217417 SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8/26/2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #:	7002103
% purity	84.4%
Doses in definitive study:	5, 15, and 45 mg/kg
Frequency of dosing:	Single dose
Route of administration:	Intravenous infusion
Dose volume:	10 mL/kg
Formulation/vehicle:	1.25% Tween® 80, (b) (4)% mannitol, (b) (4) [pH adjusted to (b) (4)]
Species/strain:	Rat (Sprague Dawley)
Number/sex/group:	5 animals/group
Basis of dose selection:	A 4-Week Once Every 3 Days (9 Doses) Intravenous (Slow Bolus Push) Toxicity and Toxicokinetic Study of CD101 in Sprague Dawley Rats with a 4-Week Recovery Period (NC-025), in which deaths were recorded at 15, 30, and 45 mg/kg
Negative control:	1.25% Tween® 80, (b) (4)% mannitol, (b) (4) [pH adjusted to (b) (4)]
Positive control:	60 mg/kg cyclophosphamide monohydrate

Source: Reviewer generated table.
Abbreviations: GLP, good laboratory practices; QA, quality assurance

Key Study Findings

- Rezafungin was negative in the in vivo micronucleus assay
- Rezafungin did not produce an increase in the mean percent micronucleated polychromatic erythrocytes compared to the vehicle control group at the doses tested.

Study Validity

The study was valid. Negative and positive controls were acceptable based on historical data. The mean values for both micronucleated polychromatic erythrocytes and polychromatic erythrocytes: total erythrocytes ratios for the vehicle and positive control groups were within the respective historical control ranges. Positive controls produced a statistically significant increase compared with the concurrent controls. Selection of the highest dose was based on mortality in previous studies.

Results

Table 97. Micronucleus Assay Data for Male Sprague Dawley Rats Between 24 to 26 Hours After Dose Administration

TREATMENT	ANIMAL No.	MN PCEs/ 4000 PCEs	% MN-PCEs	PCEs	NCEs	PCE:TE Ratio
Vehicle Control	3568	10	0.25	307	193	0.61
	3571	2	0.05	361	139	0.72
	3573	9	0.23	253	247	0.51
	3587	0	0.00	373	127	0.75
	3596	1	0.03	301	199	0.60
Mean ± SD			**0.11 ± 0.12**			**0.64 ± 0.10**
CD101 (5 mg/kg)	3552	5	0.13	140	360	0.28
	3575	2	0.05	162	338	0.32
	3576	0	0.00	316	184	0.63
	3578	4	0.10	367	133	0.73
	3590	1	0.03	253	247	0.51
Mean ± SD			**0.06 ± 0.05**			**0.50 ± 0.19**
CD101 (15 mg/kg)	3555	1	0.03	339	161	0.68
	3565	7	0.18	394	106	0.79
	3566	4	0.10	348	152	0.70
	3567	2	0.05	300	200	0.60
	3580	8	0.20	349	151	0.70
Mean ± SD			**0.11 ± 0.08**			**0.69 ± 0.07**
CD101 (45 mg/kg)	3569	1	0.03	345	155	0.69
	3582	6	0.15	333	167	0.67
	3584	2	0.05	352	148	0.70
	3585	5	0.13	258	242	0.52
	3586	12	0.30	387	113	0.77
Mean ± SD			**0.13 ± 0.11**			**0.67 ± 0.10**
Cyclophosphamide (60 mg/kg)	3556	64	1.60	200	300	0.40
	3577	43	1.08	97	403	0.19
	3579	82	2.05	289	211	0.58
	3600	90	2.25	170	330	0.34
	3601	136	3.40	221	279	0.44
Mean ± SD			**2.08 ± 0.87***			**0.39 ± 0.14***

MN = Micronucleated
NCE = Normochromatic Erythrocyte
TE = Total erythrocytes (PCE + NCE)
PCE = Polychromatic Erythrocyte
Vehicle Control = 1.25% Tween 80 (b) (4)% mannitol, (b) (4) adjusted to pH (b) (4)
*Statistically different than vehicle control $p \leq 0.05$ using an ANOVA test followed by Dunnett's test, if applicable.
A full description of the statistical decision can be found in the final report for this study.
Source: Applicant's table from study report

Table 98. Micronucleus Assay Data for Male Sprague Dawley Rats Between 46 to 48 Hours After Dose Administration

TREATMENT	ANIMAL No.	MN PCEs/ 4000 PCEs	% MN-PCEs	PCEs	NCEs	PCE:TE Ratio
Vehicle Control	3547	3	0.08	383	117	0.77
	3551	0	0.00	199	301	0.40
	3553	3	0.08	372	128	0.74
	3557	3	0.08	179	321	0.36
	3558	0	0.00	140	360	0.28
Mean ± SD			**0.05 ± 0.04**			**0.51 ± 0.23**
CD101 (45 mg/kg)	3545	1	0.03	407	93	0.81
	3546	0	0.00	253	247	0.51
	3550	1	0.03	316	184	0.63
	3554	0	0.00	276	224	0.55
	3562	0	0.00	356	144	0.71
Mean ± SD			**0.01 ± 0.01**			**0.64 ± 0.12**

MN = Micronucleated
NCE = Normochromatic Erythrocyte
TE = Total erythrocytes (PCE + NCE)
PCE = Polychromatic Erythrocyte
Vehicle Control = 1.25% Tween 80 (b) (4)% mannitol, (b) (4) adjusted to pH (b) (4)

Source: Applicant's table from study report

Table 99. Historical Control Data for Rat Bone Marrow Micronucleus From GLP Studies Finalized From 2011 Through 2012

Vehicle Control

	Ratio of PCE/Total Erythrocytes		%MN PCEs	
	Males	**Females**	**Males**	**Females**
Mean	0.54	0.57	0.09	0.07
SD	0.12	0.11	0.08	0.07
Range	0.27-0.92	0.24-0.85	0.00-0.43	0.00-0.30
N	135	130	135	130

Positive Control (Cyclophosphamide, 60 mg/kg)

	Ratio of PCE/Total Erythrocytes		%MN PCEs	
	Males	**Females**	**Males**	**Females**
Mean	0.41	0.39	1.74	0.96
SD	0.14	0.14	1.35	0.48
Range	0.11-0.75	0.10-0.78	0.45-10.45	0.35-3.65
N	125	120	125	119

Source: Applicant's table from study report
Abbreviations: MN, micronucleated; PCE, polychromatic erythrocyte

13.2.3. Other Toxicology/ Specialized Studies

13.2.3.1. Phototoxicity

Study # NC-103. Neutral Red Uptake Phototoxicity Assay of CD101 in BALB/c 3T3 Mouse

Study report location: EDR NDA 217417 SDN #1

Methods and Results

This assay measured the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to rezafungin and ultraviolet radiation (+UVR), as compared with the viability of fibroblasts exposed to rezafungin in the absence of ultraviolet radiation (-UVR).

Table 100. Results for Study Number NC-103. Neutral Red Uptake Phototoxicity Assay of CD101 in BALB/c 3T3 Mouse

Test Material	IC50 (µg/mL) -UVR	IC50 (µg/mL) +UVR	Photo Irritancy Factor	Mean Photo Effect	UVR Percent Survival	OD540
Promethazine	129	1.3	97	0.6	88	0.8
Rezafungin Assay #1	14	1.5	9	0.3	86	0.9
Rezafungin Assay #2	16	1.6	10	0.3	88	0.8

Source: Reviewer generated table
Abbreviations: IC_{50}, half maximal inhibitory concentration; OD_{540}, optical density at 540 nm; UVR, ultraviolet radiation

Rezafungin demonstrated phototoxic potential since photo irritation factor >5 is considered the criterion for phototoxic potential and mean photo effect >0.15 is considered the criterion for phototoxic potential.

Study NC-113: A Multiple Dose Phototoxicity Study to Determine the Effects of Intravenous Administration of CD101 on Eyes and Skin in Pigmented Rats

Study report location: EDR NDA 217417 SDN #1

Key Findings

- A dose-related minimal phototoxic response (increased incidence of erythema and edema in pigmented and nonpigmented skin reactions), was observed at C_{max} plasma concentrations ≥6.9-fold above those achieved clinically following a 400 mg dose.

Methods and Results

Rezafungin was tested for phototoxicity potential in pigmented rats.

Table 101. Phototoxic Effect of Rezafungin in Pigmented Rats

Species/Strain: Rat/ (b) (4)	**Duration of dosing:** Administered on Days 1, 3 and 7		**Study no.** NC-113	
Initial age: ~16 weeks	**Duration of post-dose:** 72 hours			
Date of first dose: 01-Nov-2016	**Method of administration:** Intravenous slow bolus (3-4 minutes) via tail vein			
	Vehicle/Formulation: 2.5% Tween 80 (b) (4)% mannitol, (b) (4) pH (b) (4)		**GLP Compliance:** Yes	
Special features: Ultraviolet radiation dose: 10.29 J/cm^2 UVA and 145 mJ/cm^2 UVB. Duration of UVR exposure 42 minutes starting approximately 75 minutes after last (third) dose.				
No observed adverse effect level for phototoxicity: 15 mg/kg				
Daily dose (mg/kg)	**0 (Control)**	**15**	**30**	**45**
Number of animals (Main)	**Females: 5**	**Females: 8**	**Females: 8**	**Females: 8**
Body weight (%)	-	-	-	-
Skin Reactions Number of animals evaluated for skin reactions at 1, 4, 24, 48, and 72 hours after last dose	5	3	6	7
Nonpigmented skin reactions (total number of animals affected)	-	-	3	5
Erythema (Grade 1) / Last observed	-	-	3 / 24 hours	3 / 72 hours
Erythema (Grade 2) / Last observed	-	-	-	1 / 24 hours
Edema (Grade 1) / Last observed	-	-	-	3 / 24 hours
Pigmented skin reactions (total number of animals affected)	-	-	4	2
Erythema (Grade 1) / Last observed	-	-	4 / 4 hours	2 / 24 hours
Edema (Grade 1) / Last observed	-	-	-	2 / 4 hours
Ophthalmological findings	-	-	-	-
Histopathology (eye)	-	-	-	-

Erythema: Grade 1 = barely perceptible light redness; Grade 2 = distinct redness
Edema: Grade 1 = mild, raised < 1mm)

Source: Applicant's table from study report
Abbreviations: GLP, good laboratory practices; UVR, ultraviolet radiation

14. Clinical Pharmacology

This section contains the clinical pharmacology review team's assessments and conclusions from the clinical pharmacology pertinent studies submitted by the Applicant. Any differences between the Applicant's and FDA reviewer's conclusions are noted.

14.1. In Vitro Studies

14.1.1. Protein Binding

Rezafungin (REZ) plasma protein binding (PPB) has been studied in mouse, rat, monkey, chimpanzee, and human plasma (Studies NC-008, NC-121, NC-137, CD101.IV.1.15, ReSTORE, CD101.IV.1.06, STRIVE).

The reported PPB values were determined by ultracentrifugation and equilibrium dialysis methods. PPB estimates were independent of concentration. As shown in Table 102, in vitro, the bound REZ fraction, expressed as a percentage, was on average 97.4% (2.6% unbound) in healthy subjects. The unbound REZ fraction, expressed as a percentage, was 2.6- and 2.8-fold higher in Candidemia/IC subjects than in healthy subjects, possibly in part because of the high prevalence of hypoalbuminemia in patients (Table 102 and Table 103). The unbound REZ

fraction estimate was higher in postdose sample studies than spiked predose sample studies (i.e., 12.5% versus 6.4% in patients and 4.4% versus 2.4% in healthy subjects, respectively; Table 102 and Table 103). The reason for this observation is not known. The REZ PPB estimates were also dependent on the method (Table 102). One in vitro study (NC-008) showed that by ultracentrifugation REZ PPB was 98.2% (1.8% free); however, by equilibrium dialysis, REZ PPB could not be determined reliably due to analytical sensitivity issue and was reported estimates were >98.7% (<1.3% unbound) (NC-008). Thus, discrepancies are observed in the healthy adult REZ PPB determined by ultracentrifugation and equilibrium dialysis methods.

Table 102. Median (25th and 75th Percentiles) % Free REZ in Healthy/Noninfected Adult Plasma Samples

Study	Healthy Adults	Plasma Drug Sample Type	Method
NC-121 & NC-137 (in vitro)	2.6% (2.2% to 3.8%)	Pre-dose spiked	Ultracentrifugation
CD101.IV.1.06 (QTc study)	4.4% (3.2% to 5.2%)	Post-dose	
CD101.IV.1.15 (hepatic impairment study)	2.4% (1.8% to 3.9%)	Pre-dose spiked	
NC-008[b] (in vitro)	<1.3%[c]	Pre-dose spiked	Equilibrium Dialysis
	1.8% (1.5% to 2%)	Pre-dose spiked	Ultracentrifugation

Source: Reviewers Table; Adapted from Summary of Clinical Pharmacology, Table 2 (pg 14)
[a] Range of mean estimates across different rezafungin concentrations
[b] The same study evaluated anidulafungin protein binding by ultracentrifugation and the estimates were same as REZ, i.e., averaged 1.8% unbound fraction (98.2% bound). This anidulafungin plasma protein binding value differs from that in its USPI of >99% bound.
[c] All rezafungin samples were below the level of quantification. The lower limit of quantitation concentration, 10 ng/mL, was used to compute the % Free value that it must be less than.
Abbreviations: REZ, rezafungin; USPI, United States Prescribing Information

Table 103. Median (25th and 75th Percentiles) % Free REZ in Candidemia/IC Patient Adult Plasma Samples

Study	Patients	Plasma Drug Sample Type	Method
CD101.IV.2.03 (Phase 2/STRIVE)	12.5% (8.9% to 18.4%)	Post-dose	Ultracentrifugation
CD101.IV.3.05 (Phase 3/ReSTORE)	6.4% (4.2 to 8.9%[a])	Pre-dose spiked	

Source: Reviewers Table; Adapted from Summary of Clinical Pharmacology, Table 2 (pg 14)
Abbreviations: REZ, rezafungin

The Applicant conducted in vitro PPB studies, using plasma from noninfected mouse and human individuals based on ultracentrifugation methods, to show that the unbound drug fraction in humans is approximately 3-fold to the unbound drug fraction in mice.

Taken together, the review of Applicant-submitted information suggests that REZ is highly bound to plasma proteins with the median estimates of the bound REZ fraction (expressed as a percentage) ranging from 87.5% to >98.7% in patients with candidemia or invasive candidiasis. Therefore, we agree with the Applicant that REZ likely exhibits high plasma protein binding (>90%), but do not agree with the Applicant's proposal to note (b) (4) % value for REZ PPB in the product labeling. The review team recommends noting the observed variability and the range in REZ PPB as follows: Mean estimates varied from 87.5% to 93.6% in patients and from 95.6% to

>98.7% in healthy adults. Of note, based on the noted uncertainty in REZ PPB, the review team performed independent probability of target attainment (PTA) sensitivity analyses utilizing a range of PPB values (see Section 14.5.6).

14.1.2. In Vitro Metabolism

The metabolism of REZ was investigated in human liver microsomes, intestinal microsomes, and hepatocytes (Studies NC-010, NC-011, NC-048, NC-014).

Overall, the study findings showed that REZ is not significantly metabolized and there were no phase 1 metabolites detected after incubation of REZ with hepatocytes, liver microsome, or intestinal microsomes. REZ has no or low potential to be a cytochrome P450 (CYP) enzyme substrate.

14.1.3. Potential for CYP Enzyme-Mediated Drug-Drug Interactions

The Applicant conducted in vitro enzyme-mediated drug-drug interaction (DDI) studies evaluating CYP enzyme inhibition and induction potentials of REZ.

REZ in vitro inhibition studies were conducted with either recombinant human CYP isoenzymes (Study NC-012) or pooled human liver microsomes (Studies NC-013, NC-153).

REZ induction studies were conducted with human donor hepatocyte cultures (Study NC-161).

Based on the 2020 FDA In Vitro DDI Guidance document, in vivo thresholds were determined for REZ as either a victim or perpetrator of potentially significant clinical DDIs (see Table 104) (January 2020b). Overall, REZ has no or low potential as a direct inhibitor of CYPs 1A2, 2B6, 2C9, 2C19, or 2D6.

Half-maximal inhibitory concentration (IC_{50}) estimates utilized for DDI predictions were >25µM and the predicted unbound C_{max} was 1.8µM. The assumptions for predicting unbound C_{max} and no/low CYP inhibition potential were as follows: (i) REZ C_{max} of 17.7 µg/mL or 14.4µM following a dose 400 mg REZ IV infusion over 1 hour; (ii) unbound fraction ($f_{u,p}$) of 0.125 based on in vivo postdose PPB data in patients with candidemia or invasive candidiasis, worst case; (iii) nominal in vitro drug concentrations (e.g., $IC_{50,}$ based on amount of drug that is expected to be present).

In addition, REZ has no potential for time-dependent CYP inhibition.

Two clinical studies (CD101.IV.1.09 and CD101.IV.1.17) were also conducted to further evaluate REZ as an inhibitor of CYPs 2C8 and 3A4 or interact with pharmacokinetics (PK) of commonly administered drugs (see Sections 14.2.7 and 14.2.8).

Table 104. In Vitro Assessment of REZ as Substrate, Inhibitor, or Inducer of CYP Enzymes

	In Vitro Findings			In Vivo Potential Predictions[e]		
Enzyme	% Drug Consumed After Incubation[a]	IC_{50}[b,c] (μM)	Induction FC[d]	Basic Model Predictions (Reviewer Analysis)	Interpretation (Substrate/ Inhibitor/ Inducer)	Clinical Study Conducted
CYP1A2	0	>25	<2	R_1<1.02	---	
CYP2B6		>25	<2	R_1<1.02	---	
CYP2C8		~25		R_1>1.02	Inhibitor	Yes
CYP2C9		>25		R_1<1.02	---	
CYP2C19		>25		R_1<1.02	---	
CYP2D6		>25		R_1<1.02	---	
CYP3A4/5		~25	<2	R_1>1.02	Inhibitor	Yes

Source: Reviewer's analysis.
[a] No metabolism in human liver microsomes, intestinal microsomes, and hepatocyte model systems
[b] Assay solubility limit was 25 μM.
[c] No evidence of time-dependent metabolism ($IC_{50,\ 30\ min\ incubation}$ / $IC_{50,\ 30\ min\ incubation\ +\ NADPH}$ <2)
[d] Human hepatocytes (mRNA expression); 3 cell lots up to 1.2 μM REZ (anticipated unbound REZ concentration =1.8 μM); no observed concentration dependent increase in CYP450 enzyme mRNA.
[e] Predictions based on equations and thresholds specified in the 2020 FDA In Vitro DDI Guidance document
Abbreviations: CYP, cytochrome P450; DDI, drug-drug interaction; FC, fold change; IC_{50}, half-maximal inhibitory concentration; R_1, ratio using basic model of reversable inhibition in liver; (---), not significant

14.1.4. Potential for Transporter-Mediated Drug-Drug Interactions

The Applicant conducted in vitro transporter-mediated DDI studies evaluating hepatic and renal transporter substrate and inhibition potentials of REZ.

Studies evaluated OATP1 B1/B3, P-gp, MRP2, BCRP, OCT1, OCTN1, and OCTN2 mediated transport of REZ in overexpressing cell culture monolayers or membrane vesicles (Studies NC-049, NC-052, NC-160).

Studies also evaluated OATP1 B1/B3, BSEP, MRP2, OAT 1/3, P-gp, BCRP, $OCT_{1/2}$, OCTN1, OCTN2, MATE1, and MATE2-K transport inhibition by REZ in in overexpressing cell culture monolayers or membrane vesicles (Studies NC-152, NC-160).

Based on the 2020 FDA In Vitro DDI Guidance document, in vivo thresholds were determined for REZ as either a victim or perpetrator of potentially significant clinical DDIs (Table 105).

REZ is not a substrate of drug transporters (net flux ratio <2). REZ has a low inhibition potential for P-gp, BCRP, OATP1B3, and MATE1 drug transporters. It is noteworthy that the worst-case anticipated unbound C_{max} is 1.8 μM (2.21 μg/mL) in patients with candidemia or invasive candidiasis and no IC_{50} could be determined for P-gp or BCRP as inhibition did not exceed 20% at 10 μM. In addition, REZ's P-gp and BCRP inhibition potential appear similar (P-gp: 22% inhibition at 10 μM REZ; BCRP: 9% inhibition at 6 μM REZ). Clinical studies were conducted to further evaluate REZ as an inhibitor of the P-gp, BCRP, OATP1B3, and MATE1 transporters (see CD101.IV.1.09).

The assumptions for predicting unbound C_{max} were same as the assumptions noted above for the CYP enzyme mediated DDI potential evaluations.

Table 105. In Vitro Assessment of REZ as Substrate or Inhibitor of Human Uptake and Efflux Transporters

	In Vitro Findings		In Vivo Potential Predictions[e]		
Transporter	Max Flux Rate Ratio	IC_{50} (μM)	Basic Model Predictions (Reviewer Analysis)	Interpretation (Substrate/Inhibitor)	Clinical Study Conducted
BCRP	---	>10	I_1[c] / IC_{50}≥0.1	Inhibitor	Yes
P-gp	---	>10	I_1[c] / IC_{50}≥0.1	Inhibitor	Yes
MRP2[a]	---	NT	[a]	---	
BSEP[a]	NT	>100	[a]	---	
	---	19.3	ER <2	---	
OATP1B1			R <1.1[d]		
	---	6.7	ER >2	Inhibitor	Yes
OATP1B3			R =1.1≥1.1[d]		
OAT1	NT[b]	>30	$I_{max,\ u}$ / IC_{50}<0.1	---	
OAT3	NT[b]	>30	$I_{max,\ u}$ / IC_{50}<0.1	---	
OCT1[a]	---	8.2	[a]	---	
OCT2	NT[b]	21.4	$I_{max,\ u}$ / IC_{50}>0.1	---	
OCTN1[a]	---	NT	[a]		
OCTN2[a]	---	NT	[a]		
MATE1	NT[b]	6.3	$I_{max,\ u}$ / IC_{50}>0.1	Inhibitor	Yes
MATE2	NT[b]	21.5	$I_{max,\ u}$ / IC_{50}<0.1	---	

Source: Reviewer's analysis
[a] Not specified in FDA in vitro DDI guidance
[b] renal clearance of parent drug REZ is <25% of total REZ clearance
[c] I_1 = Total REZ C_{max} =17.7 μg/mL or 14.4 μM
[d] $I_{in,\ max}$ =11 μg/mL or 9 μM; estimated max plasma concentration of inhibitor at the inlet to the liver.
[e] Predictions based on equations and thresholds specified in the 2020 FDA In Vitro DDI Guidance document.
Abbreviations: DDI, drug-drug interaction; IC_{50}, half-maximal inh bitory concentration; $I_{max,\ u}$, maximum unbound plasma concentration of interacting drug at steady-state; NT, not tested; R, ratio using basic model of reversable inh bition in liver and $I_{in,\ max}$; REZ, rezafungin; (---), not significant

14.2. In Vivo Studies

14.2.1. Pharmacokinetics-Pharmacodynamics of REZ in Mice

Several studies have examined the systemic PK of rezafungin following administration by the intraperitoneal route in mice (Study reports NC-005, NC-95, NC-122, and NC-146).

Within dose ranging studies, REZ exposure measures appear to increase in an approximate dose-proportional manner. There is some variability observed in dose normalized PK parameter values between studies. From Study NC-005, a REZ dose of approximately 6.5 mg/kg or 5.5 mg/kg in mice is expected to result in a systemic REZ AUC_{0-24} or C_{max} comparable to that in patients with the proposed REZ dosing regimen. From Study NC-122, a REZ dose of approximately 8.5 mg/kg or 11 mg/kg in mice is expected to result in a systemic REZ AUC_{0-24} or C_{max} comparable to that in patients with the proposed REZ dosing regimen. The geometric mean REZ C_{max} was 18 μg/mL and REZ AUC_{0-24hr} was 214 μg h/mL in pooled phase 2 and phase 3 subjects with candidemia and invasive candidiasis following the proposed initial dose of 400 mg.

There does not appear to be a substantial difference in PK exposure measures between infected and noninfected mice.

14.2.2. REZ Pharmacokinetics-Pharmacodynamics Index-Mycological Kill Relationship in a Neutropenic Invasive-Candidiasis Murine Model

Overall, the REZ pharmacokinetics-pharmacodynamics (PK-PD) relationship that best correlated with kidney fungal burden reduction was free-drug $AUC_{0\text{-}168}$/minimum inhibitory concentration (MIC) or free-drug C_{max}/MIC.

In Study NC-043, REZ free-drug (*f*)$AUC_{0\text{-}24}$/MIC (r^2=0.97) or *f*C_{max}/MIC (r^2=0.97) following single REZ dosing best correlated with kidney fungal burden reduction in a 1-day (24 hr) neutropenic candidiasis murine model of *C. albicans* (1 isolate). In a follow-up study (NC-100), *f*$AUC_{0\text{-}168}$/MIC (r^2=0.905) and *f*C_{max}/MIC (r^2=0.0907) following single REZ dosing best correlated with kidney fungal burden reduction in a 7-day (168 hr) neutropenic candidiasis murine model of *C. albicans* (1 isolate). There was greater degree of fungal killing when given once weekly than when the total cumulative dose was divided into daily regimens.

14.2.3. REZ PK-PD Targets Against Specific *Candida* Species

Studies (Lepak et al. 2018a; Lepak et al. 2018b; Lepak et al. 2019) evaluated REZ dosing in a mouse candidiasis model expanded to selected *C. albicans* (n=4), *C. glabrata* (n=3), *C. parapsilosis* (n=3), *C. tropicalis* (n=4), and *C. dubliniensis* (n=4) isolates. Immunosuppressed mice were infected (via IV) with each strain, treated with a single dose of REZ 2 hours after inoculation, and monitored for seven days, after which time kidney colony forming unit (CFU) burdens were determined. In (Lepak et al. 2018b), the REZ plasma PK was characterized following single intraperitoneal doses of 1, 4, 16, and 64 mg/kg with blood sampling at 1,3, 6, 12, 24, 48, and 72 hours postdose, whereas the PD evaluations were performed over the dose levels that ranged from 0.25 to 64 mg/kg and administered once in a 0.2-ml volume by intraperitoneal route for the 168-hour study period. Due to the enhanced effect against a single isolate, additional PD evaluations at 0.0156 and 0.0625 mg/kg REZ were performed for that *C. glabrata* isolate (Lepak et al. 2018b). In separate studies, REZ PD following multiple doses (days 0, 3, 6) were evaluated at 1, 4, 16, 64 mg/kg intraperitoneally (Lepak et al. 2018a) and 0.25, 1, 4, 16, 64 mg/kg intraperitoneally (Lepak et al. 2019). For all these assessments, groups of three mice were used for each dosing regimen and control group and both kidneys were evaluated and treated as independent findings.

The PK findings showed mean REZ C_{max} and $AUC_{0\text{-}\infty}$ ranged from 2.6 to 76.7 µg/mL and 93.2 to 40,464 µg·h/L, respectively. The REZ elimination half-life ranged from 28 to 41 hr. The REZ $AUC_{0\text{–}\infty}$ increased in an approximately dose-proportional manner over the dose range (Lepak et al. 2018b).

Species specific MICs and PK-PD target estimates from PD assessments are displayed in Table 106. It is noteworthy that species specific growth values from start of therapy were not reported for untreated controls. For *C. albicans, C. parapsilosis, C. auris, C. tropicalis,* and *C. dubliniensis* >1 log10 CFU/kidney growth from baseline was associated with <1 free-REZ

AUC/MIC (Lepak et al. 2018a; Lepak et al. 2018b; Lepak et al. 2019). For *C. glabrata*, approximately no growth from baseline (stasis) was associated with <0.1 free-REZ AUC/MIC (Lepak et al. 2018b). Stasis endpoint was achieved against all but a single strain of *C. parapsilosis*, and 1-log_{10} kill endpoint was achieved against all *C. albicans* and *C. glabrata* strains, 2 out of 3 *C. auris* strains, and none of the *C. parapsilosis* strains (Lepak et al. 2018a; Lepak et al. 2018b; Lepak et al. 2019). The PK-PD targets for the 1-log_{10} kill endpoint were generally 2- to 4-fold higher than stasis targets. Potency of REZ was more pronounced against *C. glabrata* but less pronounced against *C. parapsilosis* (as measured by 1-log10 kill) *or C. tropicalis and C. dubliniensis* (as measured by stasis or 1-log10 kill) compared to *C. albicans.*

Table 106. Summary of *Candida* Species MICs and Murine Invasive Candidiasis PK-PD Targets

	REZ PK-PD Target (*f*AUC_{0-168}/MIC[a,b]) by MIC				
	Individual Data			Median (Range)	
Organism	MIC (µg/mL)	REZ PK-PD Target Stasis	REZ PK-PD Target 1-log_{10} Kill	Stasis	1-log_{10} Kill
C. albicans	0.03	25.9	47	20.5 (14.2-25.9)	37.2 (21.3-48.1)
	0.06	25.6	48		
	0.06	14.2	21.3		
	0.06	15.4	27.5		
C. glabrata	0.125	0.4	2.5	0.5 (0.35-3.4)	2.9 (2.5-8.4)
	0.5	0.5	3		
	1	3.4	8.4		
C. parapsilosis	0.5	9.7	N/A	18.2 (9.7-26.7)	NA
	1	26.7	N/A		
	1	N/A	N/A		
C. auris	0.06	8.1	55.3	12.1 (4.6-23.8)	38.4 (27.4-55.3)
	0.125	23.8	38.43		
	0.25	16.1	27.4		
	2	4.6	N/A		
C. tropicalis	0.016	107.6	214.5	86.5 (44.7-108.6)	148.9 (73.5-214.5
	0.03	65.4	117		
	0.03	108.6	180.7		
	0.06	44.7	73.5		
C. dubliniensis	0.03	175.3	404.4	35.1 (21.5-175.3)	228.3 (30.1, 431.5)
	0.06	41.6	52.2		
	0.06	28.6	431.5		
	0.06	21.5	30.1		

Source: Reviewer's Table
[a] The fraction of REZ bound to plasma proteins in mice as measured by ultracentrifugation was 0.992 (NC-137 study report)
[b] The published *f*AUC_{0-24}/MIC target was multiplied by 7 to get weekly ratio to match all the rest.
Abbreviations: *f*AUC_{0-168}/MIC, area under the free rezafungin plasma concentration-time curve from time zero to 168 hours relative to MIC; MIC, minimum inh bitory concentration; PK-PD, pharmacokinetic-pharmacodynamic; NA = not applicable/attained; REZ, rezafungin

From the reported findings the following is noted:

- The Applicant's proposed *C. albicans, C. parapsilosis, and C. tropicalis* susceptibility test interpretive criteria (STIC) values were not within the range of REZ MICs tested (e.g., *C. albicans*: 0.25 µg/mL versus 0.06 µg/mL). To support the Applicant proposed STICs, REZ's antifungal activity would need to be extrapolated 2-fold, 2-fold, and 1-fold above the MICs of *C. albicans*, *C. tropicalis*, and *C. parapilosis,* respectively.

- In general, the magnitude of the PK-PD targets (associated with the stasis endpoint) do not remain constant across a range of MIC values. It is acknowledged that the quantity of data limits conclusive findings, especially given the small numbers of strains with variable susceptibilities per *Candida* species.
- Poor *C. glabrata* growth is observed during the conduct of aforementioned PK-PD studies, which calls into question the reliability of the REZ PK-PD targets
- REZ PK-PD targets (associated with endpoints on Day 7) against *C. auris, C. tropicalis, C. dubliniensis* are difficult to interpret from every three day dosing in the absence of murine PK data and considering REZ is proposed to be administered once weekly. In addition, while AUC/MIC is proposed to be the best PK-PD index, the C_{max}/MIC was also observed as a strong index making inferences on magnitude of the PK-PD targets from thrice weekly dosing difficult.
- The model may reflect a post-exposure prophylaxis more than treatment state with rezafungin treatment initiated 2 hours after inoculation

In addition to the limitations noted above, it remains to be established within the scientific community, how to generate robust and informative nonclinical in vivo fungal infection model efficacy data, what considerations are important during PK-PD evaluations/predictions, and how to verify such information to support PK-PD based translation of an antifungal drug's effectiveness from animal infection models to humans. Thus, while the clinical meaningfulness of these nonclinical findings is valuable in dosage selection for clinical studies, the translational utility of these findings to patient care with candidemia/IC is unclear.

14.2.4. Mass Balance

Study CD101.IV.1.12 was a phase 1 study that evaluated the excretion, metabolism, and mass balance following a single IV dose of ^{14}C-radiolabeled REZ in nine healthy male subjects 30 to 54 years of age. Radiolabeled IV drug (400 mg [~200 μCi)]) was infused over one hour.

Blood, urine, and fecal samples were collected up to 1,440 hours postdose to measure total radioactivity (in whole blood, plasma, pooled urine, and pooled feces samples) as well to characterize REZ and its metabolic profiles (pooled plasma, urine, and feces samples). The following are summary findings. Percentages described below refer to percent of dose.

- Mean radioactive recoveries in total excreta (urine+feces) was estimated to be 88.3% (min to max: 79.3% to 93.2%) (interpolated using initial confinement period [18 days] and data from the subjects' return visits to the clinical research unit on Day 29 and Day 60)
  - 25.7% of the total recovery in urine
  - 74.3% of the total recovery in feces
- The blood to plasma total radioactivity ratio ranged from 0.86 to 1.02
- From the circulating plasma radioactivity (plasma AUC/ blood AUC radioactivity-ng equivalents), REZ was the most abundant circulating component (77%) and all metabolites accounted for ≤9% (M1241_1 (9%), M1241_2 (5%), M1241_3 (7%))

- Parent/Metabolite profiling and identification in excreta (urine or feces):
  - Urinary excretion is minor route with no parent (REZ) detected
    - 25.7% of the dose was eliminated via urine with minor metabolites (all <10% of the dose) as most abundant urinary components
    - REZ accounted for <1% of radiolabeled components excreted
    - Metabolism was localized predominantly to the pentoxy or terphenylpentoxy side chain. Primary metabolism of REZ was mediated by hydroxylation and, to a lesser extent, oxidation, and oxidative O-dealkylation.
  - Fecal excretion of parent (REZ) is major route
    - 74.3% of the dose eliminated via feces
    - In pooled fecal samples, [^{14}C] rezafungin-derived radioactivity after an intravenous dose accounted for a mean of 37.4% of dose through 672 hours postdose, from which unchanged REZ accounted for 93% of radiolabeled components excreted.
- Mean terminal half-life for REZ in plasma, total radioactivity in plasma, and total radioactivity in whole blood was 341 hours, 387 hours, and 408 hours, respectively.

14.2.5. Single Ascending Dose

Study CD101.IV.1.01 was a randomized, double-blind, single-dose, dose-escalation study that evaluated the safety, tolerability, and PK of REZ in 32 (n=8 placebo, 24 REZ) healthy adults (including 15 (47%) females) with mean (range) age of 43 (25 to 54) years and weight of 76 (58 to 102) kg.

There were eight subjects (n=2 placebo, 6 REZ) enrolled in each of the four REZ dosing cohorts as follows: 50 mg, 100 mg, 200 mg, and 400 mg. Assigned treatment (REZ or placebo) was administered via 1-hour infusion. Blood samples were collected over the period of predose to 21 days postdose for PK assessments. REZ plasma concentrations were determined using a validated bioanalytical method and PK parameter estimates were derived using noncompartmental analysis (Table 107). The resultant REZ plasma exposure estimates (C_{max} and AUC) were evaluated for dose proportionality using a power model and findings are presented in Table 108.

Table 107. REZ Plasma PK Parameters (Geo Mean [%GCV])

Dose (mg)	C_{max} (µg/mL)	AUC_{inf} (µg·h/mL)	$t_{1/2}$[a] (hr)
50	2.7 (22)	225 (16)	134.8 (10)
100	4.8 (11)	418.5 (8)	145.7 (4)
200	10.7 (20)	918 (11)	127.3 (7)
400	22.4 (16)	1795.6 (18)	132.8 (12)

Source: Study report CD101.IV.1.01 – Table 22 (pg 82)
[a] Presented as mean (standard deviation)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from. time zero to infinity; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; PK, pharmacokinetic; REZ, rezafungin; $t_{1/2}$, half-life

Table 108. REZ Dose Proportionality

Exposure Parameter	Dose Range (mg)	Estimated Slope	95% CI of Slope Lower	95% CI of Slope Upper	Dose-Proportional
Ln C_{max}/dose	50 to 400	1.03	0.94	1.13	Yes
Ln AUC_{inf}/dose	50 to 400	1.01	0.94	1.09	Yes

Source: Study report CD101.IV.1.01 – Table 23 (pg 83)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity; C_{max}, maximum plasma concentration of drug; REZ, rezafungin

The REZ C_{max} and AUC increase in a dose-proportional manner over a dose range of 50 mg to 400 mg.

14.2.6. Multiple Ascending Dose

Study CD101.IV.1.02 was a randomized, double-blind, multiple-dose, dose-escalation study to evaluate the safety, tolerability, and PK in 24 (n=6 placebo, 18 REZ) healthy adults (including 12 (50%) females) with mean (range) age of approximately 43 (22 to 54) years of age and weight of 76 (57 to 97) kg.

There were eight subjects (n=2 placebo, 6 REZ) enrolled in each of the three REZ dosing cohorts as follows: 100 mg on Days 1 and 8, 200 mg on Days 1 and 8, and 400 mg on Days 1, 8, and 15. Assigned treatment (REZ or placebo) was administered via 1-hour infusion. Blood samples were collected over the period of predose to up to 28 days postdose for PK assessments. REZ plasma concentrations were determined using a validated bioanalytical method and PK parameter estimates were derived using noncompartmental analysis (Table 109). For urine PK assessment, samples were collected within 1 hour before dosing on Days 1 and 8 as well as during intervals as follows: 0 to 6 hours, >6 to 12 hours, >12 to 24 hours, >24 to 48 hours, >48 to 72 hours, >72 to 96 hours, >96 to 120 hours, and >120 to 144 hours after the start of study drug infusion on Days 1 and 8. Additional, spot urine samples were collected at the follow-up visits on Days 21 and 28. REZ plasma concentrations were determined using a validated bioanalytical method and PK parameter estimates were derived using noncompartmental analysis (Table 109).

Table 109. REZ Plasma PK Parameters (Geo Mean [%GCV])

Dose (mg)	Day	C_{max} (µg/mL)	AUC_{0-168} (µg·h/mL)	AUC_{inf} (µg·h/mL)	$t_{1/2}$[a] (hr)
100	1	5.6 (17)	297.5 (10)	388.4 (8)	79 (7)
	8	6.5 (11)	387.7 (11)	676.2 (15)	153 (17)
200	1	10.4 (20)	558.5 (24)	747.7 (29)	85 (12)
	8	12 (29)	797.7 (28)	1345.3 (30)	149.7 (9)
400	1	22.3 (22)	1171.3 (20)	1503.5 (20)	78.4 (5)
	15	28.7 (38)	1,813 (19)	3205.4 (15)	152 (13)

Source: Study report CD101.IV.1.02 – Tables 22-24 (pg 81-83)
[a] Presented as mean (standard deviation)
Abbreviations: AUC_{0-168}, area under the plasma concentration-time curve from 0 to 168 hours; AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; PK, pharmacokinetic; REZ, rezafungin; $t_{1/2}$, half-life

A very small amount (<0.26%) of the REZ dose was excreted in urine following 100, 200, or 400 mg REZ. Renal elimination does not play a significant role in total body clearance.

The half-life following multiple dosing on Day 8 is twice the estimate following the Day 1 dosing. This can be explained by the longer sampling time following multiple dosing and thus providing a better estimate of the rate of elimination. The half-life estimate following multiple dosing is similar to the half-life determined in the single REZ dose Study CD101.IV.1.01.

Exposures following the first dose were comparable to that observed in the single ascending dose study, with AUC and C_{max} generally increasing in a dose proportional manner. Minor REZ accumulation was observed for the 400 mg REZ dose. Mean ratio (last/first dose after 3 doses) was 1.33-fold (by C_{max}) or 1.55-fold (by the AUC_{0-168}).

14.2.7. Drug-Drug Interaction Studies Evaluating the Effect of Rezafungin on Other Drugs

Effect of REZ on Tacrolimus (TAC), Repaglinide (REP), Metformin (MET), Rosuvastatin (ROS), Pitavastatin (PIT), Caffeine (CAF), Efavirenz (EFA), Midazolam (MID), and Digoxin (DIG) Exposure

Study CD101.IV.1.09 was a single-center, open-label, two-period, cross-over cocktail DDI study that evaluated a 600 mg loading REZ IV dose on Day 1 followed by two 400 mg IV doses once weekly on Day 10 and Day 15, which is higher than the proposed 400 mg IV dose followed by 200 mg IV once weekly. REZ doses of 600 mg and 400 mg were administered over 1.5 hour and 1-hour infusions, respectively. The study enrolled 26 healthy subjects (24 males) with mean (range) age of approximately 39 (26 to 55) years of age and weight of 87 (58 to 107) kg. The study evaluated three cocktails (Cocktail 1: TAC + REP, Cocktail 2: MET + ROS + PIT, and Cocktail 3: CAF + EFA + MID + DIG) without REZ (Dose period 1) and with REZ (Dose period 2) as per the following treatment sequence:

Treatment Sequence:

- Dose period 1: Potential victim drug PK alone
  - Day -21: 5 mg TAC, 1 mg REP
  - Day -15: 500 mg MET, 5 mg ROS, 2 mg PIT
  - Day -9: 100 mg CAF, 50 mg EFA, 2 mg MID, 0.25 mg DIG
- Dose period 2: Potential victim drug + potential perpetrator REZ
  - Day 1: 600 mg REZ IV (1.5 h infusion) +5 mg TAC and 1 mg REP
  - Day 10: 400 mg REZ IV (1 h infusion) +500 mg MET, 5 mg ROS, and 2 mg PIT
  - Day 15: 400 mg REZ IV (1 h infusion) +100 mg CAF, 50 mg EFA, 2 mg MID, and 0.25 mg DIG

The washout period between treatment periods was reasonable based on potential victim drug half-lives. All potential victim (substrate) drugs were administered orally per drug specific United States Prescribing Information (USPI). REZ and substrate drug plasma PK samples were collected up to 144 to 168 hours postdose during both the dose periods. Substrate drug concentrations were evaluated using a validated bioanalytical method and PK parameter were compared based on geometric mean ratios (between the dosing period 2 (test) and dosing period 1 (reference) and associated 90% CIs. The findings for each substrate drugs are reported in Table 110 through Table 118.

Table 110. TAC PK Parameters After Single PO Administration of 5 mg TAC With and Without 600 mg IV REZ

Parameter	REZ+TAC (T) Geo Mean (%GCV)	TAC (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	283 (46)	329 (63)	86 (75-99)
C_{max} (ng/mL)	29 (45)	30.4 (58)	95 (80-112)
$T_{1/2}$ (h)	42 (13)	40 (12)	NC

Source: Study Report CD101.IV.1.09. Table 13 (pg. 64) and PK Report CD101.IV.1.09 Table 8.1.2 (pg. 94)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life; TAC, tacrolimus

Table 111. REP PK Parameters After Single PO Administration of 1 mg REP With and Without 600 mg IV REZ

Parameter	REZ+REP (T) Geo Mean (%GCV)	REP (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	26 (35)	22 (45)	116 (106-126)
C_{max} (ng/mL)	12 (44)	12 (55)	102 (89-117)
$T_{1/2}$ (h)	1 (40)	1 (40)	NC

Source: Study Report CD101.IV.1.09. Table 15 (pg. 67) and PK Report CD101.IV.1.09 Table 8.2.2 (pg. 101)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REP, repaglinide; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

Table 112. MET PK Parameters After Single PO Administration of 500 mg MET With and Without 400 mg IV REZ

Parameter	REZ+MET (T) Geo Mean (%GCV)	MET (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	7373 (30)	7447 (23)	99 (92-107)
C_{max} (ng/mL)	1116 (35)	1074 (25)	104 (94-115)
$T_{1/2}$ (h)	5 (41)	6 (52)	NC

Source: Study Report CD101.IV.1.09. Table 17 (pg. 70) and PK Report CD101.IV.1.09 Table 8.3.2 (pg. 108)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; MET, metformin; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

Table 113. ROS PK Parameters After Single PO Administration of 5 mg ROS With and Without 400 mg IV REZ

Parameter	REZ+ROS (T) Geo Mean (%GCV)	ROS (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	32 (43)	29 (42)	113 (102-127)
C_{max} (ng/mL)	4 (45)	3 (46)	112 (100-125)
$T_{1/2}$ (h)	11 (66)	8 (51)	NC

Source: Study Report CD101.IV.1.09. Table 19 (pg. 73) and PK Report CD101.IV.1.09 Table 8.4.2 (pg. 116)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; ROS, rosuvastatin; T, test; $T_{1/2}$, terminal half-life

Table 114. PIT PK Parameters After Single PO Administration of 2 mg PIT With and Without 400 mg IV REZ

Parameter	REZ+PIT (T) Geo Mean (%GCV)	PIT (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	89 (45)	86 (47)	106 (99-114)
C_{max} (ng/mL)	36 (63)	36 (52)	99 (84-115)
$T_{1/2}$ (h)	7 (46)	7 (38)	NC

Source: Study Report CD101.IV.1.09. Table 21 (pg. 76) and PK Report CD101.IV.1.09 Table 8.5.2 (pg. 123)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; NC, not calculated; PIT, pitavastatin; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

Table 115. CAF PK Parameters After Single PO Administration of 100 mg CAF With and Without 400 mg IV REZ

Parameter	REZ+CAF (T) Geo Mean (%GCV)	CAF (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	20853 (38)	18898 (37)	110 (105-116)
C_{max} (ng/mL)	2233 (25)	2075 (20)	108 (102-113)
$T_{1/2}$ (h)	6 (36)	7 (39)	NC

Source: Study Report CD101.IV.1.09. Table 23 (pg. 79) and PK Report CD101.IV.1.09 Table 8.6.2 (pg. 130)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CAF, caffeine; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

Table 116. EFA PK Parameters After Single PO Administration of 50 mg EFA With and Without 400 mg IV REZ

Parameter	REZ+EFA (T) Geo Mean (%GCV)	EFA (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	16156 (51)	14414 (36)	112 (103-123)
C_{max} (ng/mL)	300 (21)	299 (21)	100 (95-105)
$T_{1/2}$ (h)	170 (58)	149 (48)	NC

Source: Study Report CD101.IV.1.09. Table 25 (pg. 84) and PK Report CD101.IV.1.09 Table 8.7.2.1 (pg. 138)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; EFA, efavirenz; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

Table 117. MID PK Parameters After Single PO Administration of 2 mg MID With and Without 400 mg IV REZ

Parameter	REZ+MID (T) Geo Mean (%GCV)	MID (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	24 (35)	23 (40)	101 (93-110)
C_{max} (ng/mL)	9 (31)	9 (38)	97 (88-106)
$T_{1/2}$ (h)	4 (20)	4 (20)	NC

Source: Study Report CD101.IV.1.09. Table 27 (pg. 88) and PK Report CD101.IV.1.09 Table 8.8.2 (pg. 148)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; MID, midazolam; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

Table 118. DIG PK Parameters After Single PO Administration of 0.25 mg DIG With and Without 400 mg IV REZ

Parameter	REZ+DIG (T) Geo Mean (%GCV)	DIG (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	19 (19)	17 (22)	110 (102-117)
C_{max} (ng/mL)	0.8 (36)	0.8 (31)	99 (89-109)
$T_{1/2}$ (h)	45 (15)	44 (21)	NC

Source: Study Report CD101.IV.1.09. Table 29 (pg. 91) and PK Report CD101.IV.1.09 Table 8.9.2 (pg. 156)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; DIG, digoxin; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

The study findings reported above show REZ does not clinically significantly influence the PK of CYP1A2, 2B6, 2C8, and 3A enzymes or P-gp, OATP, OCT-1/2, MATE1/2 transporter substrate drugs. An absence of a DDI, as defined by the default no-effect boundary (80 to 125%), was observed for six of the nine substrate drugs (MET, PIT, CAF, EFA, MID, DIG). However, three substrate drugs (TAC, REP, and ROS) were observed to have a 90% confidence limit value marginally beyond the default boundary. Notably, a higher (than proposed) REZ dosing regimen of 600 mg on Day 1, then 400 mg on Day 10 and 15 reduced, on average, the tacrolimus AUC by 14% when coadministered. No significant effect of REZ on the PK of midazolam (CYP3A clinical index substrate drug) and digoxin (P-gp clinical index substrate drug) was observed. This suggests that the decrease in the overall exposure of tacrolimus observed following repeat administration of REZ (three doses over 14 days), may not be a result of altered CYP3A mediated metabolism or P-gp mediated transport. Therefore, the reason for the reduced TAC concentrations following oral administration when coadministered with REZ 600 mg IV remains unknown. Importantly, therapeutic drug monitoring of TAC is a standard practice.

14.2.8. Effect of REZ on Cyclosporine, Ibrutinib, Mycophenolate Mofetil, and Venetoclax Exposure

Study CD101.IV.1.17 was a single-center, open-label, two-period, 2-cohort, cross-over cocktail DDI study that evaluated a 400 mg loading REZ IV dose on Day 1 followed by 200 mg IV dose on Days 8 and 15. REZ doses of 400 mg were administered via 1-hour infusion. The study enrolled 34 healthy subjects in two cohorts (Cohort 1: 18 males, Cohort 2: 16 females) with mean (range) age of approximately 39 (21 to 59) years of age and weight of 79 (50 to 114) kg. The substrate drugs were administered substrate drugs over three days without REZ and with REZ as per the following treatment sequence:

Treatment Sequence

- Dose period 1: Potential victim drug PK alone
  - Day -16: 200 mg cyclosporine (CYS) by mouth (PO) (Cohorts 1+2)
  - Day -10: 280 mg ibrutinib (IBR) PO (Cohorts 1+2)
  - Day -7: 500 mg mycophenolate mofetil (MYC) PO (Cohort 1) or 50 mg venetoclax (VEN) PO (Cohort 2)
- Dose period 2: Potential victim drug + potential perpetrator REZ
  - Day 1: 400 mg REZ IV (1 h infusion) +200 mg CYS PO (Cohorts 1+2)
  - Day 8: 200 mg REZ IV (1 h infusion) +280 mg IBR PO (Cohorts 1+2)
  - Day 15: 200 mg REZ IV (1 h infusion) +500 mg MYC PO (Cohort 1) or 50 mg VEN PO (Cohort 2)

The washout period between treatment periods was reasonable based on potential victim drug half-lives. All potential victim (substrate) drugs were administered orally per drug specific USPI. REZ and substrate drug plasma PK samples were collected up to 144 to 168 hours postdose. Substrate drug concentrations were evaluated using a validated bioanalytical method and PK parameter were compared based on geometric mean ratios (between the dosing period 2 (test) and dosing period 1 (reference) and associated 90% CI. The findings for each substrate drugs are reported in Table 119 through Table 122.

Table 119. CYS PK Parameters After Single PO Administration of 200 mg CYS With and Without 400 mg IV REZ

Parameter	REZ+CYS (T) Geo Mean (%GCV)	CYS (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	4729 (27)	5002 (29)	95 (89-101)
C_{max} (ng/mL)	919 (23)	990 (29)	93 (84-102)
$T_{1/2}$ (h)	22 (33)	21 (50)	NC

Source: Study Report CD101.IV.1.17. Table 11-2 (pg. 54) and PK Report CD101.IV.1.17 Tables 14.2.1.2.1 and 14.2.1.2.2 (pg. 27, 29)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; CYS, cyclosporine; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

Table 120. IBR PK Parameters After Single PO Administration of 280 mg IBR With and Without 200 mg IV REZ

Parameter	REZ+IBR (T) Geo Mean (%GCV)	IBR (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	244 (68)	277 (59)	88 (80-96)
C_{max} (ng/mL)	66 (76)	79 (61)	83 (72-97)
$T_{1/2}$ (h)	7 (31)	7 (29)	NC

Source: Study Report CD101.IV.1.17. Table 11-4 (pg. 57) and PK Report CD101.IV.1.17 Tables 14.2.2.1.1 and 14.2.2.1.2 (pg. 43, 46)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IBR, ibrutin b; IV, intravenous; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

Table 121. MYC PK Parameters After Single PO Administration of 500 mg MYC With and Without 200 mg IV REZ

Parameter	REZ+MYC (T) Geo Mean (%GCV)	MYC (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	28622 (19)	28274 (25)	101 (91-112)
C_{max} (ng/mL)	7741 (54)	9541 (33)	81 (63-105)
$T_{1/2}$ (h)	14 (45)	12 (41)	NC

Source: Study Report CD101.IV.1.17. Table 11-6 (pg. 60) and PK Report CD101.IV.1.17 Tables 14.2.3.2.1 and 14.2.3.2.2 (pg. 61, 64)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; MYC, mycophenolate mofetil; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life

Table 122. VEN PK Parameters After Single PO Administration of 50 mg VEN With and Without 200 mg IV REZ

Parameter	REZ+VEN (T) Geo Mean (%GCV)	VEN (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng·hr/mL)	2585 (48)	3083 (43)	90 (80-102)
C_{max} (ng/mL)	227 (48)	254 (43)	95 (83-108)
$T_{1/2}$ (h)	15 (28)	17 (31)	NC

Source: Study Report CD101.IV.1.17. Table 11-8 (pg. 63) and PK Report CD101.IV.1.17 Tables 14.2.4.2.1 and 14.2.4.2.2 (pg. 77, 80)
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; IV, intravenous; NC, not calculated; PK, pharmacokinetic; PO, by mouth; R, reference; REZ, rezafungin; T, test; $T_{1/2}$, terminal half-life; VEN, venetoclax

The study findings reported above show REZ does not clinically significantly influence the PK of commonly coadministered drugs. An absence of a DDI, as defined by the default no-effect boundary (80 to 125%), was observed for all four substrate drugs (CYS, IBR, MYC, VEN) as measured by AUC. Note, contrary to the Applicant, the IBR USPI states it is not a BCRP substrate. For BCRP assessments refer to Study CD101.IV.1.09 and Section 14.1.4.

14.2.9. Comparison of REZ DDI Potential With FDA-Approved Azole and Echinocandin DDI Potential

To assess and compare DDI potential between REZ and the FDA-approved azole and echinocandin antifungal drug products indicated to treat candidemia and IC, DDI information was compiled (Table 123 and Table 124). 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 (USPI). All azole drugs are both victims and perpetrators of PK DDIs to varying degrees, posing potentially frequent DDI risks. For echinocandins, REZ may have a relatively better DDI profile compared to caspofungin. Indeed, caspofungin's USPI recommends an alternative dosing regimen when administered concomitantly with drugs that are CYP enzyme inducers. However, REZ appears to have a similar DDI profile to anidulafungin and micafungin.

Table 123. DDI Risk 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 are 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 the 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; DDI, drug-drug interaction; OATP, organic anion transporter peptide; P-gp, P-glycoprotein; PK, pharmacokinetics; PM, poor metabolizer; USPI, United States Prescribing Information

Table 124. DDI Risk Comparisons: As Perpetrator of PK Drug Interactions

Drug	Risk	Key Highlights
Fluconazole	High	There are DDI management and dose modification recommendations in 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 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 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 inh bitors 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

14.2.10. Hepatic Impairment

Study CD101.IV.1.15 was an open-label study to determine the safety and PK of a 400 mg REZ dose (via 1-hour infusion) in hepatically impaired (HI) individuals. Eight individuals with moderate HI (Child-Pugh Scores 7 to 9) and eight individuals with severe HI (Child-Pugh Scores 10 to 12) were enrolled together with healthy volunteers (HV) with normal hepatic function (n=16) matched for age (±10 years), gender, and body mass index (±20%). Enrolled individuals were 41 to 68 years of age, 71 to 137 kg, and majority (63%) were male. Individuals received a single 400 mg REZ IV dose infused over 1 hour. Blood samples were collected predose and up to 336 hours postdose for determination of plasma REZ PK. Plasma protein binding of REZ was

also determined using predose spiked samples, as well as samples at 45 minutes and 72 hours after the start of infusion. REZ drug concentrations were evaluated using a validated bioanalytical method and PK parameter were compared based on geometric mean ratios (between the subjects with moderate or severe HI and respective matched HV) and associated 90% CI. The PK parameters from subjects with and without HI as well as comparison of exposure parameter estimates is shown in Table 125. Protein binding information (% mean fraction unbound) and unbound exposure parameter (C_{max} and AUC) estimates from the different HI groups are reported in Table 126 and Table 127, respectively. Distribution of unbound exposure parameter estimates across individuals with the different degree of HI were also compared (Figure 3). Additional analysis was conducted by the Reviewer to evaluate correlation between total bilirubin concentrations and total REZ AUC_{inf} (Figure 4).

Table 125. Total (Bound + Unbound) REZ PK Parameters and Statistical Comparisons After Single Dose Administration in Individuals With Varying Degree of Hepatic Impairment

	Moderate HI	Matched HV	Severe HI	Matched HV
Group	**Group 1a (N=8)**	**Group 1b (N=8)**	**Group 2a (N=8)**	**Group 2b (N=8)**
Parameter	**Geo Mean (%GCV)**			
C_{max} (µg/mL)	18 (22)	20 (27)	17 (13)	23 (18)
AUC_{inf} (µg*h/mL)	1170(27)	1730 (25)	1230 (19)	1810 (19)
$T_{1/2}$ (h)	110 (11)	122 (15)	120 (10)	122 (21)
	HI vs. Matched HV Geometric Mean Ratio, % (90% CI)			
Parameter Comparison	**Moderate HI vs. Matched HV**		**Severe HI vs. Matched HV**	
C_{max}	88 (71-109)		72 (63-83)	
AUC_{inf}	68 (54-85)		68 (58-80)	

Source: Summary Clinical Pharmacology, Table 11 (pg 27) and CD101.IV.1.15 clinical study report Table 14.2.1.2- Table 14.2.1.2.4 (pg 33-70).
Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; %GCV, geometric coefficient of variation expressed as a percent; Geo, geometric; HI, hepatic impairment; N, number of observations; PK, pharmacokinetic; REZ, rezafungin; $T_{1/2}$, terminal half-life

Table 126. Summary of Plasma REZ Fraction Unbound Data After Single Dose Administration in Individuals With Varying Degree of Hepatic Impairment

	Moderate HI	Matched Normal	Severe HI	Matched Normal
Time Point (h)	**Group 1a (N=8)**	**Group 1b (N=8)**	**Group 2a (N=8)**	**Group 2b (N=8)**
	Arithmetic Mean Fraction Unbound, % (%CV)			
Pre-dose (spiked)	2.78 (53)	3.24 (65)	4.09 (56)	2.11 (34)
0.75	3.06 (51)	3.05 (60)	5.18 (51)	2.98 (44)
Day 1 pooled[a]	2.88 (50)	3.76 (57)	3.74 (57)	2.59 (39)
72	3.95 (31)	4.11 (61)	5.65 (50)	2.89 (31)
Mean f_u[b]	3.3 (38)	3.64 (58)	4.85 (51)	2.82 (34)

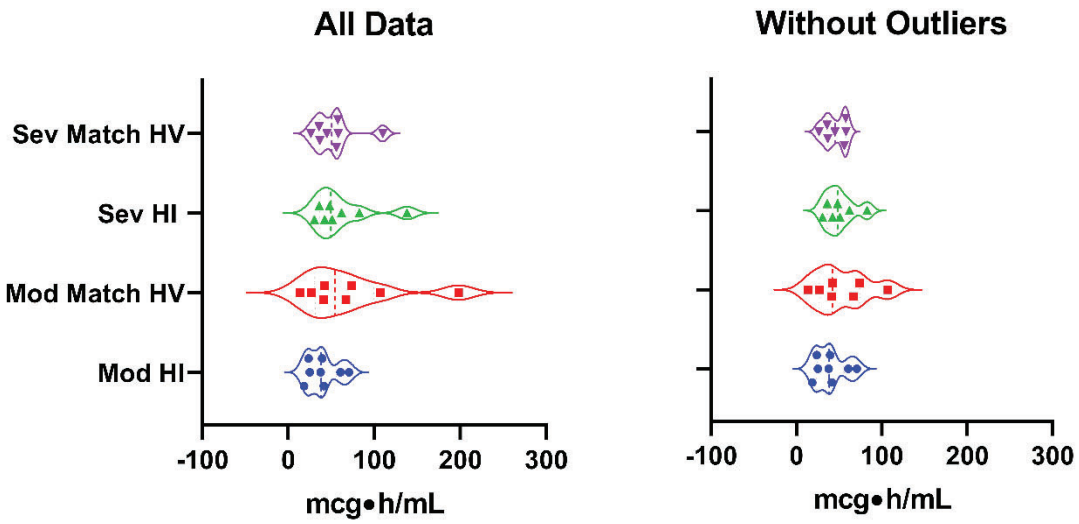
Source: CD101.IV.1.15 clinical study report, Table 11-4 (pg 57).
[a] On Day 1, samples were pooled from 3.00 hours to 12.00 hours post-dose for protein binding analysis.
[b] Mean f_u was estimated as the mean from the individual percent fraction unbound values taken post rezafungin dose administration (i.e., at 0.75 hr, 72 hr, and from the Day 1 pooled sample).
Abbreviations: CV, coefficient of variation; f_u, fraction unbound; HI, Hepatic Impairment; N, number of observations; REZ, rezafungin

Table 127. Unbound REZ PK Parameters After Single Dose Administration in Individuals With Varying Degree of Hepatic Impairment

Time Point (h)	Moderate HI Group 1a (N=8)	Matched HV Group 1b (N=8)	Severe HI Group 2a (N=8)	Matched HV Group 2b (N=8)
	Arithmetic Mean Unbound PK Parameter, (%CV)			
$C_{max, u}$ (µg/mL)	0.59 (46)	0.84 (87)	0.8 (55)	0.66 (47)
$AUC_{inf, u}$ (µg*h/mL)	39.7 (46)	71.4 (83)	61.4 (57)	53.3(48)

Source: CD101.IV.1.15 clinical study report, Table 11-5 (pg 59)
Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity after drug administration; C_{max}, maximum plasma concentration of drug; CV, coefficient of variation; HI, Hepatic Impairment; N, number of observations; PK, pharmacokinetics; REZ, rezafungin; u, unbound parameter

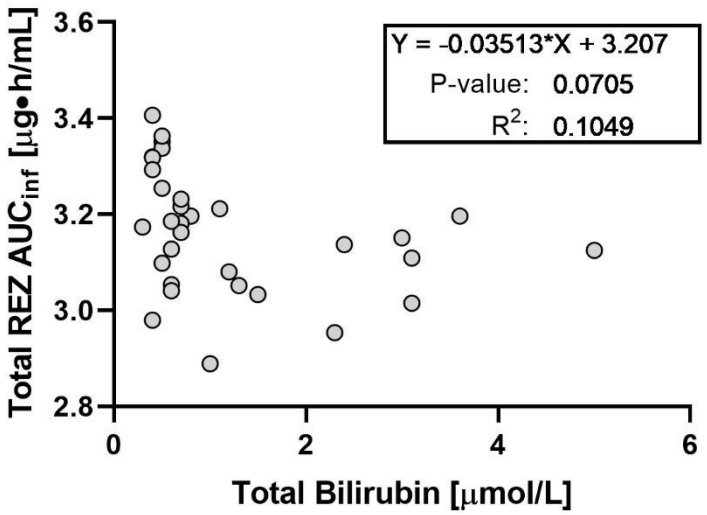
Figure 3. Violin Plot Showing Distribution of Unbound REZ PK After Single Dose Administration in Individuals With Varying Degree of Hepatic Impairment



Source: Reviewer's analysis.
Abbreviations: HI, hepatic impairment; HV, healthy volunteers; Mod, moderate; PK, pharmacokinetics; REZ, rezafungin; Sev, severe; (---), median

Considering all data, the median AUC_{inf} is approximately 39 (n=8), 55 (n=8), 49 (n=8), and 51 (n=8) µg·h/mL in individuals with moderate HI, HV matched to moderate HI, individuals with severe HI, and HV matched to severe HI, respectively. After removal of three potential outliers (one each from HV matched to severe HI, severe HI, and HV matched to moderate HI groups), the median AUC_{inf} is 39 (n=8), 42 (n=7), 48 (n=7), and 45 (n=7) µg·h/mL in individuals with moderate HI, HV matched to moderate HI, individuals with severe HI, and HV matched to severe HI, respectively. To identify potential outliers, the ROUT method available in GraphPad Prism (build 8.4.3) was utilized with the set false discovery rate (Q) of 10%, i.e., at least 90% of the identified outliers are expected to be real.

Figure 4. Correlation Between Total Bilirubin Concentrations and Total (Bound + Unbound) REZ AUC_{inf} After Single Dose Administration in Individuals With Varying Degree of Hepatic Impairment



Source: Reviewer's analysis
Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity after drug administration; REZ, rezafungin

Mean REZ PK exposure was reduced by approximately 30% (with all available data) in individuals with moderate and severe hepatic impairment compared to matched individuals with normal hepatic function. Based on the study findings, the Applicant proposes no dosage adjustment is needed in patients with HI.

The Applicant's proposal appears reasonable as a 30% reduction in total (bound + unbound) REZ AUC is not anticipated to be clinically relevant based on the following:

(1) For REZ, the observed exposure-response (E-R) relationship is flat over the exposure range anticipated from the proposed REZ dosage (see Section 14.5.6)
(2) REZ PK was similar in individuals with moderate and severe HI, indicating that REZ exposure did not change with increasing degree of HI.
(3) Unbound REZ PK exposures were similar between moderate and severe HI and matched HVs (Figure 3), after considering potential outliers (n=approximately 1/group).
(4) Individual post hoc (Bayesian) estimates of the rezafungin Day 1 C_{max} and AUC_{0-168} did not indicate a difference between candidemia and IC patients with moderate hepatic impairment (n=5 phase 2 and phase 3 individuals with Child-Pugh score 7 to 9) and those without hepatic impairment (data not shown; FDA reviewer analysis).

It is noteworthy that plasma protein binding was similar between individuals without HI and with moderate HI, however, was lower in subjects with severe HI. This may have been reflective of reduced baseline albumin levels in individuals with severe HI albumin levels have been found to be correlated with REZ PK data from healthy subjects and patients (see Section 14.4).

As REZ undergoes minimal or no hepatic metabolism, the mechanism for the observed reduction in plasma REZ exposure is not clear. Correlation analysis evaluating the relationship between total bilirubin concentrations and total REZ AUC_{inf} did not show a clear relationship (Figure 4).

Overall, based on the review of available information, we agree with the Applicant's proposal that no dosage adjustment is needed in patients with hepatic impairment.

14.3. Bioanalytical Method Validation and Performance

Clinical studies utilized validated high-performance liquid chromatography with tandem mass spectrometry bioanalytical methods for quantification of REZ in PK samples. Briefly, the bioanalytical methods' validation and performance, as summarized in Table 128, met the criteria recommended in the Bioanalytical Method Validation Guidance for Industry (November 2022). Methods were adequately validated, and the submitted validation reports included dilution linearity and extraction efficiency (recovery) information, when applicable. The bioanalytical performance reports included chromatograms, which are acceptable. In addition, concentrations were precisely and accurately measured with samples stored and processed in the time frame supported by stability data. Incurred sample re-analyses were conducted, and findings are acceptable.

Table 128. Summary of Bioanalytical Method Validation and Performance for Rezafungin

Method Parameters	Method Details		
Study no.	CD101.IV.1.01 CD101.IV.1.02 CD101.IV.1.06 CD101.IV.2.03	CD101.IV.1.07 CD101.IV.1.09 CD101.IV.1.12	CD101.IV.1.15 CD101.IV.3.05
Drug	REZ		REZ
Biological matrix	Plasma		
Anticoagulant	K_2EDTA		
Extraction methods	Protein precipitation extraction		
Internal standard	[$^2H_9$]REZ		
Validation range (ng/mL)	10 to 10000		50 to 50000
QC levels (ng/mL)	10, 30, 300, 3000, and 8000		50, 150, 15000, and 37500
Inter-day accuracy (RE%)[a]	-3 to 6.7	-3.3 to 1.3	-8.3 to 4
Inter-day precision (CV%)[a]	≤6.4	≤4.9	≤15
Incurred sample reanalysis[b]	93 to 100%	98 to 100%	92 to 100%
Validation report	NC-173	NC-175	NC-204
Study no.	CD101.IV.1.01 CD101.IV.1.02		
Drug	REZ		
Biological matrix	Urine		
Extraction methods	Protein precipitation extraction		
Internal standard	[$^2H_9$]REZ		
Validation range (ng/mL)	5 to 5000		
QC levels (ng/mL)	5, 15, 150, 2000, and 4000		
Inter-day accuracy (RE%)[a]	-2 to 4.2		

Method Parameters	Method Details
Inter-day precision (CV%)[a]	≤5.7
Incurred sample reanalysis[b]	82.7 to 100%
Validation report	NC-174

Source: Reviewer's analysis
[a] The inter-day accuracy and precision values from validation and performance reports are combined and presented as an overall range.
[b] At least 10% of samples reanalyzed
Abbreviations: CV%, co-efficient of variation expressed as percent; QC, quality control; RE%, relative error expressed as percent; REZ, rezafungin

14.4. Immunogenicity Assessment-Impact of PK/PD, Efficacy, and Safety

N/A

14.5. Pharmacometrics Assessment

14.5.1. Review Summary

Rezafungin is an echinocandin antifungal for the treatment of candidemia and/or invasive candidiasis. Efficacy and safety of rezafungin monotherapy (against active comparator) were evaluated in a multicenter, prospective, randomized, double-blind phase 2 study (STRIVE) and a multicenter, prospective, randomized, double-blind, double-dummy phase 3 study (ReSTORE).

In general, the Applicant's population pharmacokinetic analysis of pooled PK data from healthy subjects and patients is considered acceptable for characterization of rezafungin PK and evaluation of the impact of clinically relevant covariates. Additionally, the final population PK model is acceptable for generation of exposure metrics for exposure-response analyses and PTA analysis. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 129.

Table 129. Specific Comments on Applicant's Final Population PK Model

Utility of the Final Model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	No clinically relevant effects on the pharmacokinetics of rezafungin were observed based on age, sex, race, weight. No clinically relevant effect on the pharmacokinetics of rezafungin were observed based on renal impairment (creatinine clearance: 10 mL/min to above 120 mL/min) and no effect is expected in patients undergoing hemodialysis.	These statements are acceptable. Covariate analysis using the Applicant's basic model demonstrates that no evident difference exists based on age, sex, body weight, or renal function.
	Extrinsic factor	N/A	N/A
Derive exposure metrics for Exposure-response analyses	Bayesian posterior predicted Day 1 AUC_{0-168}, C_{max}, and AUC_{0-168}/MIC (Both total and unbound rezafungin AUC_{0-168} were derived assuming 2.6% fraction unbound)		The Applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses.
Predict exposures at alternative dosing regimen	N/A		N/A

Source: reviewer analysis
Abbreviations: AUC_{0-168}, area under the concentration-time curve from time 0 to 168 hours; C_{max}, maximum concentration; MIC, minimum inhibitory concentration; N/A, not applicable; PK, pharmacokinetic

14.5.2. Introduction

Rezafungin is an echinocandin antifungal for the treatment of candidemia and/or invasive candidiasis. The primary objectives of Applicant's pharmacometric analysis was to:

- Develop a population PK model to describe rezafungin disposition in healthy subjects and patients
- Evaluate the impact of intrinsic and extrinsic covariates on rezafungin PK
- Generate individual rezafungin exposure metrics using posterior predictions for E-R analysis

14.5.3. Model Development

Data

The population PK analysis was based on pooled PK data from five phase 1 studies, one phase 2 study, and one phase 3 study. The studies are summarized in detail Table 130. Rezafungin dosing regimens and PK sampling times are described in Table 131.

The final NONMEM data file for population PK analysis contained 2512 PK observations from 277 subjects. A summary of demographic characteristics of the analysis population by study is provided in Table 132. Height, body weight and AST were missing for seven, five, and one subject, respectively, and were imputed using study- and sex-specific median values.

Table 130. Studies Included in the Population PK Analysis

Study Number Phase	Study Title	Participants	Duration of Dosing	Major Exclusions
CD101.IV.1.01 Phase 1	A Phase 1, randomized, double-blind, single-dose, dose escalation study to determine the safety, tolerability, and pharmacokinetics of CD101 injection in healthy subjects	32 subjects; 4 cohorts of 8 subjects (6 active, 2 placebo)	Single dose of 60-minute infusion	Placebo subjects
CD101.IV.1.02 Phase 1	A Phase 1, randomized, double-blind, multiple-dose, dose-escalation study to determine the safety, tolerability, and pharmacokinetics of CD101 injection in healthy subjects	24 subjects; 3 cohorts of 8 subjects (6 active, 2 placebo)	Cohorts 1 and 2: two 60-minute weekly infusions Cohort 3: three 60-minute weekly infusions	Placebo subjects
CD101.IV.1.06 Phase 1	A Phase 1, randomized, double-blind, comparative, placebo and positive controlled study to evaluate the safety, pharmacokinetics, and effects on the electrocardiogram of CD101 for injection in healthy subjects	60 subjects; 2 cohorts of 30 subjects	3.5 hours of infusion	Placebo and moxifloxacin subjects
CD101.IV.1.07 Phase 1	A Phase 1, multiple-dose, assessor-blinded study to determine the photosensitivity of CD101 for injection in healthy subjects	24 subjects (12 CD101, 12 placebo)	Total of 4 weekly infusion doses	Placebo subjects
CD101.IV.1.15 Phase 1	An open-label, single-dose, Phase 1 study to evaluate the safety, tolerability, and pharmacokinetics of rezafungin in adult subjects with hepatic impairment relative to matched controls	Stage 1 – 16 subjects: 8 subjects with moderate hepatic impairment (Group 1a); 8 healthy adults with normal hepatic function (Group 1b) matched to hepatic impaired subjects in Group 1a Stage 2 – 16 subjects: 8 subjects with severe hepatic impairment (Group 2a); 8 healthy adults with normal hepatic function (Group 2b) matched to hepatic impaired subjects in Group 2a	Single injection	None
Study Number Phase	**Study Title**	**Participants**	**Duration of Dosing**	**Major Exclusions**
CD101.IV.2.03; STRIVE Phase 2	A Phase 2, multicenter, randomized, double-blind study of the safety, tolerability, and efficacy of intravenous CD101 vs intravenous caspofungin followed by oral fluconazole step-down in the treatment of subjects with candidemia and/or invasive candidiasis	Part A: 107 subjects Part B: 100 subjects	2 weekly infusions followed by 2 optional weekly infusions	Caspofungin subjects
CD101.IV.3.05; ReSTORE Phase 3	A Phase 3, multicenter, randomized, double-blind study of the efficacy and safety of rezafungin for injection versus intravenous caspofungin followed by optional oral fluconazole step-down in the treatment of subjects with candidemia and/or invasive candidiasis (the ReSTORE study)	218 subjects (109 rezafungin, 109 caspofungin)	2 weekly doses followed by 2 optional weekly doses	Caspofungin subjects

Abbreviations: CD101, rezafungin.

Source: Applicant's Population PK report, Table 1, pages 43-44
Abbreviations: PK, pharmacokinetic

Table 131. Dosing Regimens and PK Samplings

Study Number/ Phase	Dosing Regimen	Pharmacokinetic Sampling Plan
CD101.IV.1.01/ Phase 1	Single doses of 50, 100, 200, or 400 mg rezafungin or placebo infused IV over 1 hour	15 minutes predose, 15, 30, and 60 minutes, and 1.5, 2, 4, 6, 8, 12, 24, 48, 120, 168 (Day 7), 336 (Day 14), and 504 (Day 21) hours after the start of study drug infusion
CD101.IV.1.02/ Phase 1	Cohorts 1 and 2: 2 weekly doses of 100 or 200 mg rezafungin infused IV over 1 hour Cohort 3: 3 weekly doses of 400 mg rezafungin infused IV over 1 hour	Days 1 and 8 predose within 15 minutes before dosing; at 30 minutes, 1, 1.5, 2, 4, 6, 8, and 12 hours after the start of the infusions; at 24 hours (Days 2 and 9), 48 hours (Days 3 and 10), and 120 hours (Days 6 and 13) after the start of the infusions; on Days 7 and 14; and at the follow-up visits on Days 21 and 28
CD101.IV.1.06/ Phase 1	Single dose of 600 or 1400 mg rezafungin or placebo. 600-mg dose infused over 1.5 hours followed by IV placebo infusion over 2 hours; 1400-mg dose infused as a divided dose of 375 mL over 1.5 hours followed by a 500-mL infusion over 2 hours: oral dosing of moxifloxacin (400 mg) as positive control	15 minutes before dosing; at 1.5, 2.5, 3.5, 5, 6, 8, 12, and 24 hours after the start of the infusion or oral dosing. Subjects in the rezafungin and IV placebo dose groups had additional PK samples collected at 48, 96, and 168 hours after the start of the infusion
CD101.IV.1.07/ Phase 1	4 weekly doses of 400 mg rezafungin or placebo infused IV over 1 hour	Predose, and 1, 2, 6, 12, 24, 48, 72, and 168 hours relative to the start of infusion on Day 1 and Day 22, and predose on Day 15
CD101.IV.1.15/ Phase 1	IV infusion of 400 mg rezafungin over 1 hour	At the end of infusion, 1.5, 3, 6, 8, 12, 24, 48, 96, 168, and 336 hours from the start of infusion
CD101.IV.2.03; STRIVE/ Phase 2	Part A: Group 1: 2 doses of 400 mg rezafungin followed by 2 optional weekly doses of 400 mg rezafungin administered IV over 1 hour Group 2: 400 mg of rezafungin followed by 3 optional weekly doses of 200 mg rezafungin administered IV over 1 hour Part B: Group 1: 2 doses of 400 mg rezafungin followed by 2 optional weekly doses of 400 mg rezafungin administered IV over 1 hour In both Part A and Part B, subjects may receive oral step-down therapy of placebo after ≥ 3 days of IV therapy	Day 1 (within 10 minutes) before the end of infusion, at 4 and 8 hours after the end of infusion, or between 15 minutes and 1 hour after the end of infusion, and between 2 hours and 12 hours after the end of infusion, Day 2, Day 4, Day 8 (predose only), and Day 15 (predose only)
CD101.IV.3.05; ReSTORE/ Phase 3	IV infusion of 400 mg of rezafungin on Week 1, 200 mg rezafungin on Week 2, followed by up to 2 optional weekly doses of 200 mg or step-down therapy (placebo)	Day 1 (10 minutes before the end of infusion, and 1 sample taken any time between end of infusion and 12 hours after the end of infusion), Days 2, 3, 4, or 5 (1 sample taken at any time on 1 day only), Day 8 (predose), Day 14 (for subjects not receiving a Day 15 dose: 1 sample taken at any time), Day 15 (predose, if applicable), Day 22 (predose, if applicable)

Abbreviations: IV, intravenous; PK, pharmacokinetic.

Source: Applicant's Population PK report, Table 2, page 45

Table 132. Summary of Baseline Characteristics by Study

Subject Characteristic	Statistics	Study							Overall
		CD101.IV.1.01	CD101.IV.1.02	CD101.IV.1.06	CD101.IV.1.07	CD101.IV.1.15	CD101.IV.2.03	CD101.IV.3.05	
Baseline Age (y)	Mean (SD)	42.2 (8.3)	41.1 (9.9)	36.1 (8.2)	38.3 (9.8)	57.1 (5.9)	57.3 (14.9)	59.9 (15.5)	53.2 (15.5)
	Median	41.0	44.5	36.0	38.5	57.0	57.5	59.0	53.0
	Min, Max	25, 54	22, 54	20, 51	22, 51	41, 68	24, 88	27, 89	20, 89
	n	24	18	24	12	32	70	97	277
Baseline Body Weight (kg)	Mean (SD)	76.39 (9.82)	76.01 (12.90)	76.33 (12.83)	81.78 (14.05)	90.06 (13.65)	74.46 (21.13)	73.01 (22.76)	76.50 (19.50)
	Median	75.00	74.75	78.60	79.05	89.35	71.00	68.00	74.70
	Min, Max	57.8, 101.6	57.1, 96.5	51.1, 102.1	62.2, 117.6	72.1, 134.2	34.0, 154.5	37.2, 149.9	34.0, 154.5
	n	24	18	24	12	32	70	97	277
Baseline BMI (kg/m^2)	Mean (SD)	28.21 (2.71)	27.07 (2.80)	26.73 (3.16)	26.66 (3.74)	30.69 (3.08)	26.25 (7.69)	25.22 (6.97)	26.69 (6.17)
	Median	28.45	27.20	26.00	26.15	30.85	25.45	23.50	26.39
	Min, Max	22.7, 32.0	22.5, 31.7	20.2, 31.8	21.3, 35.1	24.5, 35.4	13.9, 64.4	13.7, 51.9	13.7, 64.4
	n	24	18	24	12	32	70	97	277
Baseline BSA (m^2)	Mean (SD)	1.83 (0.15)	1.85 (0.20)	1.90 (0.21)	2.02 (0.20)	2.09 (0.19)	1.87 (0.29)	1.85 (0.31)	1.89 (0.27)
	Median	1.81	1.83	1.90	2.00	2.10	1.90	1.80	1.90
	Min, Max	1.5, 2.2	1.6, 2.2	1.5, 2.3	1.7, 2.5	1.8, 2.7	1.2, 2.6	1.3, 2.7	1.2, 2.7
	n	24	18	24	12	32	70	97	277
Baseline IBW (kg)	Mean (SD)	58.71 (9.38)	61.32 (10.17)	61.50 (8.79)	67.21 (8.72)	63.76 (7.45)	61.93 (8.56)	62.89 (8.07)	62.35 (8.54)
	Median	57.80	62.30	58.40	68.65	63.15	63.75	64.00	62.90
	Min, Max	41.5, 75.0	43.3, 81.3	50.4, 78.3	53.0, 77.6	52.0, 83.0	43.9, 79.0	38.7, 77.6	38.7, 83.0
	n	24	18	24	12	32	70	97	277
Baseline CrCL (mL/min)	Mean (SD)	124.65 (18.45)	112.42 (22.99)	124.95 (20.04)	128.60 (30.83)	122.27 (33.00)	97.71 (63.16)	101.15 (122.59)	108.74 (81.33)
	Median	127.10	106.20	129.85	129.35	112.60	81.35	82.30	104.90
	Min, Max	77.8, 166.2	76.9, 159.8	87.9, 166.8	80.3, 176.0	66.8, 245.5	11.7, 331.8	9.3, 1097.9	9.3, 1097.9
	n	24	18	24	12	32	70	97	277

Subject Characteristic	Statistics	Study							Overall
		CD101.IV.1.01	CD101.IV.1.02	CD101.IV.1.06	CD101.IV.1.07	CD101.IV.1.15	CD101.IV.2.03	CD101.IV.3.05	
Capped CrCL at Baseline (mL/min)	Mean (SD)	123.67 (17.37)	112.42 (22.99)	124.81 (19.93)	128.60 (30.83)	119.91 (25.82)	88.79 (47.65)	82.99 (46.41)	99.76 (42.98)
	Median	127.10	106.20	129.85	129.35	112.60	81.35	82.30	104.42
	Min, Max	77.8, 166.2	76.9, 159.8	87.9, 166.8	80.3, 176.0	66.8, 170.8	11.7, 210.4	9.3, 218.5	9.3, 218.5
	n	24	18	24	12	32	70	97	277
Adjusted CrCL at Baseline (mL/min)	Mean (SD)	96.04 (14.88)	91.01 (17.19)	102.61 (18.74)	109.26 (24.43)	89.48 (27.45)	81.75 (51.21)	88.01 (99.91)	89.68 (65.98)
	Median	94.80	91.05	105.40	116.20	85.35	69.10	71.80	85.00
	Min, Max	73.1, 125.3	61.1, 123.4	68.5, 133.7	66.6, 142.9	43.9, 201.9	10.2, 207.1	9.5, 854.3	9.5, 854.3
	n	24	18	24	12	32	70	97	277
Baseline SCR (mg/dL)	Mean (SD)	0.79 (0.18)	0.88 (0.16)	0.82 (0.18)	0.89 (0.17)	0.83 (0.18)	1.37 (1.43)	1.31 (1.11)	1.14 (1.01)
	Median	0.90	0.85	0.81	0.86	0.81	0.82	0.92	0.84
	Min, Max	0.5, 1.1	0.7, 1.3	0.6, 1.1	0.7, 1.3	0.5, 1.2	0.3, 7.1	0.1, 5.9	0.1, 7.1
	n	24	18	24	12	32	70	97	277
Baseline ALB (g/dL)	Mean (SD)	4.46 (0.23)	4.47 (0.26)	4.52 (0.22)	4.53 (0.29)	4.03 (0.56)	2.62 (0.61)	2.63 (0.70)	3.31 (1.03)
	Median	4.50	4.50	4.50	4.45	4.10	2.70	2.70	3.20
	Min, Max	4.1, 4.8	4.0, 4.8	4.1, 5.0	4.2, 5.1	2.6, 4.7	1.5, 4.6	1.2, 4.3	1.2, 5.1
	n	24	18	24	12	32	70	97	277
Baseline ALT (U/L)	Mean (SD)	25.29 (10.19)	18.33 (7.05)	17.42 (6.95)	27.17 (17.89)	25.22 (13.39)	44.03 (45.31)	42.05 (55.50)	34.84 (41.70)
	Median	24.00	16.50	16.00	21.00	23.50	30.00	24.00	24.00
	Min, Max	11.0, 56.0	10.0, 34.0	6.0, 35.0	13.0, 70.0	5.0, 65.0	6.0, 221.0	3.0, 425.0	3.0, 425.0
	n	24	18	24	12	32	70	97	277
Baseline AST (U/L)	Mean (SD)	22.00 (5.86)	18.94 (4.52)	17.25 (3.19)	23.58 (10.45)	29.75 (15.25)	50.09 (45.88)	40.00 (51.42)	35.75 (40.19)
	Median	21.00	18.00	16.50	20.00	25.50	34.50	28.00	24.00
	Min, Max	12.0, 32.0	13.0, 31.0	12.0, 27.0	13.0, 47.0	12.0, 69.0	8.0, 247.0	4.0, 437.0	4.0, 437.0
	n	24	18	24	12	32	70	97	277

Subject Characteristic	Statistics	Study							Overall
		CD101.IV.1.01	CD101.IV.1.02	CD101.IV.1.06	CD101.IV.1.07	CD101.IV.1.15	CD101.IV.2.03	CD101.IV.3.05	
Race, n (%)	White	23 (95.8)	15 (83.3)	22 (91.7)	12 (100.0)	23 (71.9)	57 (81.4)	60 (61.9)	212 (76.5)
	Black or African American	0 (0.0)	3 (16.7)	2 (8.3)	0 (0.0)	7 (21.9)	10 (14.3)	5 (5.2)	27 (9.7)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	1 (1.4)	26 (26.8)	28 (10.1)
	American Indian or Alaska Native	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	2 (0.7)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	1 (1.4)	0 (0.0)	2 (0.7)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	5 (5.2)	6 (2.2)
Sex, n (%)	Male	12 (50.0)	10 (55.6)	11 (45.8)	9 (75.0)	20 (62.5)	42 (60.0)	64 (66.0)	168 (60.6)
	Female	12 (50.0)	8 (44.4)	13 (54.2)	3 (25.0)	12 (37.5)	28 (40.0)	33 (34.0)	109 (39.4)
Ethnicity, n (%)	Not Hispanic or Latino	1 (4.2)	5 (27.8)	6 (25.0)	9 (75.0)	27 (84.4)	61 (87.1)	88 (90.7)	197 (71.1)
	Hispanic or Latino	23 (95.8)	13 (72.2)	18 (75.0)	3 (25.0)	5 (15.6)	7 (10.0)	7 (7.2)	76 (27.4)
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	2 (2.1)	4 (1.4)
Dialysis Flag, n (%)	No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	64 (91.4)	87 (89.7)	151 (54.5)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (8.6)	10 (10.3)	16 (5.8)
	Unknown	24 (100.0)	18 (100.0)	24 (100.0)	12 (100.0)	32 (100.0)	0 (0.0)	0 (0.0)	110 (39.7)

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CrCL, creatinine clearance; IBW, ideal body weight; Max, maximum; Min, minimum; n, number of subjects; SCR, serum creatinine; SD, standard deviation.

Source: Applicant's Population PK report, Table 6, pages 49-51

Base Model

The final base model describing the PK of rezafungin was a 3-compartment clearance (CL) model with zero-order input and with V1, V2, V3, Q2, and Q3, where V1 is the central volume of distribution and V2 and V3 are the peripheral volume of distribution. Inter-individual variability was modelled assuming a log-normal distribution for patient level random effects. Residual variability modeled was tested as additive, proportional, or combined. Proportional error model was selected in the final base model. Base model development can be found in the Applicant's population PK report on page 52.

Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value, accuracy of parameter estimation (i.e., 95% CI excluding zero), successful model convergence, and diagnostic plots.

Covariate Analysis

The following covariates were evaluated to explain PK variability during rezafungin population PK model development (from the final base model): age, body mass index (kg/m^2), weight (kg), body surface area (m^2), gender, race, baseline serum creatinine (mg/dL), derived creatinine clearance (CL_{cr}, mL/min), baseline albumin (g/dL), baseline ALT and AST (U/L), infection status, assay, APACHE II (Acute Physiology and Chronic Health Evaluation II) scores, study, and dose (mg). Covariates underwent forward selection and backwards elimination procedures.

All covariates were time-invariant and assumed constant throughout study period, and covariate values at baseline for each subject were used. CL_{cr} was calculated using Cockcroft and Gault equation. An additional covariate was created with an upper bound limit (CL_{cr} =140 * (body surface area/1.73m^2) based on Tietz (Tietz and Wu 2006).

Reviewer comments: The reviewer was able to verify the final base model and confirm the results. The Applicant indicated that individual study effects were modeled on CL during model development; however, it was noted that the covariate impacts from studies with healthy subjects were of similar magnitude on the parameter. The same was noted for covariate impacts from studies with patients. As such, a categorical variable was created to model healthy versus infected status for CL and V1. The reviewer agreed with this approach based on the clinical relevance, model diagnostic results, and rule of parsimony. Details on the candidate models can be found in Section 4.4 in the Applicant's Population PK report.

14.5.4. Final Model

The parameter estimates for the final covariate model are listed in Table 133. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 5. ETA distribution for the PK parameters is shown in Figure 6. The visual predictive check (VPC) plots for the final covariate model stratified by dose levels and first dose indicator is shown in Figure 7.

Table 133. Parameter Esimtates and RSE% of the Final PopPK Model

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL	Central Clearance (L/h)	0.328	2.77	30.5 %CV	13.7
	Proportional Shift in CL for Healthy	-0.276	9.25		
	Exponent of (BSA/1.9) for CL	0.882	16.4		
V1	Central Volume (L)	17.7	3.96	37.6 %CV	14.7
	Exponent of (BSA/1.9) for V1	1.56	9.47		
	Proportional Shift in V1 for Healthy	-0.222	18.1		
Q2	Distribution Clearance 1 (L/h)	0.236	5.38	NE	NA
V23	Peripheral Volume 1 and 2 (L)	19.1	2.41	29.3 %CV	18.9
	Exponent of (ALB/3.2) for V23	-0.708	11.4		
	Exponent of (BSA/1.9) for V23	1.17	14.9		
Q3	Distribution Clearance 2 (L/h)	12.4	4.37	NE	NA
cov(IIV in V1, IIV in CL)		0.0560[a]	17.3	NA	NA
cov(IIV in V23, IIV in CL)		0.0619[b]	18.8	NA	NA
cov(IIV in V23, IIV in V1)		0.0373[c]	38.8	NA	NA
Residual variability		0.00949	9.34	9.74 %CV	NA
Minimum Value of the Objective Function = 2067.21					

Abbreviations: ALB, albumin; BSA, body surface area; CL, clearance; %CV, coefficient of variation expressed as a percent; IIV, interindividual variability; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent.

[a] The calculated correlation coefficient (r) associated with cov(IIV in V1, IIV in CL) was 0.516 with $r^2 = 0.266$.

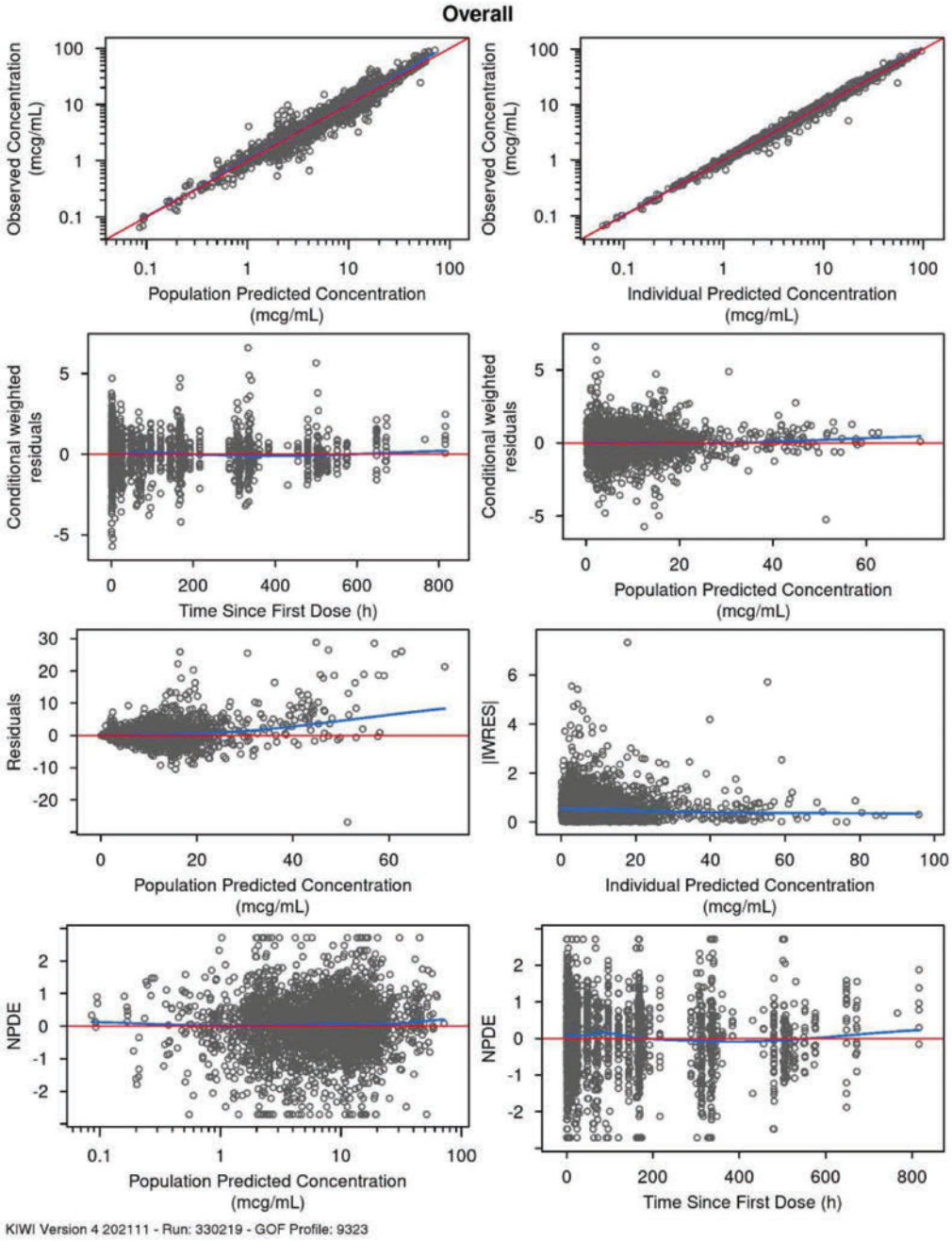
[b] The calculated correlation coefficient (r) associated with cov(IIV in V23, IIV in CL) was 0.723 with $r^2 = 0.523$.

[c] The calculated correlation coefficient (r) associated with cov(IIV in V23, IIV in V1) was 0.357 with $r^2 = 0.128$.

Shrinkage estimates: 3.5% for IIV in CL, 5.2% for IIV in V1, and 10.7% for IIV in V23.

Source: Applicant's Population PK report, Table 12, page 58
Abbreviations: PopPK, population pharmacokinetic

Figure 5. Goodness-of-Fit Plots of the Final PopPK Model

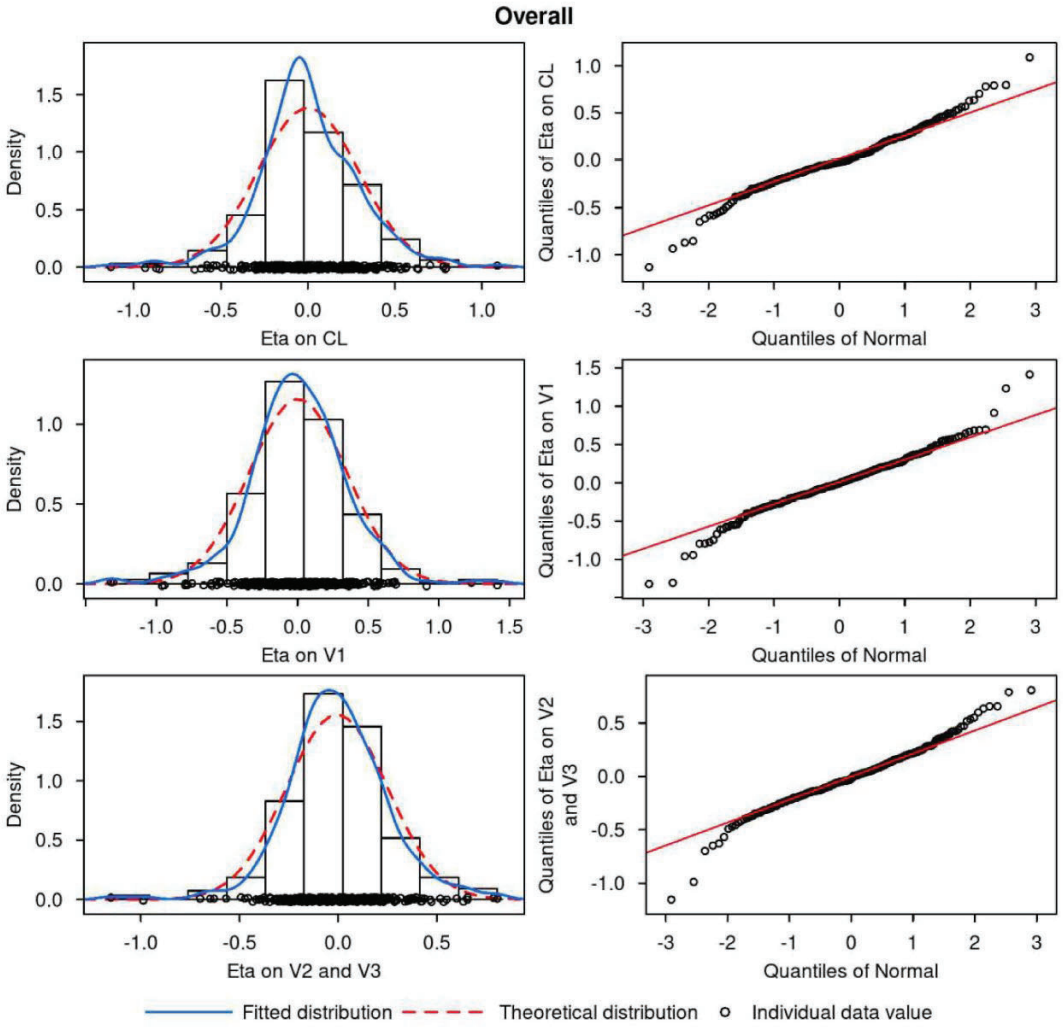


Abbreviations: |IWRES|, absolute value of the individual weighted residuals; NPDE, normalized prediction distribution error.

Note: Red line, reference line; blue curve, loess smoother line.

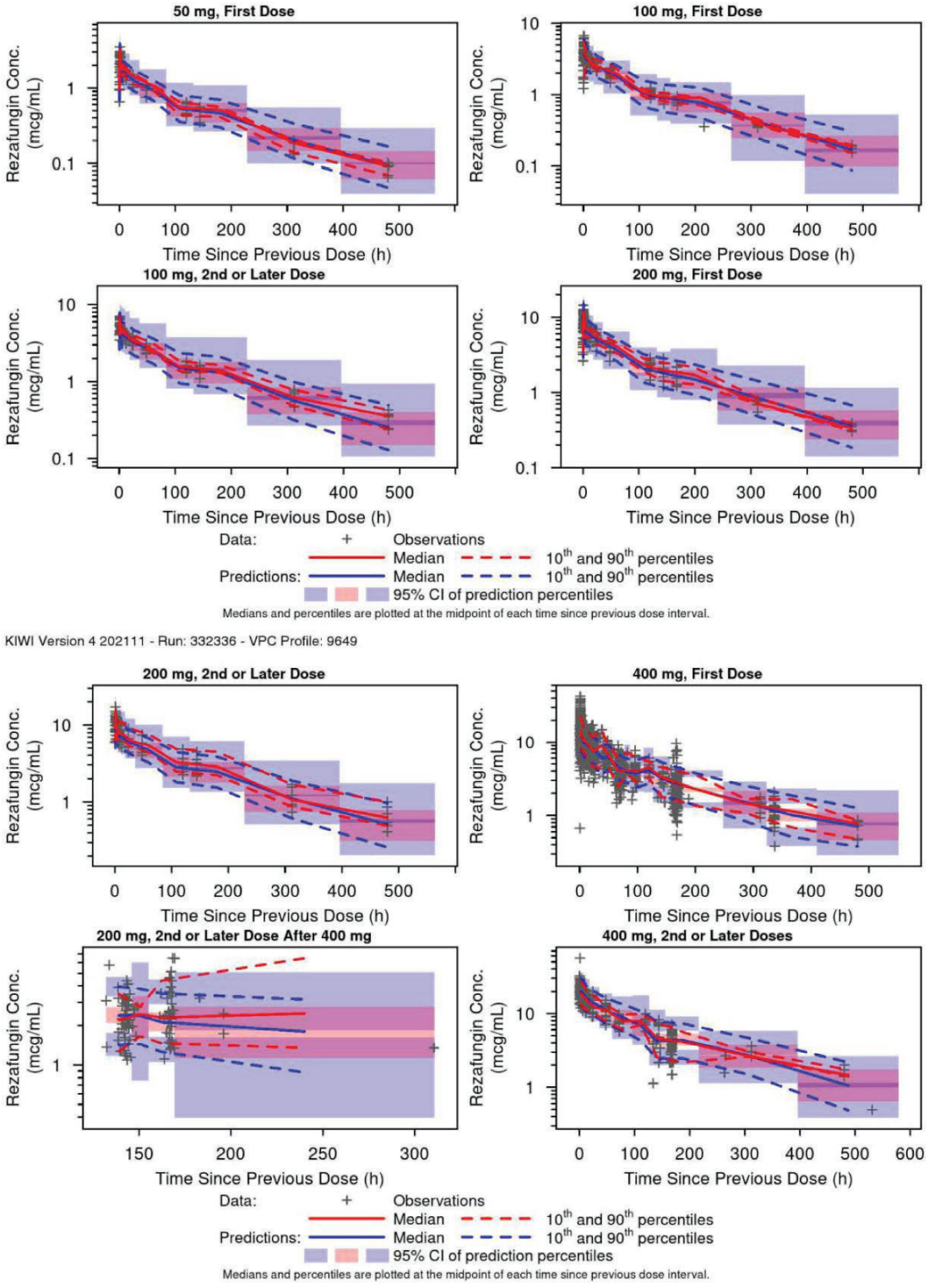
Source: Applicant's Population PK report, Figure 12, page 96
Abbreviations: PopPK, population pharmacokinetics

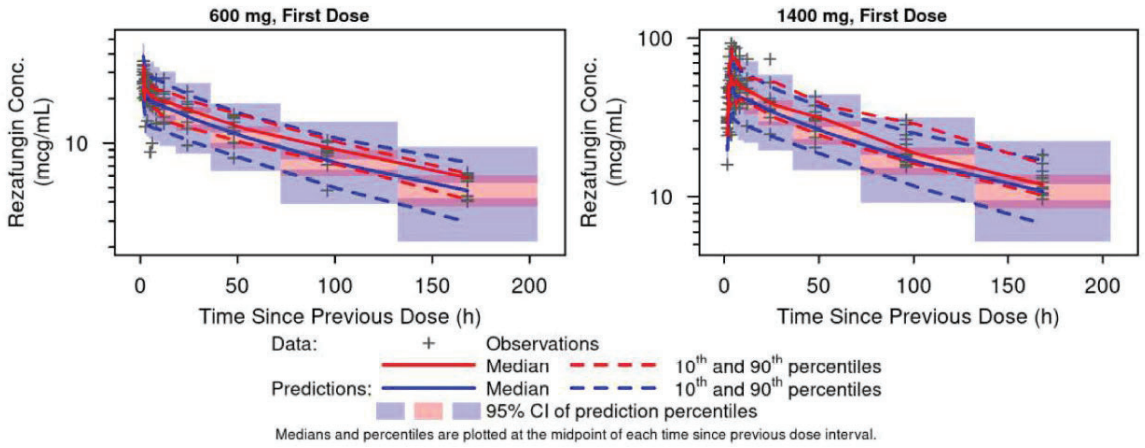
Figure 6. ETA Distributions of the Parameters



Source: Applicant's Population PK report, Figure 13, page 97
Abbreviations: CL, clearance

Figure 7. Visual Predictive Checks by Dose and First Dose



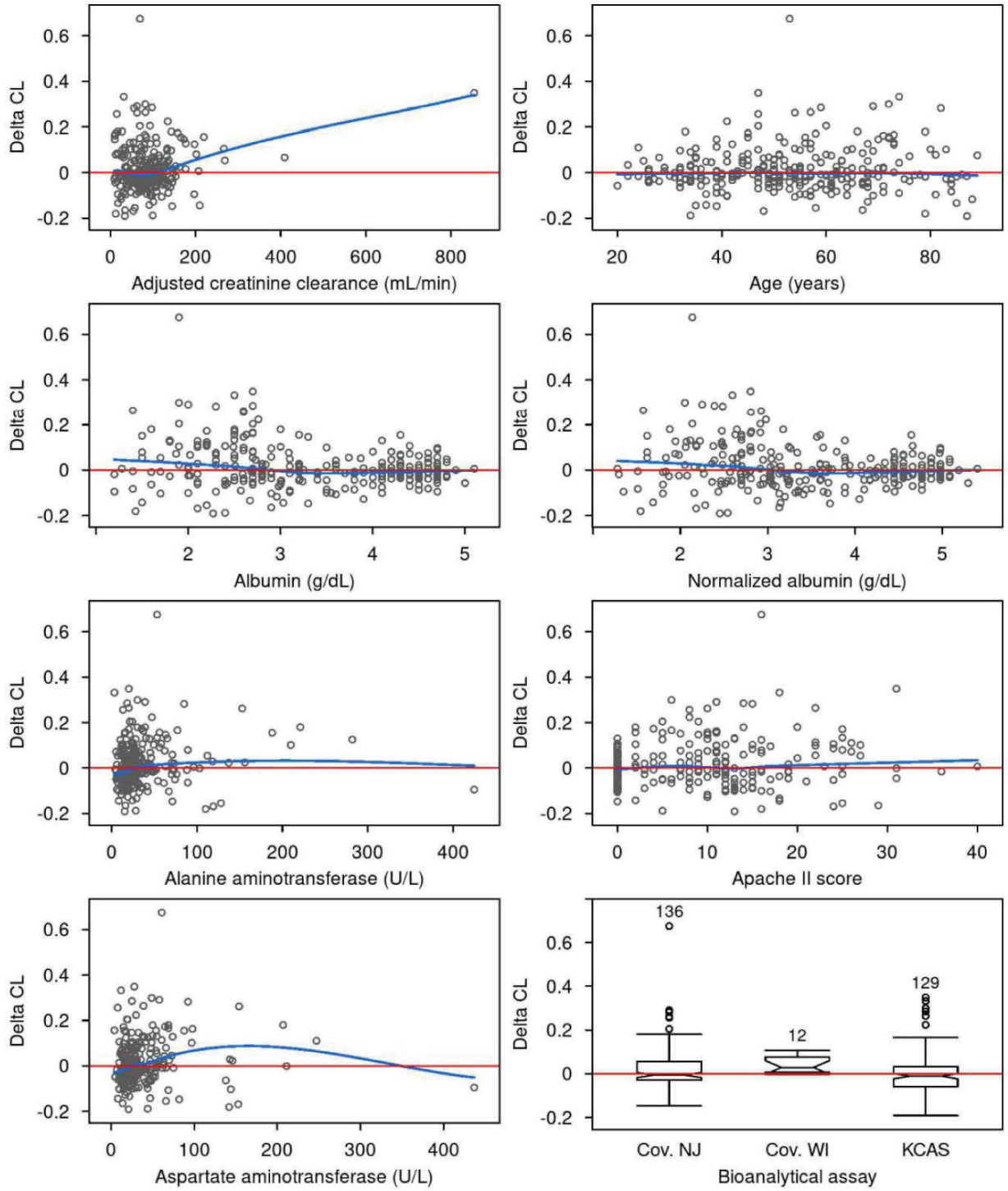


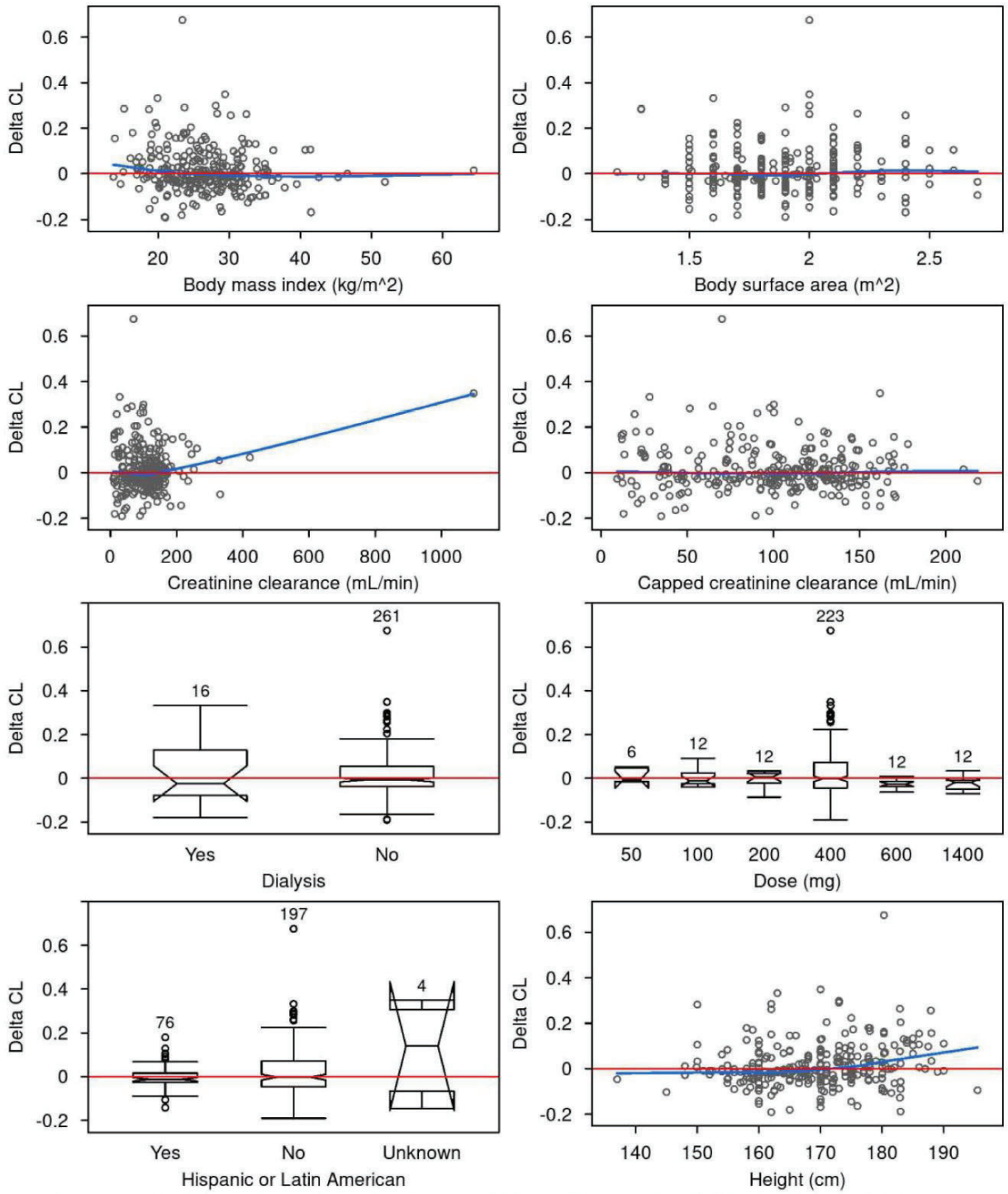
Source: Applicant's Population PK report, Figure 15, pages 99-100

Reviewer comments: The final covariate model adequately describes the pooled PK data of rezafungin. This is demonstrated through the goodness-of-fit plots. The fitted model for both individual and population predictions versus observed data demonstrated acceptable agreements without bias or misspecification (deviate from line of unity). The residuals, CWRES, and NPDE plots did not show obvious trends and/or deviations from y =0. Further evaluation was performed with VPCs stratified by dose levels and first dose levels as categorical variables. Acknowledging the limited sample size of subjects receiving 50 mg and 100 mg dosages (led to slight over- and under-predictions), the population PK model generally showed good agreement between model predictions and observed data in the dosing groups. Note that while underpredictions were also observed at the 5th percentile of 600 mg and 1400 mg dosage groups and 50th percentile of the 600 mg dosage group, the overall central tendency is reasonably captured across all VPCs. The final population PK model for rezafungin is acceptable for generating exposure metrics for steady-state exposure summary and subsequent E-R analyses.

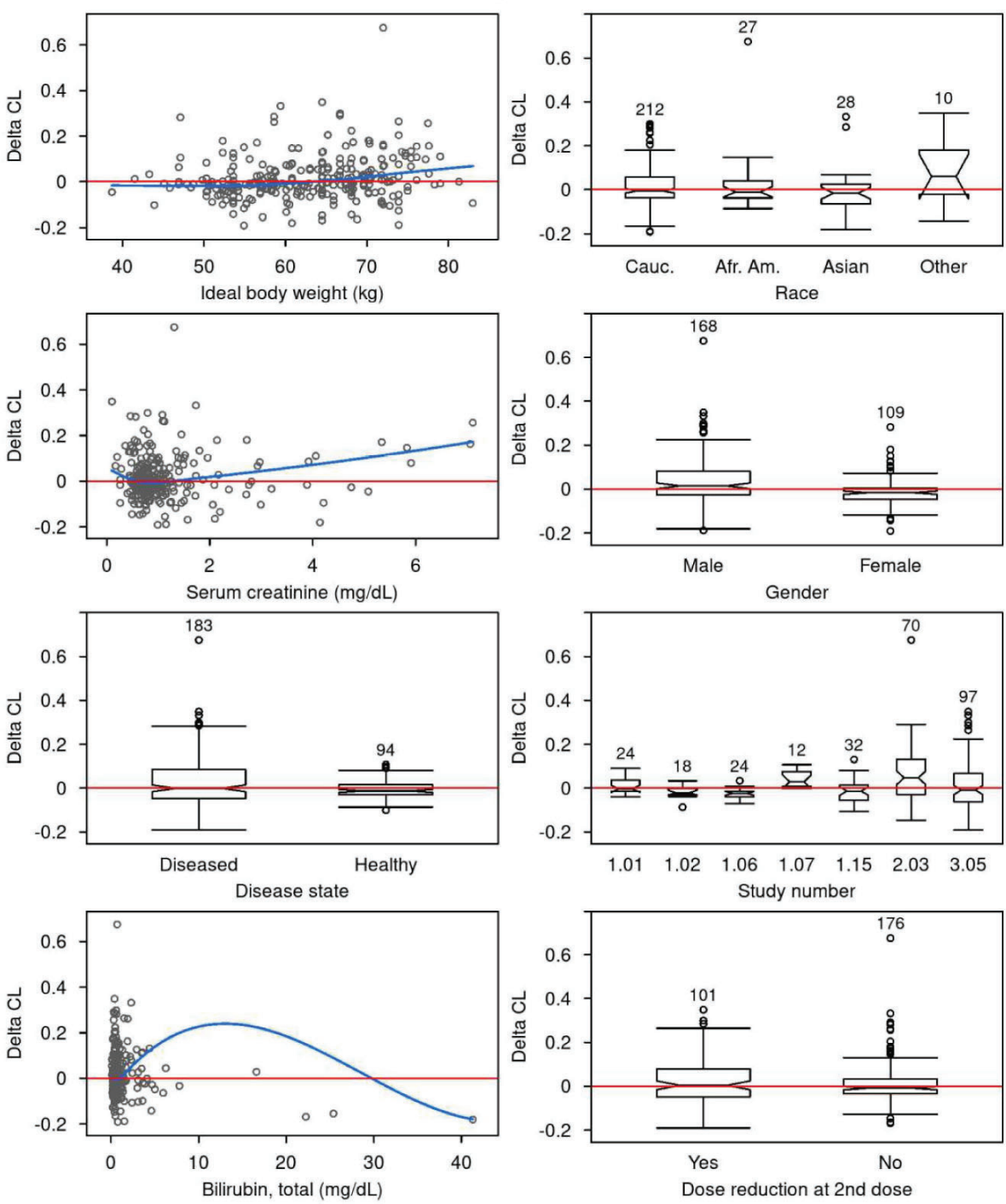
Additionally, differences between individual parameter estimates and typical parameter values versus covariates (delta plots) of the final population PK model are shown in Figure 8. Clinically relevant covariate impacts on rezafungin $AUC_{0\text{-}168h}$ are demonstrated through forest plots for all subjects (healthy subjects and patients) and patients (i.e., phase 2 and phase 3 subjects) in Figure 9 and Figure 10, respectively.

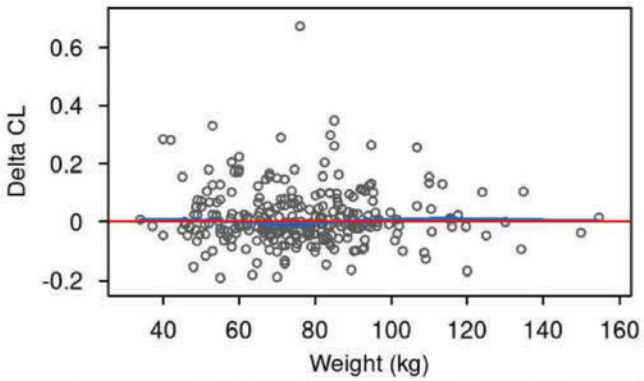
Figure 8. Delta Plots of Parameters





Boxes represent the 25th and 75th percentiles and lines the median. Notches provide an approximate 95% C.I. about the median. Whiskers extend to the most extreme values within the 1.5 interquartile range. Values outside this range are marked with open circles or subject ID. The numbers of values for each box are displayed in the upper region.

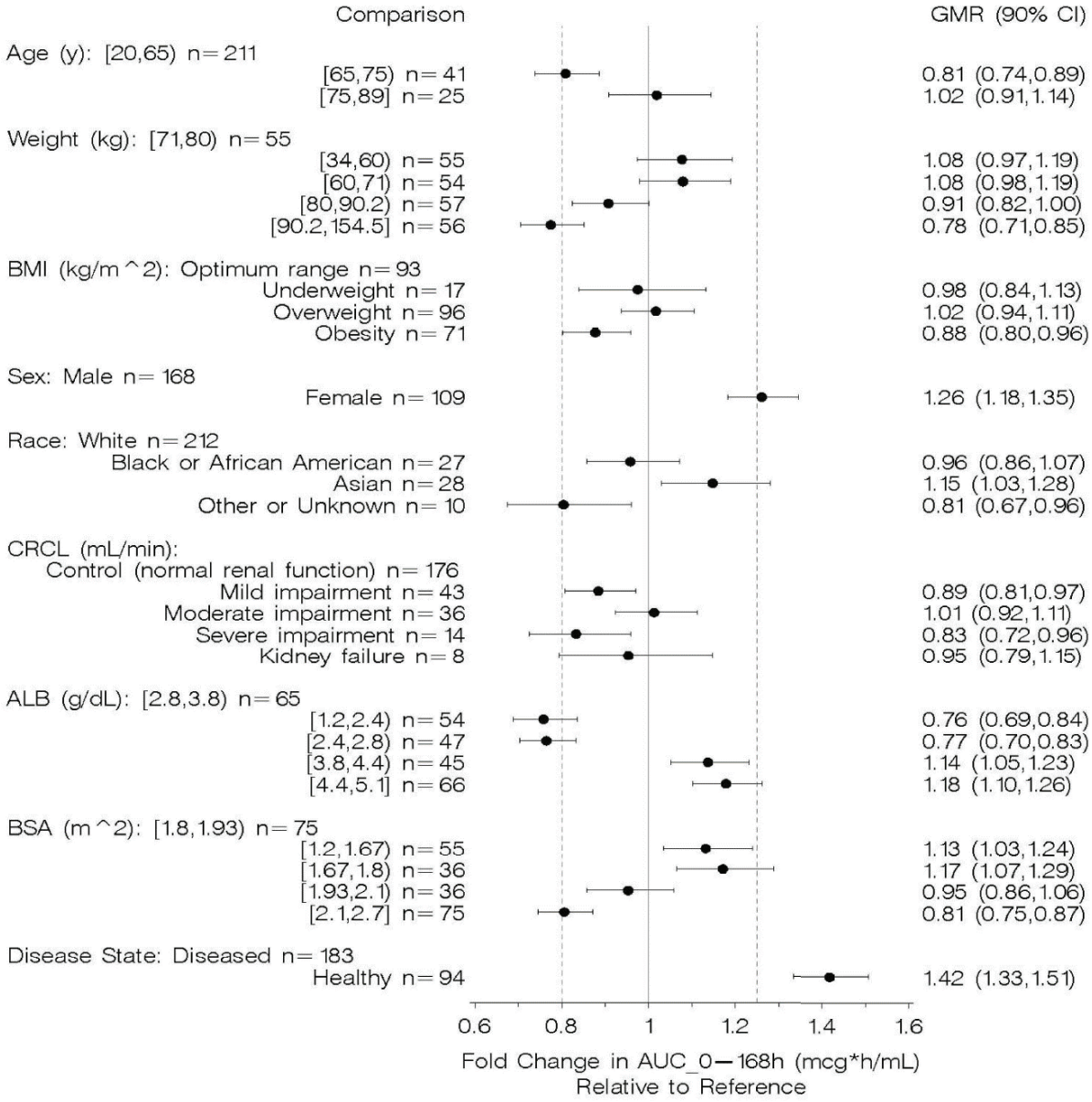

Delta CL
Ideal body weight (kg)
Race
Cauc.
Afr. Am.
Asian
Other
212
27
28
10
Serum creatinine (mg/dL)
Gender
Male
Female
168
109
Disease state
Diseased
Healthy
183
94
Study number
1.01
1.02
1.06
1.07
1.15
2.03
3.05
24
18
24
12
32
70
97
Bilirubin, total (mg/dL)
Dose reduction at 2nd dose
Yes
No
101
176



Boxes represent the 25th and 75th percentiles and lines the median. Notches provide an approximate 95% C.I. about the median. Whiskers extend to the most extreme values within the 1.5 interquartile range. Values outside this range are marked with open circles or subject ID. The numbers of values for each box are displayed in the upper region.

Source: Applicant's Population PK report, Appendix 9, pages 259-262
Abbreviations: Afr. Am., African American; APACHE II, Acute Physiology and Chronic Health Evaluation II; Cauc., Caucasian; CL, clearance; (b) (4)

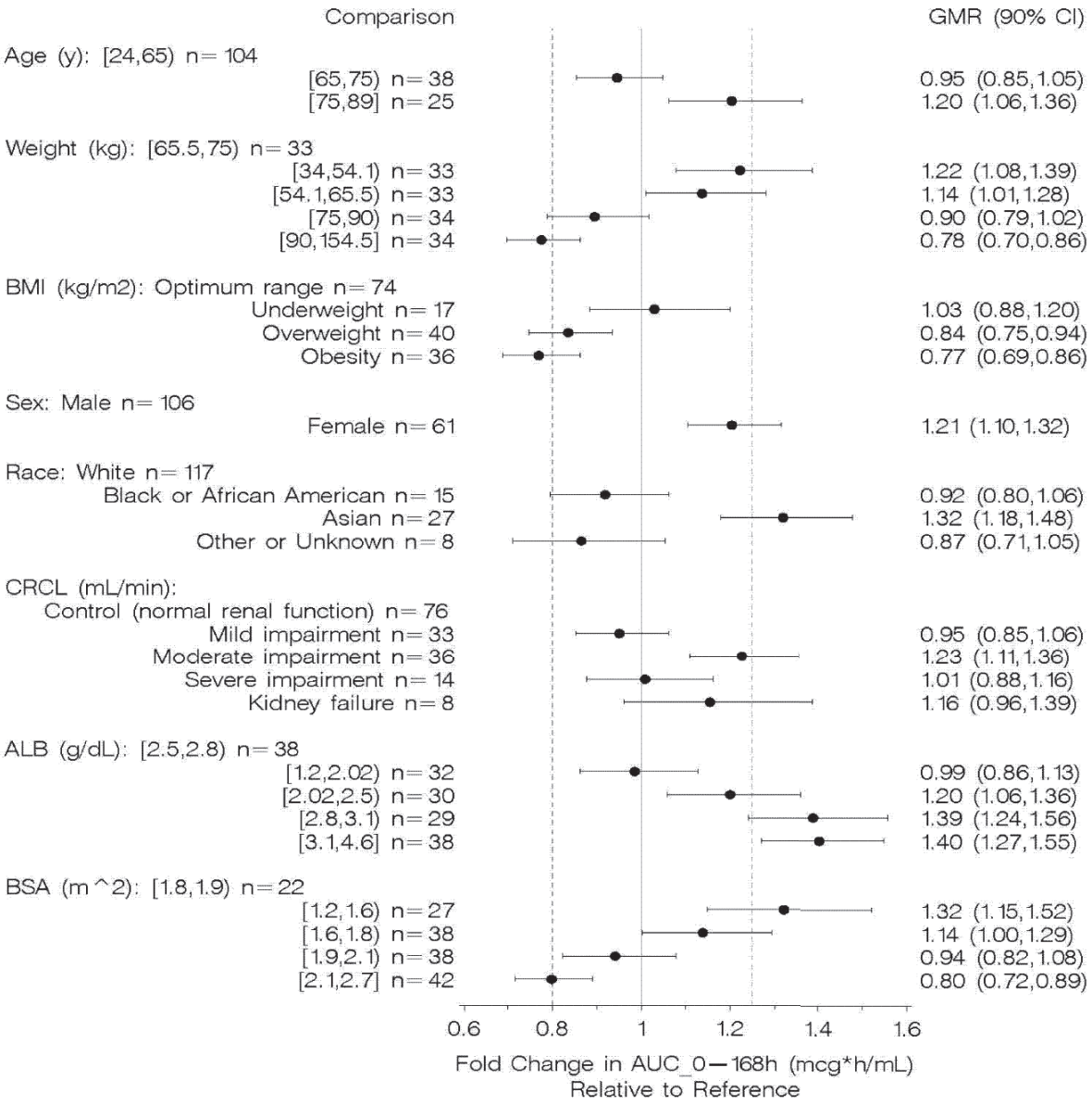
Figure 9. Covariate Effects on Rezafungin Exposures Following a Single 400 mg Dose for All Subjects



n is the number of patients in each group.
[or] indicates respective endpoint is included in the interval.
(or) indicates respective endpoint is not included in the interval.

Source: Applicant's Population PK report, Figure 17, page 104
All PK subjects include all healthy subjects and patients.
Abbreviations: ALB, albumin; AUC, area under the concentration-time curve; BMI, body mass index; BSA, body surface area; CRCL, creatinine clearance; GMR, geometric means ratio

Figure 10. Covariate Effects on Rezafungin Exposures Following a Single 400 mg Dose for Patients in STRIVE or CD.101.IV.3.05



n is the number of patients in each group.
[or] indicates respective endpoint is included in the interval.
(or) indicates respective endpoint is not included in the interval.

Source: Applicant's Population PK report, Figure 18, page 107
Abbreviations: ALB, albumin; AUC, area under the concentration-time curve; BMI, body mass index; BSA, body surface area; CRCL, creatinine clearance; GMR, geometric means ratio

Reviewer comments: While the reviewer did not see an obvious relationship between albumin and central volume of distribution in patients who contributed PK data (relatively flat fitted loess function, Reviewer's analysis not shown), the reviewer noticed a trend between increasing baseline albumin and decreasing peripheral volumes of distribution (V2 and V3). Confounding factors preclude an explanation, but the exposure change is unlikely to be clinically meaningful, and no dose adjustment is warranted based on available data.

14.5.5. Reviewer's Independent Analysis

14.5.5.1. Introduction

This analysis aims to summarize exposure metrics for rezafungin at steady-state after a loading dose of 400 mg followed by two doses of 200 mg rezafungin in patients, administered via 1-hour infusion. The analysis of the PK data from phase 2 and phase 3 subjects provides support for differentiating exposures between healthy subjects and patients, supports PK-PD analysis, and supports the review of Applicant proposed USPI language.

14.5.5.2. Objectives

Analysis objective is to:

- Generate Bayesian posterior predictions from Week 1 through Week 3 for the patients from phase 2 and phase 3 studies (who contributed PK data)
- Summarize steady-state AUC, C_{max}, and C_{min}

14.5.5.3. Methods

PK subjects from phase 2 and phase 3 (i.e., patients) were extracted from the NONMEM output to construct a simulation dataset. Dosages of 400 mg (initial dose) and 200 mg were administered at 0, 168, 336, and 504 hours, corresponding to Weeks 1 through 3. C_{min} was derived at predicted concentrations at 0.1 hour preceding the weekly dosages. Posterior predictions were generated at 0.25 hourly increments (i.e., every 15 minutes). All subject-level final population PK parameter estimates and baseline covariates were retained to construct the final simulation dataset. Data manipulation and formatting was done in R (R Core Team 2021).

Model prediction was performed in NONMEM 7.4.3 using the final model file with fixed final parameters. A simulation dataset for healthy subjects (phase 1) was generated using the same methodology (results not shown). Exposure summary is measured using geometric mean and geometric coefficient of variation percent. Source files are summarized in Table 134.

Table 134. Analysis Datasets From the Applicant

File Type	Name	Link to EDR
Model	fin001.ctl	\\CDSESUB1\EVSPROD\nda217417\0001\m5\datasets\nc-200\misc\pk\programs\
PopPK Dataset	poolpk2.xpt	\\CDSESUB1\EVSPROD\nda217417\0001\m5\datasets\nc-200\misc\pk\datasets\

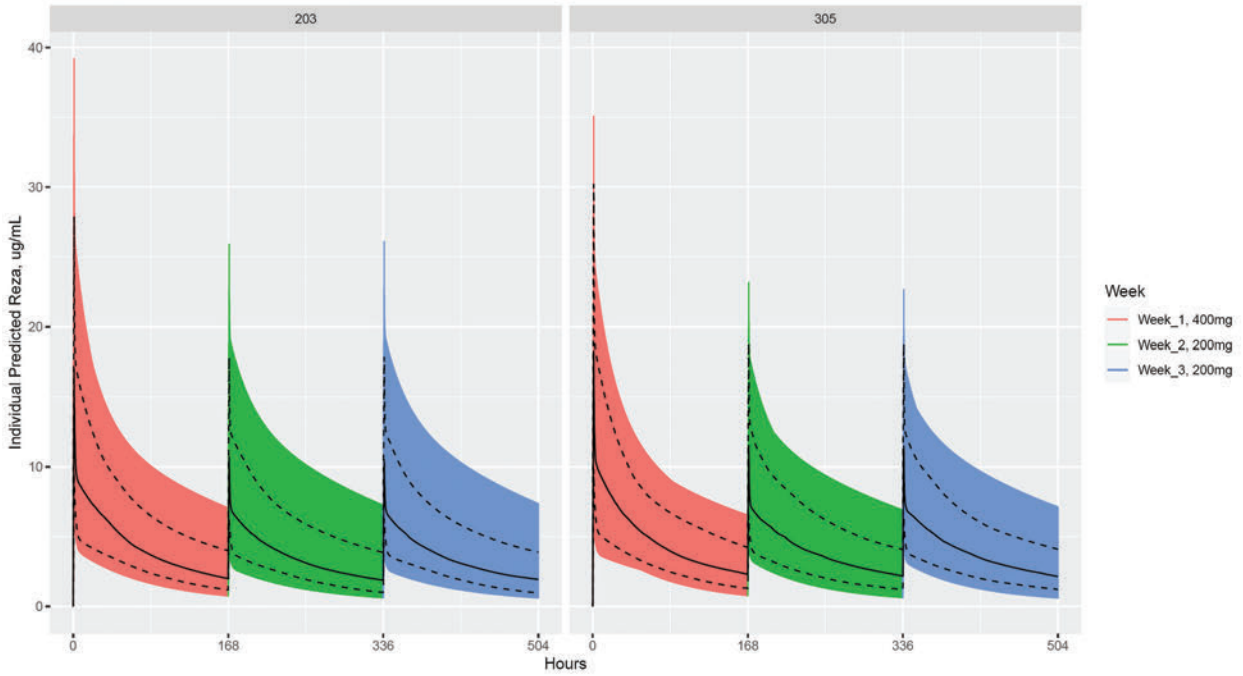
Source: Applicant's submission

14.5.5.4. Results

A total of 167 subjects from phase 2 and phase 3 studies were included in the patient simulation. The concentration-time profiles in phase 2 and phase 3 subjects are shown in Figure 11. Rezafungin exposures from Week 1 through Week 3 by study is summarized in Table 135.

The result provides support for differentiating exposures between healthy subjects and patients, supports PK-PD analysis, and supports the review of Applicant proposed USPI language.

Figure 11. Simulated Concentration-Time Profiles of Rezafungin in Patients



Source: Reviewer's independent analysis
Shaded area, range of simulated values; dashed lines, 5th and 95th percentiles of simulated values; solid lines, 50th percentiles of simulated values

Table 135. Summary of Simulated Rezafungin Exposures by Study and Weeks

Simulation Period (Dose, mg)	Exposure Metrics (Geomean, CV%)	STRIVE (N=70)	ReSTORE (N=97)	Overall (N=167)
Week 1 (400)	$AUC_{0\text{-}168h}$	788 (29.9%)	794 (33.4%)	791 (31.9%)
	C_{max}	17.1 (32.3%)	17.6 (36.7%)	17.4 (34.8%)
	C_{min}	2.12 (44.5%)	2.30 (40.8%)	2.22 (42.5%)
Week 2 (200)	$AUC_{0\text{-}168h}$	650 (32.1%)	647 (34.7%)	648 (33.5%)
	C_{max}	10.9 (30.2%)	11.1 (34.5%)	11.0 (32.6%)
	C_{min}	1.97 (48.6%)	2.16 (43.2%)	2.08 (45.6%)
Week 3 (200)	$AUC_{0\text{-}168h}$	642 (32.0%)	636 (34.2%)	639 (33.2%)
	C_{max}	10.8 (30.0%)	10.9 (34.3%)	10.9 (32.5%)
	C_{min}	1.97 (48.6%)	2.16 (43.2%)	2.08 (45.6%)

Source: Reviewer's independent analysis
$AUC_{0\text{-}168h}$, µg*h/mL; C_{max} and C_{min}, µg/mL
Abbreviations: $AUC_{0\text{-}168h}$, area under the concentration-time curve from 0 to 168 hours; C_{max}, maximum concentration; C_{min}, minimum concentration; CV%, percent coefficient of variation; Geomean, geometric mean

14.5.5.5. Listing of Analyses Codes and Output Files

Table 136. Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for the final model	poolpk2.csv	…\NDA_217417_Rezafungin_JIAJUNLIU\PPK_Analysis\runs\final_743
NONMEM code for the final model	fin001.mod	…\NDA_217417_Rezafungin_JIAJUNLIU\PPK_Analysis\runs\final_743
NONMEM run for the base model	b047-poolpk2.mod	…\NDA_217417_Rezafungin_JIAJUNLIU\PPK_Analysis\runs\base
Simulation runs and output graphs		…\NDA_217417_Rezafungin_JIAJUNLIU\PPK_Analysis\sim
sim_6wks_15min_MDV.csv	Simulation dataset	…\NDA_217417_Rezafungin_JIAJUNLIU\PPK_Analysis\sim\data\patient
sim15min_MDV.csv	Simulation dataset	…\NDA_217417_Rezafungin_JIAJUNLIU\PPK_Analysis\sim\data\healthy

Source: Reviewer's analysis

14.5.6. E-R Analysis and PTA

The Applicant conducted E-R analyses of rezafungin data from the patient population from phase 2 (STRIVE) and phase 3 (ReSTORE) studies. The final population PK model was used to derive individual estimates of exposure metrics for efficacy, safety E-R analyses and PTA analysis. Assessed efficacy E-R endpoints for efficacy and safety are listed in Table 137. Selected AEs for safety E-R assessment included gastrointestinal AEs and serious AEs. Details of efficacy and safety endpoints, as well as sampling methodology for blood cultures, can be found in the Applicant's E-R analysis report.

Table 137. Summary of Clinical Endpoints in the E-R Graphical Analyses

Endpoints in Analysis	Patient Population	Contributing Study
Global assessment of cure on Day 5	mITT	ReSTORE
Global assessment of cure on Day 14	mITT	ReSTORE
TTNBC	mITT	STRIVE, ReSTORE
Safety	mITT	STRIVE, ReSTORE

Source: Adapted from the Applicant's E-R Analysis report
Abbreviations: E-R, exposure-response; mITT, modified intend-to-treat; TTNBC, time to negative blood culture, an exploratory endpoint

For exposure-efficacy, individual $AUC_{0\text{-}168h}$ was used as the exposure metric. $AUC_{0\text{-}168h}$ /MIC was also derived using baseline MIC of organism of interest (predominant interest in *C. albicans* and *C. galabrata*) for each patient. For exposure-safety, $AUC_{0\text{-}168h}$ and C_{max} were used against the selected safety endpoints. Demographics of subjects Included the overall E-R analyses are described in Table 138, Table 139, and Table 140.

Table 138. Summary of Demographics by Treatment Arms for E-R Efficacy of Global Cure

Patient Characteristic	Statistics	Caspofungin	Rezafungin 400/200 mg	Overall
Age (y)	Mean (SD)	61.9 (14.6)	60.0 (15.3)	60.9 (14.9)
	Median	62.0	59.0	61.0
	Min, Max	20, 91	27, 89	20, 91
	n	94	92	186
APACHE II Score	Mean (SD)	13.0 (7.2)	12.4 (7.5)	12.7 (7.3)
	Median	11.5	12.0	12.0
	Min, Max	0, 37	0, 40	0, 40
	n	94	91	185
ANC at Randomization (cells/µL)	Mean (SD)	8649.05 (6224.70)	8451.30 (6872.19)	8552.87 (6530.25)
	Median	7282.16	7500.00	7434.36
	Min, Max	0.0, 37220.0	0.0, 41174.0	0.0, 41174.0
	n	94	89	183
Race, n (%)	Black or African American	4 (4.3)	5 (5.4)	9 (4.8)
	American Indian or Alaska Native	1 (1.1)	1 (1.1)	2 (1.1)
	Asian	31 (33.0)	23 (25.0)	54 (29.0)
	White	55 (58.5)	59 (64.1)	114 (61.3)
	Other	3 (3.2)	4 (4.3)	7 (3.8)
Sex, n (%)	Male	56 (59.6)	61 (66.3)	117 (62.9)
	Female	38 (40.4)	31 (33.7)	69 (37.1)
Geographic Region, n (%)	North America/United States	24 (25.5)	24 (26.1)	48 (25.8)
	Europe/Israel/Turkey	37 (39.4)	38 (41.3)	75 (40.3)
	Asia-Pacific	27 (28.7)	21 (22.8)	48 (25.8)
	China/Taiwan	6 (6.4)	8 (8.7)	14 (7.5)
	South America	0 (0.0)	1 (1.1)	1 (0.5)
ANC at Randomization (cells/µL), n (%)	< 500	5 (5.3)	7 (7.6)	12 (6.5)
	≥ 500	89 (94.7)	82 (89.1)	171 (91.9)
	Missing	0 (0.0)	3 (3.3)	3 (1.6)
Final Diagnosis, n (%)	Candidemia only	67 (71.3)	64 (69.6)	131 (70.4)
	Invasive candidiasis	27 (28.7)	28 (30.4)	55 (29.6)
Diagnosis at Randomization, n (%)	Candidemia only	67 (71.3)	67 (72.8)	134 (72.0)
	Invasive candidiasis	27 (28.7)	25 (27.2)	52 (28.0)
Severity of Disease, n (%)	APACHE II < 20 and ANC ≥ 500 cells/µL	74 (78.7)	71 (77.2)	145 (78.0)
	APACHE II ≥ 20 or ANC < 500 cells/µL	20 (21.3)	21 (22.8)	41 (22.0)

Abbreviations: ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation; Max, maximum; Min, minimum; n, number of patients; SD, standard deviation.

Source: Applicant's E-R Analysis report, Table 6, page 55
Abbreviation: E-R, exposure-response

Table 139. Summary of Demographics by Study for E-R Efficacy of TTNBC

Patient Characteristic	Statistics	Study		Overall
		CD101-IV-2-03	CD101-IV-3-05	
Age (y)	Mean (SD)	57.7 (15.8)	61.4 (15.1)	59.8 (15.5)
	Median	60.0	61.0	61.0
	Min, Max	24, 93	21, 91	21, 93
	n	114	138	252
APACHE II Score	Mean (SD)	13.7 (7.5)	13.5 (7.5)	13.6 (7.5)
	Median	12.0	12.0	12.0
	Min, Max	1, 35	2, 40	1, 40
	n	110	137	247
ANC at Randomization (cells/µL)	Mean (SD)	8449.20 (7567.78)	8175.77 (6995.24)	8297.30 (7241.29)
	Median	6425.00	7240.00	6674.00
	Min, Max	936.0, 61800.0	0.0, 41174.0	0.0, 61800.0
	n	108	135	243
Race, n (%)	Black or African American	11 (9.6)	5 (3.6)	16 (6.3)
	American Indian or Alaska Native	0 (0.0)	2 (1.4)	2 (0.8)
	Asian	3 (2.6)	47 (34.1)	50 (19.8)
	White	96 (84.2)	79 (57.2)	175 (69.4)
	Other	1 (0.9)	5 (3.6)	6 (2.4)
	Unknown	3 (2.6)	0 (0.0)	3 (1.2)
Sex, n (%)	Male	66 (57.9)	87 (63.0)	153 (60.7)
	Female	48 (42.1)	51 (37.0)	99 (39.3)
Geographic Region, n (%)	North America/United States	40 (35.1)	22 (15.9)	62 (24.6)
	Europe/Israel/Turkey	74 (64.9)	61 (44.2)	135 (53.6)
	Asia-Pacific	0 (0.0)	41 (29.7)	41 (16.3)
	China/Taiwan	0 (0.0)	13 (9.4)	13 (5.2)
	South America	0 (0.0)	1 (0.7)	1 (0.4)
ANC at Randomization (cells/µL), n (%)	< 500	0 (0.0)	12 (8.7)	12 (4.8)
	≥ 500	108 (94.7)	123 (89.1)	231 (91.7)
	Missing	6 (5.3)	3 (2.2)	9 (3.6)
Final Diagnosis, n (%)	Candidemia only	105 (92.1)	131 (94.9)	236 (93.7)
	Invasive candidiasis	9 (7.9)	7 (5.1)	16 (6.3)
Diagnosis at Randomization, n (%)	Candidemia only	105 (92.1)	134 (97.1)	239 (94.8)
	Invasive candidiasis	9 (7.9)	4 (2.9)	13 (5.2)
Severity of Disease, n (%)	APACHE II < 20 and ANC ≥ 500 cells/µL	89 (78.1)	101 (73.2)	190 (75.4)
	APACHE II ≥ 20 or ANC < 500 cells/µL	25 (21.9)	37 (26.8)	62 (24.6)

Abbreviations: ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation; Max, maximum; Min, minimum; n, number of patients; SD, standard deviation.

Source: Applicant's E-R Analysis report, Table 19, page 68
Abbreviations: E-R, exposure-response; TTNBC, time to negative blood culture

Table 140. Summary of Demographics by Study for E-R Safety Analysis

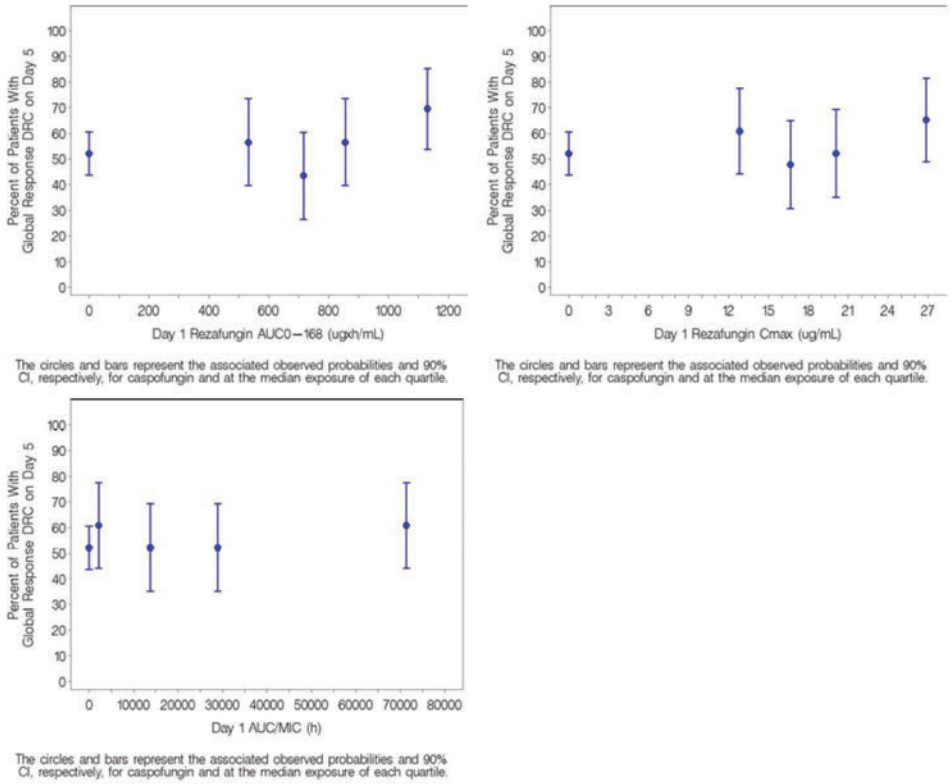
Patient Characteristic	Statistics	Study		Overall
		CD101-IV-2-03	CD101-IV-3-05	
Age (y)	Mean (SD)	57.9 (15.5)	61.1 (15.0)	59.8 (15.3)
	Median	60.0	61.0	61.0
	Min, Max	24, 93	20, 91	20, 93
	n	134	195	329
APACHE II Score	Mean (SD)	13.6 (7.0)	12.8 (7.4)	13.1 (7.3)
	Median	12.0	12.0	12.0
	Min, Max	1, 35	0, 40	0, 40
	n	134	195	329
ANC at Randomization (cells/μL)	Mean (SD)	8230.80 (6933.52)	8489.64 (6467.77)	8384.22 (6652.19)
	Median	6505.00	7367.18	6950.40
	Min, Max	936.0, 61800.0	0.0, 41174.0	0.0, 61800.0
	n	134	195	329
Baseline ALB (g/dL)	Mean (SD)	2.89 (0.59)	2.79 (0.66)	2.83 (0.64)
	Median	2.92	2.80	2.91
	Min, Max	1.5, 5.0	1.3, 4.6	1.3, 5.0
	n	134	195	329
Baseline BSA (m^2)	Mean (SD)	1.87 (0.26)	1.82 (0.30)	1.84 (0.29)
	Median	1.87	1.80	1.81
	Min, Max	1.2, 2.8	1.2, 2.8	1.2, 2.8
	n	134	195	329
Race, n (%)	Black or African American	14 (10.4)	9 (4.6)	23 (7.0)
	American Indian or Alaska Native	0 (0.0)	2 (1.0)	2 (0.6)
	Asian	4 (3.0)	57 (29.2)	61 (18.5)
	White	115 (85.8)	119 (61.0)	234 (71.1)
	Other	1 (0.7)	8 (4.1)	9 (2.7)
Sex, n (%)	Male	76 (56.7)	120 (61.5)	196 (59.6)
	Female	58 (43.3)	75 (38.5)	133 (40.4)
Geographic Region, n (%)	North America/United States	53 (39.6)	49 (25.1)	102 (31.0)
	Europe/Israel/Turkey	81 (60.4)	78 (40.0)	159 (48.3)
	Asia-Pacific	0 (0.0)	52 (26.7)	52 (15.8)
	China/Taiwan	0 (0.0)	15 (7.7)	15 (4.6)
	South America	0 (0.0)	1 (0.5)	1 (0.3)
ANC at Randomization (cells/μL), n (%)	< 500	0 (0.0)	13 (6.7)	13 (4.0)
	≥ 500	134 (100.0)	182 (93.3)	316 (96.0)
Pooled APACHE II Score Group 1, n (%)	0-9	36 (26.9)	0 (0.0)	36 (10.9)
	10-19	69 (51.5)	0 (0.0)	69 (21.0)
	≥ 20	23 (17.2)	0 (0.0)	23 (7.0)
	Missing	6 (4.5)	195 (100.0)	201 (61.1)
Randomized Diagnosis, n (%)	Candidemia only	114 (85.1)	139 (71.3)	253 (76.9)
	Invasive candidiasis	20 (14.9)	56 (28.7)	76 (23.1)
Final Diagnosis, n (%)	Candidemia only	114 (85.1)	136 (69.7)	250 (76.0)
	Invasive candidiasis	20 (14.9)	59 (30.3)	79 (24.0)

Abbreviations: ALB, albumin; ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation; BSA, body surface area; Max, maximum; Min, minimum; n, number of patients; SD, standard deviation.

Source: Applicant's E-R Analysis report, Table 26, pages 75-76
Abbreviation: E-R, exposure-response

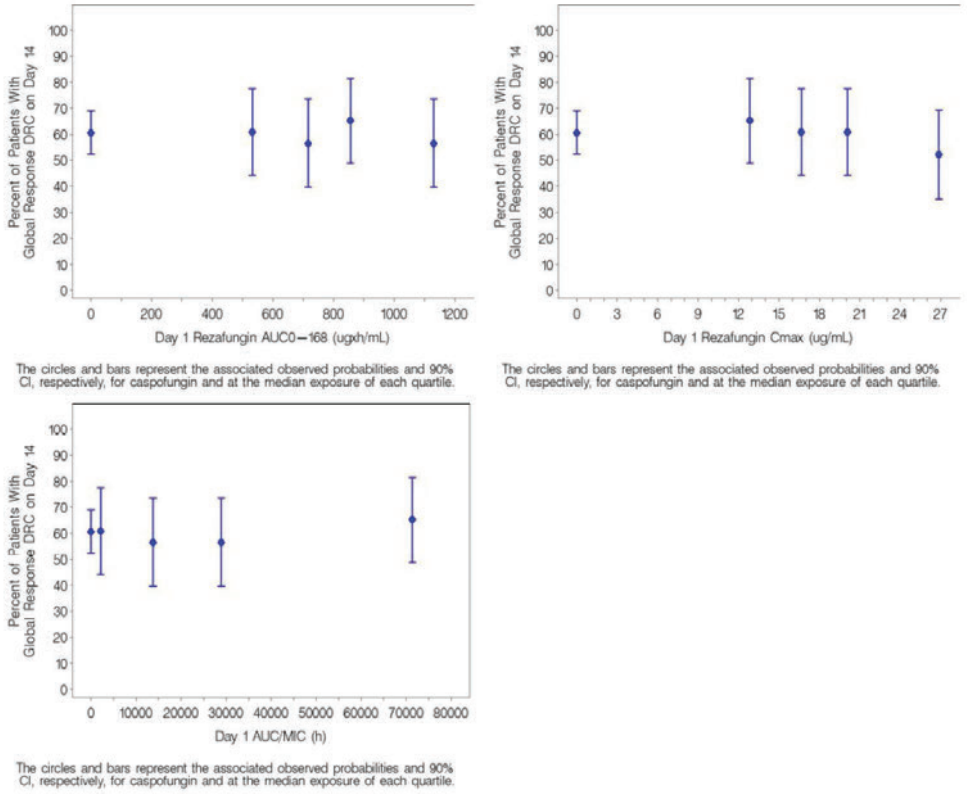
E-R efficacy results are shown in Figure 12, Figure 13, Figure 14, and Figure 15. No statistically significant relationships were identified for rezafungin exposure and global assessment of cure on Day 5, Day 14, or time-to-negative blood culture (time-to-negative blood culture is not a primary nor secondary endpoint). No relationships were observed for rezafungin exposure and gastrointestinal AEs or serious AEs (figures not shown; refer to Section 4.3 in the Applicant's E-R analysis report). Therefore, no dose adjustment is warranted.

Figure 12. Percent of Patients With Global Cure on Day 5 vs. Rezafungin Exposure Quartiles



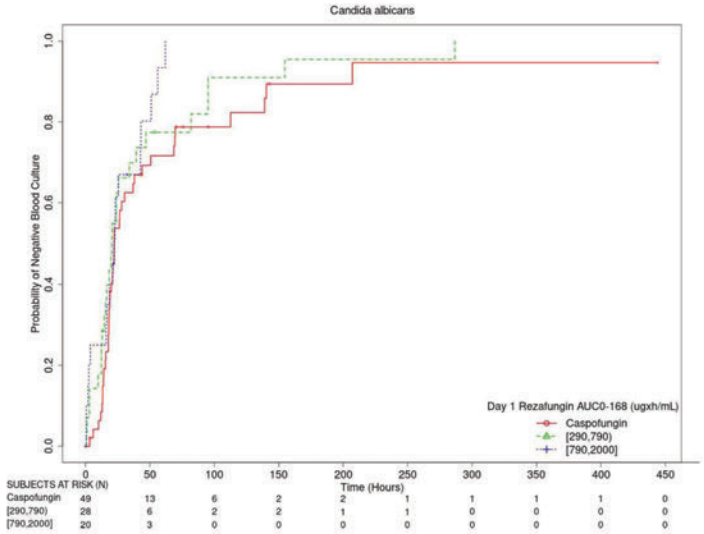
Source: Applicant's E-R Analysis report, Figure 6, page 97
Caspofungin exposure is set to zero
Abbreviations: AUC, area under the concentration-time curve; AUC0-168, area under the concentration-time curve from time 0 to 168 hours; CI, confidence interval; C_{max}, maximum drug concentration; DRC, Data Review Committee; MIC, minimum inhibitory concentration

Figure 13. Percent of Patients With Global Cure on Day 14 vs. Rezafungin Exposure Quartiles



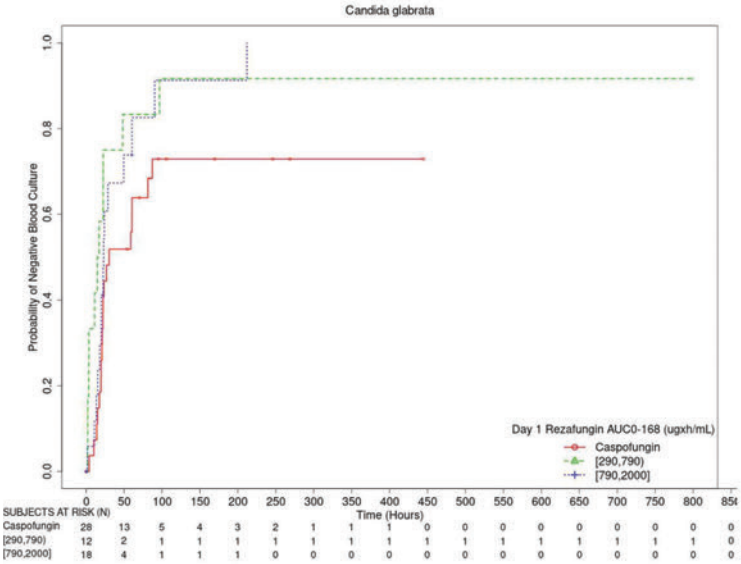
Source: Applicant's E-R Analysis report, Figure 9, page 100.
Caspofungin exposure is set to zero
Abbreviations: AUC, area under the concentration-time curve; AUC0-168, area under the concentration-time curve from time 0 to 168 hours; CI, confidence interval; C_{max}, maximum drug concentration; DRC, Data Review Committee; MIC, minimum inhibitory concentration

Figure 14. Kaplan-Meier Plot of Probability of TTNBC vs. Time by Caspofungin and Rezafungin Exposure Above and Below the Medians for *C. albicans*



Source: Applicant's E-R Analysis report, Figure 20, page 120
Abbreviation: AUC0-168, area under the concentration-time curve from time 0 to 168 hours; TTNBC, time to negative blood culture

Figure 15. KM Plot of Probability of TTNBC vs. Time by Caspofungin and Rezafungin Exposure Above and Below the Medians for *C. glabrata*



Source: Applicant's E-R Analysis report, Figure 20, page 121
Abbreviations: AUC0-168; area under the concentration-time curve from time 0 to 168 hours; KM, Kaplan-Meier; TTNBC, time to negative blood culture

For the PTA analysis, the Applicant used MIC values for six *Candida* species to support breakpoint (BP) determination. Nonclinical PK-PD targets for *Candida* species are described in Table 141. A total of 100,000 virtual patients (1,000 subjects from 100 studies) were generated and administered with 400 mg once weekly followed by 200 mg weekly dosages of rezafungin (12 weeks total for each virtual subject). Vectors of relevant covariates were resampled from the phase 2 and phase 3 distributions. The distributions of baseline albumin and body surface area were similar between the observed data and the resampled data (not shown, refer to Section 4.4 in the Applicant's E-R Analysis Report).

In the final PTA analysis presented by the Applicant, only Week 1 AUC (i.e., $AUC_{0\text{-}168h}$) was used. The $fAUC_{0\text{-}168h}$/MIC (free-drug) ratio was based on the 2.6% unbound fraction in healthy human plasma. PTA results of species of interest (i.e., *C. albicans* and *C. glabrata*) for this NDA submission are shown in Figure 16.

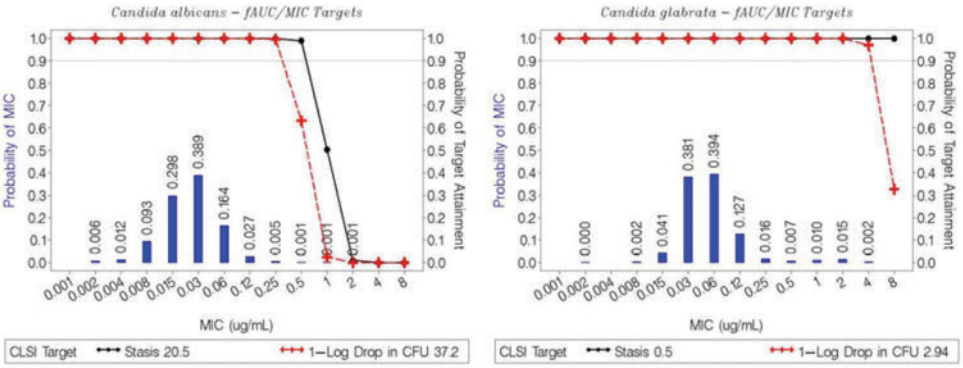
Table 141. CLSI Nonclinical PK-PD Targets by Species

Genus	Species	Stasis	1-Log Drop	Source
		*f*AUC$_{0\text{-}168}$/MIC Median	*f*AUC$_{0\text{-}168}$/MIC Median	
Candida	*albicans*	20.5	37.2	1
	glabrata	0.5	2.94	1
	parapsilosis	18.2	NA	1
	auris	12.1	38.4	2
	tropicalis	86.5	148.9	3
	dubliniensis	35.1	228.3	3

Abbreviations: *f*AUC$_{0\text{-}24}$, free area under the concentration-time curve from time 0 to 24 hours; *f*AUC$_{0\text{-}168}$, free area under the concentration-time curve from time 0 to 168 hours; CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration; NA, not applicable.
Notes: Maximum effect was stasis for *Candida parapsilosis*. For *Candida auris* values, the published *f*AUC$_{0\text{-}24}$/MIC target was multiplied by 7 to get weekly ratio to match all the rest.
Source: [1]Lepak AJ, Zhao M, VanScoy B, Ambrose PG, Andes DR. Pharmacodynamics of a long-acting echinocandin, CD101, in a neutropenic invasive-candidiasis murine model using an extended-interval dosing design. Antimicrob Agents Chemother. 2018 Jan 25;62(2):e02154-17; [2]Lepak AJ, Zhao M, Andes DR. Pharmacodynamic evaluation of rezafungin (CD101) against *Candida auris* in the neutropenic mouse invasive candidiasis model. Antimicrob Agents Chemother. 2018 Oct 24;62(11):e01572-18; [3]Lepak AJ, Zhao M, Andes DR. Determination of pharmacodynamic target exposures for rezafungin against *Candida tropicalis* and *Candida dubliniensis* in the neutropenic mouse disseminated candidiasis model. Antimicrob Agents Chemother. 2019 Oct 22;63(11):e01556-19.

Source: Applicant's E-R Analysis report, Table 2, page 51
Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic

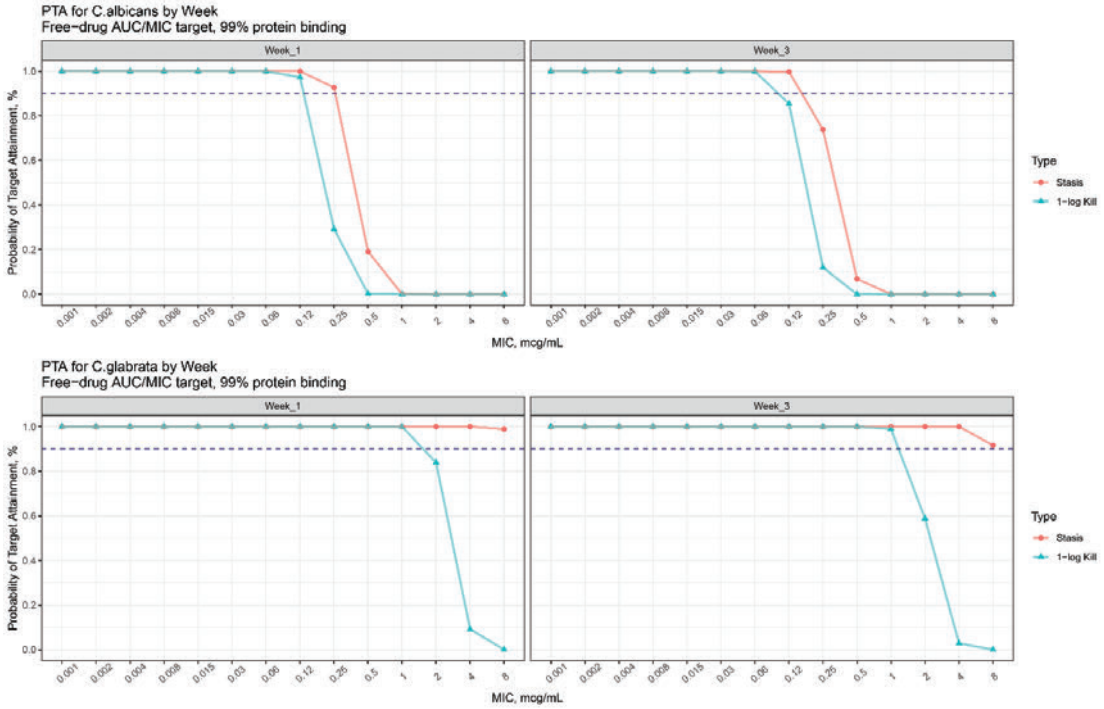
Figure 16. PTA of Rezafungin Against *Candida* Species



Source: Applicant's E-R Analysis report, figure 33, page 138
Abbreviations: *f*AUC, free area under the concentration-time curve; CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inh bitory concentration; PTA, probability of target attainment

Reviewer comments: The uncertainty in the protein binding estimate in the clinical samples prompted the reviewer to re-evaluate PTA based on a higher than proposed percent protein binding. As shown in Figure 17, a revised PTA (PK-PD target associated with 1-log$_{10}$ kill) using 99% protein binding (1% unbound fraction) suggests ≥90% PTA for C. albicans with MIC up to 0.12 mcg/mL for Week 1 and 0.06 mcg/mL for Week 3. For C. glabrata, ≥90% PTA was observed for the MICs up to 1 mcg/mL for Week 1 and Week 3, considering both stasis and 1-log kill. Refer to Sections 14.1 and 14.2 for the consideration and clinical implication of the in vivo fungal infection model and implication of STIC determination.

Figure 17. PTA of Rezafungin Against *Candida* Species Using Revised Protein Binding



Source: Reviewer's analysis using the virtual population submitted by the Applicant
Abbreviations: AUC, area under the concentration-time curve; MIC, minimum inhibitory concentration; PTA, probability of target attainment

14.5.6.1. Listing of ER Analyses Codes and Output Files

Table 142. Listing of ER Analyses Codes and Output Files

File Name	Description	Location
Tamast.xpt	Virtual population data for PTA	\nda217417\0001\m5\datasets\nc-201\misc\target-attainment\datasets\tamast.xpt
File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Reza_rscript.R	R script for re-creating PTA analysis	\NDA_217417_Rezafungin_JIAJUNLIU\PPK_Analysis

Source: Reviewer's analysis
Abbreviations: PTA, probability of target attainment

14.6. Pharmacogenetics

N/A.

15. Study/Trial Design

15.1. Phase 2 Study

15.1.1. Objectives

The primary objectives of this study were to evaluate the following:

- Safety and tolerability of rezafungin in the Safety Population
- Overall success (mycological eradication and resolution of systemic signs attributable to candidemia and/or IC) of rezafungin in subjects with candidemia and/or IC at Day 14 in the microbiological intent-to-treat (considered as modified intent-to-treat [mITT]) Population

The secondary objectives of this study were to evaluate the following:

- Overall success at Day 5, Day 28 (only for subjects with IC), and follow-up (FU; 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
- Mycological success (eradication) of rezafungin at Day 5, Day 14, Day 28 (subjects with IC), and FU in the mITT Population
- Clinical cure as assessed by the Investigator for rezafungin at Day 14, Day 28 (subjects with IC), and FU in the mITT Population
- Pharmacokinetics (PK) of rezafungin

This study was initially designed to contain Part A only. During the study, Part B was added to increase the sample size. In Part A, subjects were randomized in a 1:1:1 ratio to receive rezafungin (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 or 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 changed Part B treatment to rezafungin (400/200 mg) or caspofungin.

15.1.2. Secondary Efficacy Outcomes

Secondary efficacy outcome measures include mycological eradication and clinical cure (assessed by investigator). Additional efficacy endpoints included 30-day all-cause mortality (ACM), time to the first of two sequential negative blood cultures drawn ≥12 hours apart.

Mycological eradication and clinical response were defined as below.

Mycological Eradication

If there was a positive blood culture at baseline: two sequential negative blood cultures ≥12 hours apart. If there was a positive culture from a normally sterile site: documented mycological eradication (most recent culture ≤ Day 14 from all normally sterile sites of baseline *Candida* infection is negative) or presumed mycological eradication (FU culture not available in a subject with a successful clinical outcome and resolution or improvement of any baseline radiographic abnormalities due to IC).

Clinical Response (Assessed by Investigator)

- Cure: resolution of baseline attributable systemic signs and symptoms of candidemia/IC, no new systemic signs and symptoms, no additional systemic antifungal therapy, and subject is alive.
- Failure: progression, recurrence, or lack of resolution of attributable systemic signs and symptoms, or requirement for new or prolongation of therapy, or AE requiring discontinuation of study drug prior to assessment, or death.
- Indeterminate: lost to follow-up, withdrawal of consent, circumstances that preclude classification.

15.2. Phase 3 Study

15.2.1. Inclusion and Exclusion Criteria

Subjects were to meet *all* of the following inclusion criteria to qualify for the study:

(1) Willing and able to provide written informed consent. If the subject was unable to consent for himself/herself, a legally acceptable representative (i.e., acceptable to International Council on Harmonization and local law, as applicable) must have provided informed consent on his/her behalf.
(2) Males or females ≥18 years of age.
(3) Established mycological diagnosis of candidemia and/or invasive candidiasis from a sample taken ≤4 days (96 hours) before randomization defined as:

   a. ≥1 blood culture positive for yeast or *Candida* OR
   b. Positive test for *Candida* from a Sponsor-approved rapid IVD OR
   c. Positive gram stain (or other method of direct microscopy) for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site.

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

(5) Willing to initiate or continue medical treatment to cure infections, including receipt of antibiotics and surgical procedures, if required. Patients receiving only medications and measures for comfort and not cure were not to be enrolled.
(6) Female subjects of childbearing potential (all female subjects between 18 years and <2 years post-menopausal unless surgically sterile) agreed to use one barrier method (e.g., female condom with spermicide) plus one other highly effective method of birth control (e.g., oral contraceptive, implant, injectable, indwelling intrauterine device, vasectomized partner), or sexual abstinence (only possible if it corresponded to the subject's usual lifestyle) while participating in this study and at least 30 days from the last dose of study drug. Male subjects were to be vasectomized, abstained from sexual intercourse, or agreed to use barrier contraception (condom with spermicide), and also agreed not to donate sperm while participating in the study and for 90 days thereafter (and at least 120 days from the last dose of study drug).
(7) For candidemia only subjects, drawing of a set of blood cultures within 12 hours prior to randomization in the study. The result of these blood cultures was not required for inclusion in the study.

Exclusion Criteria

Subjects must NOT have met any of the following exclusion criteria to qualify for the study:

(1) Any of the following forms of invasive candidiasis at baseline:

a. Septic arthritis in a prosthetic joint (septic arthritis in a native joint was allowed)
b. Osteomyelitis
c. Endocarditis or myocarditis
d. Meningitis, endophthalmitis, chorioretinitis, or any central nervous system infection
e. Chronic disseminated candidiasis
f. Urinary tract candidiasis due to ascending *Candida* infection secondary to obstruction or surgical instrumentation of the urinary tract

(2) Received systemic treatment with an antifungal agent at approved doses for treatment of candidemia for >48 hours (e.g., >2 doses of a once daily antifungal agent or >4 doses of a twice daily antifungal agent) ≤4 days (96 hours) before randomization.

– Exception: Receipt of antifungal therapy to which any *Candida* spp. isolated in culture was not susceptible

(3) Alanine aminotransferase or aspartate aminotransferase levels >10-fold the upper limit of normal.
(4) Severe hepatic impairment in subjects with a history of chronic cirrhosis (Child-Pugh score >9).
(5) Presence of an indwelling vascular catheter or device that could not be removed or an abscess that could not be drained and was likely to be the source of candidemia or invasive candidiasis.
(6) Known hypersensitivity to rezafungin for injection, caspofungin, any echinocandin, or to any of their excipients, including but not limited to hereditary sugar disorders (e.g.,

fructose intolerance, sucrose-isomaltase insufficiency), anaphylaxis, or echinocandin-induced exfoliative skin disorders (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis).

(7) Met National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, criteria for ataxia, tremor, motor neuropathy, or sensory neuropathy of Grade 2 or higher.
(8) History of severe ataxia, tremor, or neuropathy or a diagnosis of multiple sclerosis or a movement disorder (including Parkinson's Disease or Huntington's Disease).
(9) Planned or ongoing therapy at Screening with a known severe neurotoxic in a patient with ataxia, tremor, motor neuropathy, or sensory neuropathy of Common Terminology Criteria for Adverse Events version 5.0 Grade 1 or higher.
(10) Previous participation in this or any previous rezafungin study.
(11) Concurrent participation in another interventional treatment trial with an investigational agent.
(12) Recently used an investigational medicinal product within 28 days of the first dose of study drug or presence of an investigational device at the time of Screening.
(13) Pregnant or lactating females.
(14) The principal investigator was of the opinion the subject should not participate in the study.

15.2.1.1. Definitions of Secondary Endpoints

Global response was determined by clinical response, radiological response, and mycological response as shown in Table 143. An independent blinded data review committee reviewed subject data and confirmed the determination of global response (including mycological eradication). Each member of the committee (five members) was an infectious disease specialist with relevant clinical study experience and expertise in assessing and evaluating study data to adjudicate protocol specified outcomes in subjects with candidemia and/or invasive candidiasis.

Table 143. 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 144. 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.

Mycological Response	Definition
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 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 145. 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

Clinical Response	Definition
	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 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 146. 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.
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 Study Report.
[a] 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.

16. Efficacy

16.1. Phase 2 Study

16.1.1. Subject Disposition

There were two parts in this study. Subject disposition for Part A and Part B is summarized in the following two tables (Table 147 and Table 148). There were no significant differences in the proportions of subjects with study completion and study treatment completion among the treatment arms.

Table 147. Subject Disposition, ITT Population, Part A, Phase 2 Study

Disposition	Rezafungin 400/400 mg N=35 n (%)	Rezafungin 400/200 mg N=36 n (%)	Caspofungin N=36 n (%)	Overall N=107 n (%)
Completed the study	23 (65.7)	28 (77.8)	22 (61.1)	73 (68.2)
Discontinued from the study	12 (34.3)	8 (22.2)	14 (38.9)	34 (31.8)
Death	3 (8.6)	4 (11.1)	6 (16.7)	13 (12.1)
Lost to follow-up	2 (5.7)	1 (2.8)	1 (2.8)	4 (3.7)
Withdrawal by subject	1 (2.9)	1 (2.8)	2 (5.6)	4 (3.7)
Physician's decision	2 (5.7)	0	1 (2.8)	3 (2.8)
Adverse event	2 (5.7)	0	1 (2.8)	3 (2.8)
Noncompliance	1 (2.9)	1 (2.8)	0	2 (1.9)
Other	1 (2.9)	1 (2.8)	3 (8.3)	5 (4.7)
Received at least 1 dose (safety population)	35	36	33	104
Completed study drug	26 (74.3)	25 (69.4)	24 (66.7)	75 (70.0)
Discontinued study drug	9 (25.7)	11 (30.6)	12 (33.3)	32 (29.9)
Death	2 (5.7)	0	2 (6.1)	4 (3.8)
Lost to follow-up	0	1 (2.8)	0	1 (1.0)
Withdrawal by subject	1 (2.9)	1 (2.8)	1 (3.0)	3 (2.8)
Physician's decision	1 (2.9)	1 (2.8)	0	2 (1.9)
Adverse event	2 (5.7)	1 (2.8)	1 (3.0)	4 (3.7)
Noncompliance	1 (2.9)	0	0	1 (1.0)
Lack of efficacy	0	1 (2.8)	2 (6.1)	3 (2.8)
Screening blood culture negative for *Candida*	0	2 (5.6)	2 (6.1)	4 (3.7)
Diagnosis of other types of IC	1 (2.9)	1 (2.8)	1 (3.0)	3 (2.8)
Other	1 (2.9)	3 (8.3)	2 (6.1)	6 (5.6)

Source: Table 7 of the Study Report and Statistics Reviewer's analysis.
Abbreviations: IC, invasive candidiasis; ITT, intent-to-treat; N, number of subjects in the ITT population; n, number of subjects in the specified category where percentages are based on the number of subjects in the ITT population.

Table 148. Subject Disposition, ITT Population, Part B, Phase 2 Study

Disposition	Rezafungin 400/400 mg N=46 n (%)	Rezafungin 400/200 mg N=21 n (%)	Caspofungin N=33 n (%)	Total N=100 n (%)
Completed the study	33 (71.7)	14 (66.7)	28 (84.8)	75 (75.0)
Discontinued from the study early	13 (28.3)	7 (33.3)	5 (15.2)	25 (25.0)
Death	8 (17.4)	3 (14.3)	5 (15.2)	16 (16.0)
Lost to follow-up	2 (4.3)	2 (9.5)	0	4 (4.0)
Withdrawal by subject	3 (6.5)	1 (4.8)	0	4 (4.0)
Adverse event	0	0	0	0
Other	0	1 (4.8)	0	1 (1.0)
Received at least 1 dose (safety population)	46	19	33	98
Completed study drug	32 (69.6)	13 (68.4)	24 (72.7)	69 (70.4)
Discontinued study drug	14 (30.4)	6 (31.6)	9 (27.3)	29 (29.6)
Death	4 (8.7)	1 (5.3)	1 (3.0)	6 (6.1)
Withdrawal by subject	3 (6.5)	0	0	3 (3.1)
Physician's decision	1 (2.2)	2 (10.5)	1 (3.0)	4 (4.1)
Adverse event	1 (2.2)	0	3 (9.1)	4 (4.1)
Noncompliance	1 (2.2)	0	1 (3.0)	2 (2.0)
Lack of efficacy	1 (2.2)	0	1 (3.0)	2 (2.0)
Screening blood culture negative for *Candida*	0	1 (5.3)	0	1 (1.0)
Diagnosis of other types of IC	2 (4.3)	0	2 (6.1)	4 (4.1)
Other	1 (2.2)	2 (10.5)	0	3 (3.1)

Source: Table 14.1.1.2B, Listing 16.2.1.2. of the Study Report and Statistics Reviewer's analysis
Percentages are based on the number of subjects randomized except for screen failures which are based on the number of subjects screened.
Abbreviations: IC, invasive candidiasis; ITT, intent-to-treat

16.1.2. Baseline Demographics and Clinical Characteristics

Baseline demographics in the ITT population are presented in Table 149. Most subjects were male (57%), White (83%), or not Hispanic or Latino (86%). The mean age was 59.7 years old. The mean estimated normalized creatinine clearance was 84.9 mL/min and mean APACHE II score was 13.8.

Table 149. Baseline Demographics (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
Min, max	24, 88	24, 91	24, 93	24, 93
Age categories, n (%)				
<65	49 (60.5)	32 (56.1)	40 (58.0)	121 (58.5)
≥65	32 (39.5)	25 (43.9)	29 (42.0)	86 (41.5)

Parameter	Rezafungin 400/400 mg N=81	Rezafungin 400/200 mg N=57	Caspofungin N=69	Total N=207
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
Min, max	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
Min, max	150.0, 190.0	145.0, 187.9	154.0, 188.0	145.0, 190.0
Missing	1	3	3	7
BMI, kg/m2				
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
Min, max	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 [female only], 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)
Country, n (%)				
BEL	9 (11.1)	9 (15.8)	12 (17.4)	30 (14.5)
BGR	4 (4.9)	1 (1.8)	2 (2.9)	7 (3.4)
CAN	1 (1.2)	1 (1.8)	3 (4.3)	5 (2.4)
ESP	22 (27.2)	15 (26.3)	13 (18.8)	50 (24.2)
GRC	6 (7.4)	6 (10.5)	8 (11.6)	20 (9.7)
HUN	2 (2.5)	0	0	2 (1.0)
ITA	7 (8.6)	2 (3.5)	5 (7.2)	14 (6.8)
ROU	2 (2.5)	0	3 (4.3)	5 (2.4)
RUS	2 (2.5)	1 (1.8)	0	3 (1.4)
USA	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)

Parameter	Rezafungin 400/400 mg N=81	Rezafungin 400/200 mg N=57	Caspofungin N=69	Total N=207
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
Min, max	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
Min, max	7.1, 331.8	5.6, 252.5	8.6, 293.3	5.6, 331.8
Missing	2	6	5	13

Source: Table 14.1.3.1C of the Study Report and Statistics Reviewer's Analysis; adsl.xpt
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BEL, Belgium; BGR, Bulgaria; BMI, body mass index; CAN, Canada; eCrCl, estimated creatinine clearance; ESP, Spain; GRC, Greece; HUN, Hungary; IQR, interquartile range; ITA, Italy; ITT,= Intention-to-treat population; Max, maximum; Min, minimum; ROU, Romania; RUS, Russia; SD, standard deviation; USA, United States of America

Fungal pathogens at baseline in the mITT population in the phase 2 study are summarized in Table 150. The most common pathogens were *Candida albicans, Candida glabrata,* and *Candida parapsilosis*. The proportion of subjects with *Candida albicans* in the rezafungin 400/200 mg arm was numerically lower; and the proportion of subjects with *Candida glabrata* in this arm was numerically higher.

Table 150. Fungal Pathogens at Baseline, mITT Population, Phase 2 Study

Pathogen	Rezafungin 400/400 mg N=76 n (%)	Rezafungin 400/200 mg N=46 n (%)	Caspofungin N=61 n (%)	Total N=183 n (%)
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 & Statistics Reviewer's Analysis
Note: Subjects with >1 *Candida* species at baseline were counted for each species and thus the numbers may not add up to the totals.
Abbreviations: mITT, modified intent-to-treat

There were no differences among arms in prior systemic antifungal medication (taken within 4 weeks prior to the first dose of the study drug), as Table 151 shows.

Table 151. Prior Systemic Antifungal Medication, mITT Population, Phase 2 Study

Parameter	Rezafungin 400/400 mg N=76 n (%)	Rezafungin 400/200 mg N=46 n (%)	Caspofungin N=61 n (%)	Total N=183 n (%)
Any prior systemic antifungal medication	46 (60.5)	32 (69.6)	45 (73.8)	123 (67.2)
Antibiotics	1 (1.3)	0	0	1 (0.5)
Amphotericin B	1 (1.3)	0	0	1 (0.5)
Other antimycotics for systemic use	27 (35.5)	20 (43.5)	28 (45.9)	75 (41.0)
Anidulafungin	1 (1.3)	6 (13.0)	4 (6.6)	11 (6.0)
Caspofungin	10 (13.2)	3 (6.5)	9 (14.8)	22 (12.0)
Micafungin	16 (21.1)	11 (23.9)	15 (24.6)	42 (23.0)
Triazole derivatives	24 (31.6)	15 (32.6)	20 (32.8)	59 (32.2)
Fluconazole	24 (31.6)	15 (32.6)	20 (32.8)	59 (32.2)

Source: Table 13 of the Study Report and Statistics Reviewer's analysis
Abbreviations: mITT, modified intent-to-treat

There were no differences among arms in use of concomitant systemic antifungal medications, as Table 152 shows.

Table 152. Concomitant Systemic Antifungal Medications, mITT Population, Phase 2 Study

Parameter	Rezafungin 400/400 mg N=76 n (%)	Rezafungin 400/200 mg N=46 n (%)	Caspofungin N=61 n (%)	Total N=183 n (%)
Any concomitant systemic antifungal medication	27 (35.5)	13 (28.3)	21 (34.4)	61 (33.3)
Antibiotics	6 (7.9)	3 (6.5)	7 (11.5)	16 (8.7)
Amphotericin B	3 (3.9)	2 (4.3)	5 (8.2)	10 (5.5)
Amphotericin B, liposome	3 (3.9)	2 (4.3)	2 (3.3)	7 (3.8)
Other antimycotics for systemic use	10 (13.2)	8 (17.4)	12 (19.7)	30 (16.4)
Micafungin	4 (5.3)	4 (8.7)	7 (11.5)	15 (8.2)
Caspofungin	5 (6.6)	3 (6.5)	3 (4.9)	11 (6)
Anidulafungin	2 (2.6)	4 (8.7)	4 (6.6)	10 (5.5)
Flucytosine	0	1 (2.2)	1 (1.6)	2 (1.1)
Triazole derivatives	17 (22.4)	8 (17.4)	14 (23)	39 (21.3)
Fluconazole	17 (22.4)	7 (15.2)	14 (23)	38 (20.8)

Source: Statistical Reviewer's Analysis
Abbreviation: mITT, modified intent-to-treat

16.1.3. Analysis of Efficacy

Primary Efficacy Endpoint: Overall Response Failure Reasons

The reasons for failure or indeterminate overall response at Day 14 in the population are listed in Table 153. The main reason for failure was mycological failure. The reasons for indeterminate overall response were almost equally due to an inadequate number of mycological cultures and incomplete assessment of systemic signs.

Table 153. 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 of the Study Report 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

Subgroup Analysis of the Primary Efficacy Endpoint

Overall response at Day 14 in subjects with candidemia only, or with invasive candidiasis in the mITT population, is summarized in Table 154. The 400/200 mg rezafungin arm had the numerically highest success proportion among the three treatment arms.

Table 154. Overall Response at Day 14: Subjects with Candidemia Only, mITT Population, Phase 2 Study

Parameter	Statistic	Rezafungin 400/400 mg N=57	Rezafungin 400/200 mg N=36	Caspofungin N=48
Candidemia only				
Success	n (%)	35 (61.4)	25 (69.4)	31 (64.6)
	95% CI	47.6, 74.0	51.9, 83.7	49.5, 77.8
Failure/Indeterminate	n (%)	22 (38.6)	11 (30.6)	17 (35.4)
Failure	n (%)	15 (26.3)	8 (22.2)	14 (29.2)
Indeterminate	n (%)	7 (12.3)	3 (8.3)	3 (6.3)
Invasive candidiasis				
Success	n (%)	11 (57.9)	10 (100.0)	10 (76.9)
	95% CI	33.5, 79.7	69.2, 100.0	46.2, 95.0
Failure/Indeterminate	n (%)	8 (42.1)	0	3 (23.1)
Failure	n (%)	5 (26.3)	0	3 (3.1)
Indeterminate	n (%)	3 (15.8)	0	0

Source: Tables 21 and 22 of the Study Report & Statistics Reviewer's Analysis
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; N, number of subjects in the mITT population with candidemia only; n, number of subjects in the specified category

Overall response at Day 14 by baseline *Candida* species is summarized in Table 155. For the species with a sample size no smaller than six in each treatment arm, there were no statistically

significant differences in success percentage between the two treatment arms. For other species, the sample sizes were too small to make reliable conclusions.

Table 155. Overall Success at Day 14 by Baseline *Candida* Species, mITT Population, Phase 2 Study

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

Source: Table 34 of the Study Report and Statistics Reviewer's analysis.
Abbreviation: mITT, modified intent-to-treat; N, number of subjects in the mITT Population.

16.2. Phase 3 Study

16.2.1. Baseline *Candida* Pathogens

Results of the *Candida* pathogens from baseline blood and sterile site cultures are summarized in Table 156 for the mITT Population. The most common fungal pathogen was *C. albicans* in 41.9% and 42.6% of subjects in the rezafungin and caspofungin treatment arms, The two treatment arms were comparable with these baseline *Candida* pathogens.

Table 156. 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)

Fungal Pathogen, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94	Total N=187
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

16.2.2. Treatment Compliance

Three subjects did not receive study drug. The durations of IV treatment and IV+oral treatment for subjects receiving study drug is summarized in Table 157. The means of durations and medians were comparable between the two treatment arms.

Table 157. Treatment Compliance for Subjects Receiving Study Drugs, ITT Population

Parameter	Rezafungin 400/200 mg N=98	Caspofungin N=98	Total N=196
Duration of IV treatment (days)			
Mean (SD)	11.1 (6.07)	12.3 (5.74)	11.7 (5.93)
Median	14.0	14.0	14.0
IQR	6.0, 14.0	8.0, 15.0	8.0, 14.0
Min, max	1.0, 28.0	1.0, 28.0	1.0, 28.0
Duration of IV + oral treatment (days)			
Mean (SD)	12.4 (6.46)	13.8 (6.16)	13.1 (6.34)
Median	14.0	14.0	14.0
IQR	7.0, 14.0	13.0, 15.0	11.0, 14.5
Min, max	1.0, 28.0	1.0, 28.0	1.0, 28.0

Source: Statistics Reviewer Analysis; adex.xpt
Abbreviations: IQR, interquartile range; ITT, intention-to-treat population; IV, intravenous; max, maximum; min, minimum; SD, standard deviation

16.2.3. Signs and Symptoms Attributable to Candidemia and/or Invasive Candidiasis

Signs and symptoms attributable to candidemia and/or invasive candidiasis are summarized in Table 158. The most common signs and symptoms were tachycardia (60.3%), followed by fever (49.2%). The two treatment arms were comparable.

Table 158. Systemic Signs and Symptoms Attributable to Candidemia and/or Invasive Candidiasis – ITT Population, Phase 3 Study

Parameter	Rezafungin 400/200 mg N=98 n (%)	Caspofungin N=98 n (%)	Total N=196 n (%)
Number of subjects with at least one sign or symptom attributable to candidemia and/or invasive candidiasis	100 (100)	99 (100)	199 (100)
Fatigue	24 (24)	29 (29.3)	53 (26.6)
Fever	47 (47)	51 (51.5)	98 (49.2)
Hypotension	23 (23)	22 (22.2)	45 (22.6)

Parameter	Rezafungin 400/200 mg N=98 n (%)	Caspofungin N=98 n (%)	Total N=196 n (%)
Hypothermia	4 (4)	3 (3)	7 (3.5)
Local signs of Inflammation	22 (22)	21 (21.2)	43 (21.6)
Myalgia	3 (3)	5 (5.1)	8 (4)
Pain	20 (20)	23 (23.2)	43 (21.6)
Tachycardia	57 (57)	63 (63.6)	120 (60.3)
Tachypnea	42 (42)	37 (37.4)	79 (39.7)

Source: Table 24 of the Study Report and Statistics Reviewer's analysis.
Abbreviations: ITT, intent-to-treat

16.2.4. Concomitant Medication

Approximately 37% of subjects were administered a concomitant systemic antifungal medication. The most common reason for concomitant antifungal medication use was for treatment of the candidemia/invasive candidiasis after discontinuation of study drug, due to treatment failure. The mean study days of initiation of concomitant antifungal medication for treatment of candidemia/IC in the ITT population during the study were 13.2 and 13.7 days for the rezafungin (n=42 events) and caspofungin (n=36 events) arms, respectively. Among those subjects who initiated concomitant antifungal medication by Day 30, excluding subjects not in the mITT population, 11 out of 33 (33.3%) and 5 out of 28 (17.9%) in the two treatment arms, respectively, died by Day 30.

Table 159. Concomitant Systemic Antifungal Medications – ITT Population, Phase 3 Study

Parameter	Rezafungin 400/200 mg N=100	Caspofungin N=99	Total N=199
Number of subjects with at least one antimycotics for systemic use	39 (39)	34 (34.3)	73 (36.7)
Fluconazole	14 (14)	19 (19.2)	33 (16.6)
Caspofungin	8 (8)	7 (7.1)	15 (7.5)
Amphotericin B	10 (10)	3 (3)	13 (6.5)
Micafungin	4 (4)	6 (6.1)	10 (5)
Voriconazole	7 (7)	2 (2)	9 (4.5)
Anidulafungin	3 (3)	3 (3)	6 (3)
Amphotericin B, liposome	3 (3)	2 (2)	5 (2.5)
Caspofungin acetate	1 (1)	2 (2)	3 (1.5)
Posaconazole	3 (3)	0	3 (1.5)
Flucytosine	1 (1)	1 (1)	2 (1)
Isavuconazonium sulfate	2 (2)	0	2 (1)
Amphotericin B cholesteryl sulfate complex	1 (1)	0	1 (0.5)
Isavuconazole	1 (1)	0	1 (0.5)
Isavuconazonium	1 (1)	0	1 (0.5)

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

All subjects in the ITT population received at least one concomitant nonantifungal therapy. Concomitant nonantifungal medications in categories with 10 or more subjects are summarized

in Table 160. More than 70% of subjects reported concomitant use of drugs for peptic ulcer and gastro-esophageal reflux disease, other beta-lactam antibacterials, and antithrombotic agents.

Table 160. Concomitant Nonantifungal Medications in Categories With 10 or More Subjects, ITT Population, Phase 3 Study

Parameter	Rezafungin 400/200 mg N=100 n (%)	Caspofungin N=99 n (%)	Total N=199 n (%)
Subjects with at least one concomitant nonantifungal therapy	100 (100)	99 (100)	199 (100)
Drugs for peptic ulcer and gastro-esophageal reflux disease	88 (88)	85 (85.9)	173 (86.9)
Other beta-lactam antibacterials	69 (69)	72 (72.7)	141 (70.9)
Antithrombotic agents	71 (71)	69 (69.7)	140 (70.4)
Other analgesics and antipyretics	68 (68)	68 (68.7)	136 (68.3)
Other antibacterials	58 (58)	64 (64.6)	122 (61.3)
Opioids	63 (63)	58 (58.6)	121 (60.8)
IV solutions	62 (62)	58 (58.6)	120 (60.3)
Beta-lactam antibacterials, penicillins	54 (54)	40 (40.4)	94 (47.2)
High-ceiling diuretics	39 (39)	52 (52.5)	91 (45.7)
Drugs for constipation	43 (43)	44 (44.4)	87 (43.7)
IV solution additives	48 (48)	37 (37.4)	85 (42.7)
Hypnotics and sedatives	43 (43)	41 (41.4)	84 (42.2)
Insulins and analogues	41 (41)	42 (42.4)	83 (41.7)
Corticosteroids for systemic use, plain	36 (36)	39 (39.4)	75 (37.7)
Beta blocking agents	28 (28)	40 (40.4)	68 (34.2)
Antiemetics and antinauseants	34 (34)	32 (32.3)	66 (33.2)
Cardiac stimulants excluding cardiac glycosides	36 (36)	28 (28.3)	64 (32.2)
Potassium	32 (32)	31 (31.3)	63 (31.7)
Anesthetics, general	32 (32)	30 (30.3)	62 (31.2)
Adrenergics, inhalants	32 (32)	28 (28.3)	60 (30.2)
Blood and related products	27 (27)	27 (27.3)	54 (27.1)
Propulsives	27 (27)	26 (26.3)	53 (26.6)
Quinolone antibacterials	26 (26)	24 (24.2)	50 (25.1)
Antihistamines for systemic use	25 (25)	24 (24.2)	49 (24.6)
Anxiolytics	25 (25)	23 (23.2)	48 (24.1)
Other mineral supplements	20 (20)	25 (25.3)	45 (22.6)
Selective calcium channel blockers with mainly vascular effects	20 (20)	23 (23.2)	43 (21.6)
Lipid modifying agents, plain	15 (15)	24 (24.2)	39 (19.6)
Stomatological preparations	23 (23)	13 (13.1)	36 (18.1)
Vitamin K and other hemostatics	16 (16)	20 (20.2)	36 (18.1)
Antidepressants	18 (18)	16 (16.2)	34 (17.1)
Antiinflammatory and antirheumatic products, nonsteroids	17 (17)	15 (15.2)	32 (16.1)
Vitamin B12 and folic acid	15 (15)	17 (17.2)	32 (16.1)
Antipsychotics	16 (16)	15 (15.2)	31 (15.6)
Vitamin B1, plain and in combination with vitamin B6 and B12	18 (18)	13 (13.1)	31 (15.6)
Anesthetics, local	18 (18)	10 (10.1)	28 (14.1)
Direct acting antivirals	16 (16)	12 (12.1)	28 (14.1)
Expectorants, excluding combinations with cough suppressants	14 (14)	14 (14.1)	28 (14.1)

Parameter	Rezafungin 400/200 mg N=100 n (%)	Caspofungin N=99 n (%)	Total N=199 n (%)
Muscle relaxants, peripherally acting agents	18 (18)	10 (10.1)	28 (14.1)
Other drugs for obstructive airway diseases, inhalants	15 (15)	13 (13.1)	28 (14.1)
All other therapeutic products	13 (13)	14 (14.1)	27 (13.6)
Aminoglycoside antibacterials	16 (16)	11 (11.1)	27 (13.6)
Vitamin A and D, including combinations of the two	11 (11)	14 (14.1)	25 (12.6)
Iron preparations	16 (16)	8 (8.1)	24 (12.1)
Sulfonamides and trimethoprim	14 (14)	10 (10.1)	24 (12.1)
Antipropulsives	15 (15)	8 (8.1)	23 (11.6)
Macrolides, lincosamides and streptogramins	13 (13)	10 (10.1)	23 (11.6)
Immunostimulants	12 (12)	10 (10.1)	22 (11.1)
Tetracyclines	14 (14)	8 (8.1)	22 (11.1)
Antipruritics, including antihistamines, anesthetics, etc.	11 (11)	10 (10.1)	21 (10.6)
Muscle relaxants, centrally acting agents	11 (11)	9 (9.1)	20 (10.1)
Ace inhibitors, plain	9 (9)	10 (10.1)	19 (9.5)
Immunosuppressants	12 (12)	7 (7.1)	19 (9.5)
Potassium-sparing agents	11 (11)	8 (8.1)	19 (9.5)
Antacids	7 (7)	11 (11.1)	18 (9)
Blood glucose lowering drugs, excluding insulins	11 (11)	7 (7.1)	18 (9)
Drugs for functional gastrointestinal disorders	7 (7)	11 (11.1)	18 (9)
Other alimentary tract and metabolism products	11 (11)	7 (7.1)	18 (9)
Thyroid preparations	11 (11)	7 (7.1)	18 (9)
Antiarrhythmics, class I and III	9 (9)	8 (8.1)	17 (8.5)
Antiepileptics	6 (6)	11 (11.1)	17 (8.5)
Calcium	8 (8)	8 (8.1)	16 (8)
Other nutrients	11 (11)	5 (5.1)	16 (8)
X-ray contrast media, iodinated	10 (10)	6 (6.1)	16 (8)
Antidiarrheal microorganisms	9 (9)	6 (6.1)	15 (7.5)
Liver therapy, lipotropics	10 (10)	5 (5.1)	15 (7.5)
Antifibrinolytics	7 (7)	7 (7.1)	14 (7)
Antigout preparations	6 (6)	8 (8.1)	14 (7)
Intestinal anti-infectives	6 (6)	8 (8.1)	14 (7)
Multivitamins, plain	5 (5)	9 (9.1)	14 (7)
Other antianemic preparations	6 (6)	8 (8.1)	14 (7)
Other vitamin products, combinations	9 (9)	5 (5.1)	14 (7)
Posterior pituitary lobe hormones	8 (8)	6 (6.1)	14 (7)
Angiotensin II antagonists, plain	2 (2)	11 (11.1)	13 (6.5)
Drugs used in benign prostatic hypertrophy	4 (4)	9 (9.1)	13 (6.5)
Hemodialytics and hemofiltrates	6 (6)	7 (7.1)	13 (6.5)
Mydriatics and cycloplegics	8 (8)	5 (5.1)	13 (6.5)
Other antineoplastic agents	7 (7)	6 (6.1)	13 (6.5)
Vitamin b-complex, including combinations	6 (6)	7 (7.1)	13 (6.5)
Other ophthalmologicals	9 (9)	3 (3)	12 (6)
Vasodilators used in cardiac diseases	6 (6)	6 (6.1)	12 (6)
Emollients and protectives	8 (8)	3 (3)	11 (5.5)
Antiadrenergic agents, peripherally acting	4 (4)	6 (6.1)	10 (5)
Arteriolar smooth muscle, agents acting on	3 (3)	7 (7.1)	10 (5)
Ascorbic acid (vitamin C), including combination	4 (4)	6 (6.1)	10 (5)
Bile therapy	7 (7)	3 (3)	10 (5)

Parameter	Rezafungin 400/200 mg N=100 n (%)	Caspofungin N=99 n (%)	Total N=199 n (%)
Cardiac glycosides	6 (6)	4 (4)	10 (5)
Digestives, including enzymes	6 (6)	4 (4)	10 (5)
Hypothalamic hormones	4 (4)	6 (6.1)	10 (5)

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

16.2.5. Protocol Deviations

Protocol deviations in the ITT population are summarized in Table 161. Major deviations corresponded to those described in International Council on Harmonization Guideline E4 as important deviations. Approximately 76% of subjects had at least one protocol deviation and 50% of subjects had at least one major protocol deviation. The most commonly reported major deviations included procedures/assessments, study treatment administration/dispensing/compliance, informed consent, and inclusion/exclusion. The two treatment arms were comparable in deviation categories, except for more subjects with prohibited concomitant medication use in the caspofungin arm. These concomitant medications included prohibited fluconazole, vincristine, amiodarone, additional caspofungin, and micafungin.

Table 161. Protocol Deviation, ITT Population, Phase 3 Study

Protocol Deviation Category, n (%)	Rezafungin N=100	Caspofungin N=99	Total N=199
Subjects with at least one protocol deviation	77 (77)	74 (74.7)	151 (75.9)
At least one major deviation	50 (50)	48 (48.5)	98 (49.2)
Procedures/assessments	35 (35)	34 (34.3)	69 (34.7)
Study treatment administration/dispensing/compliance	11 (11)	11 (11.1)	22 (11.1)
Informed consent	9 (9)	10 (10.1)	19 (9.5)
Inclusion/exclusion	6 (6)	8 (8.1)	14 (7)
Serious adverse event reporting and adverse events of special interest	5 (5)	4 (4)	9 (4.5)
Study visits	4 (4)	3 (3)	7 (3.5)
Concomitant medication	0	6 (6.1)	6 (3)
Randomization	3 (3)	2 (2)	5 (2.5)

Source: Table 18 of the Study Report and Statistics Reviewer's analysis
Abbreviations: ITT, intent-to-treat

16.2.6. Efficacy Results

16.2.6.1. Additional Analyses for the Primary and Secondary Efficacy Endpoints

All-Cause Mortality at Day 30 (-2) By Baseline Pathogen

Table 162 shows Day 30 all-cause mortality by baseline pathogen in the mITT population. There were no detected differences in mortality between treatment arms by pathogen.

Table 162. All-Cause Mortality at Day 30 (-2 Days) by Baseline Pathogen, mITT Population, Phase 3 Study

Pathogen	Rezafungin 400/200 mg N=93	Caspofungin N=94	Total N=187
Candida albicans	11/39 (28.2)	9/40 (22.5)	20/79 (25.3)
Candida dubliniensis	0/3 (0)	0	0/3 (0)
Candida glabrata	4/22 (18.2)	2/22 (9.1)	6/44 (13.6)
Candida krusei	1/2 (50)	0/1 (0)	1/3 (33.3)
Candida lusitaniae	0/1 (0)	0/1 (0)	0/2 (0)
Candida metapsilosis	0/1 (0)	0	0/1 (0)
Candida nivariensis	0	0/1 (0)	0/1 (0)
Candida parapsilosis	1/8 (12.5)	6/17 (35.3)	7/25 (28)
Candida tropicalis	5/15 (33.3)	3/12 (25)	8/27 (29.6)

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

FDA's Sensitivity Analyses of All-Cause Mortality at Day 30 (-2) Days

There were eight subjects (three in the rezafungin arm and five in the caspofungin arm) who did not satisfy all inclusion/exclusion criteria but were included in the mITT population. If those eight subjects were excluded from the analysis, the upper limit of the 95% CI also met the NI margin of 20%.

There were 44 subjects (23 and 21 in the two treatment arms, respectively) who took concomitant antifungal treatment for candidemia/IC. Twelve subjects (eight and four subjects in the two arms) died. If all subjects who received concomitant antifungal treatment were considered as deceased, the upper limit of the 95% is 14.4%, meeting the 20% NI margin.

In an analysis that excludes the eight subjects not satisfying all inclusion/exclusion criteria and considers the subjects prescribed concomitant antifungals (concomitant antifungal users) as deceased, the upper limit of the 95% CI was 16.1%, but met the 20% NI margin.

There were 10 subjects who discontinued treatment under the "other" category in the disposition table (Table 163). Eight of those subjects were included in the mITT population with Day 30 mortality rates of 3/7 and 0/1 in the two treatment arms, respectively. If all of these subjects were considered as deceased, the difference between the two treatment arms was 5.7% (upper limit of 95% CI: 17.8%).

Table 163. 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 satisfy all inclusion/exclusion (IE) criteria	22/90 (35.6)	18/89 (39.3)	4.3 (-8, 16.4)
Considering concomitant antifungal users as deceased	37/93 (39.8)	37/94 (39.4)	0.4 (-13.5, 14.4)
Both excluding IE subjects and considering concomitant antifungal users as deceased	36/90 (40.0)	34/89 (38.2)	1.8 (-12.5, 16.1)
Considering all subjects who discontinued treatment due to “other” reason as deceased	26/93 (28.0)	21/94 (22.3)	5.7 (-6.4, 17.8)

Source: Statistics Reviewer’s analysis.

Reasons for Failure or Indeterminate Global Response

Table 164 shows the reasons for failure or indeterminate global response as assessed by the data review committee at Day 14. For mycological and clinical failure, the main reasons were death and the need for new or prolonged therapy. For indeterminate status, the main reason was subject withdrawal of consent.

Table 164. Reasons for Failure or Indeterminate Global Response as Assessed by the DRC at Day 14 (±1 Day) – mITT Population, Phase 3 Study

Reason, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94
Failure	28	29
For mycological response	24	27
Positive blood culture	0	1 (3.4)
Positive culture from normally sterile site	1 (3.6)	1 (3.4)
Clinical failure or lack of improvement in radiographic abnormalities (IC Subjects only)	1 (3.6)	7 (24.1)
New or prolonged therapy	12 (42.9)	9 (31.0)
Subject died	10 (35.7)	9 (31.0)
For clinical response	27	27
Progression or recurrence of signs/symptoms of candidemia/IC requiring new or prolonged therapy	2 (7.1)	3 (10.3)
Lack of resolution of signs/symptoms of candidemia/IC requiring new or prolonged therapy	4 (14.3)	7 (24.1)
New or prolonged antifungal therapy (only allowed at follow-up visit*)	8 (28.6)	8 (27.6)
Adverse event which requires discontinuation of study drug	3 (10.7)	0
Subject died	10 (35.7)	9 (31.0)
For radiological response	2	8
Progression of radiological or other imaging findings of IC	0	1 (3.4)
New radiological or other imaging findings of IC	1 (3.6)	2 (6.9)
Lack of improvement of radiological or other imaging findings of IC	0	4 (13.8)
Subject died	1 (3.6)	1 (3.4)
Indeterminate	10	8
For mycological response	9	8
Subject was lost to follow-up	2 (20.0)	2 (25.0)
Subject withdrew consent	3 (30.0)	3 (37.5)
Blood specimen/result not available	1 (10.0)	1 (12.5)

Reason, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94
Sterile site specimen/result and clinical/radiographic assessments not available (IC subjects only)	1 (10.0)	1 (12.5)
Extenuating circumstances	2 (20.0)	1 (12.5)
For clinical response	7	6
Subject was lost to follow-up	2 (20.0)	2 (25.0)
Subject withdrew consent	3 (30.0)	3 (37.5)
Subject missed study visit	1 (10.0)	1 (12.5)
Extenuating circumstances	1 (10.0)	0
For radiological response	5	2
Subject was lost to follow-up	1 (10.0)	0
Subject withdrew consent	2 (20.0)	1 (12.5)
Radiology or other imaging not completed	2 (20.0)	1 (12.5)

Source: Table 39 of the Study Report and Statistics Reviewer's analysis
Abbreviations: IC, invasive candidiasis; mITT, modified intent-to-treat

Resolution of systemic signs and symptoms attributable to candidemia and/or IC and the combined resolution of attributable systemic sign and symptoms and mycological response by visit for subjects with assessment is summarized in Table 165. Subjects with no assessment were not included in the analysis. The two treatment arms were comparable.

Table 165. Resolution of Systemic Signs and Symptoms Attributable to Candidemia and/or Invasive Candidiasis by Visit for Subjects with Assessment, mITT Population, Phase 3 Study

Category Visit, n (%)	Rezafungin 400/200 mg N=93	Caspofungin N=94
Number of subjects with at least one attributable sign or symptom at screening[a]	93/93 (100.0)	94/ 94 (100.0)
Resolution of attributable signs or symptoms		
Day 5	64/81 (79.0)	69/85 (81.2)
Day 14 (±1 day)	68/69 (98.6)	66/75 (88.0)
Day 30 (-2 days)	56/56 (100.0)	60/64 (93.8)
Follow-up (Days 52 to 59)	53/54 (98.1)	52/56 (92.9)
Mycological eradication and resolution of attributable signs or symptoms		
Day 5	53/81 (65.4)	53/85 (62.4)
Day 14 (±1 day)	61/69 (88.4)	53/75 (70.7)
Day 30 (-2 days)	46/56 (82.1)	45/64 (70.3)
Follow-up (Days 52 to 59)	41/54 (75.9)	39/56 (69.6)

Source: Table 45 of the Study Report and Statistics Reviewer's analysis.
[a] Percentages were calculated as the number of subjects with at least one attributable sign or symptom at screening divided by the number of subjects with a nonmissing assessment of systemic signs at screening in the mITT population.
Abbreviations: mITT, modified intent to-treat

16.3. Results of Pooled Analyses, Phase 2 and 3 Studies

Baseline demographics from the pooled analysis of the ITT population from the phase 2 and phase 3 studies are summarized in the following table. There were 10% more males in the

rezafungin 400/200 mg arm than in other treatment arms. The baseline demographics were otherwise well balanced between the treatment arms.

Table 166. Baseline Demographics of Pooled Analysis, ITT Population, Phase 2 and 3 Studies

Variable	Rezafungin 400/400 mg N=81	Rezafungin 400/200 mg N=157	Caspofungin N=168	Total N=406
Sex, n (%)				
Male	44 (54.3)	103 (65.6)	94 (56.0)	241 (59.4)
Female	37 (45.7)	54 (34.4)	74 (44.0)	165 (40.6)
Age, years				
Mean (SD)	59.4 (15.86)	59.7 (15.79)	60.9 (15.12)	60.1 (15.51)
Median	61	60.0	62.5	61.0
IQR	50.0, 69.0	49.0, 70.0	52.5, 71.0	50.0, 71.0
Min, max	24.0, 88.0	19.0, 91.0	20.0, 93.0	19.0, 93.0
Age categories, n (%)				
18 to <65 years	49 (60.5)	92 (58.6)	98 (58.3)	239 (58.9)
≥65 years	32 (39.5)	65 (41.4)	70 (41.7)	167 (41.1)
Race, n (%)				
American Indian or Alaska Native	0	1 (<1)	1 (<1)	2 (<1)
Asian	0	28 (17.8)	34 (20.2)	62 (15.3)
Black or African American	8 (9.9)	12 (7.6)	8 (4.8)	28 (6.9)
Not reported	0	5 (3.2)	1 (<1)	6 (1.5)
Other	4 (4.9)	3 (1.9)	2 (1.2)	9 (2.2)
White	69 (85.2)	105 (66.9)	119 (70.8)	293 (72.2)
Missing	0	3 (1.9)	3 (1.8)	6 (1.5)
Baseline Weight (kg)				
Mean (SD)	77.6 (23.57)	74.3 (23.39)	72.2 (20.82)	74.2 (22.45)
Median	77.2	70.0	70.0	71.0
IQR	62.7, 88.1	56.0, 86.2	58.0, 82.0	58.1, 85.0
Min, max	41.8, 218.7	34.0, 154.5	33.0, 153.6	33.0, 218.7
Missing value	1	7	11	19
Weight at Baseline, kg				
Mean (SD)	169.4 (9.42)	168.9 (10.16)	167.7 (10.09)	168.5 (9.98)
Median	170.0	170.0	168.0	170.0
IQR	162.3, 177.8	160.0, 177.0	160.0, 175.0	160.5, 175.7
Min, max	150.0, 190.0	137.0, 190.0	115.0, 192.0	115.0, 192.0
Missing value	1	9	12	22
Baseline BMI (kg/m^2)				
Mean (SD)	26.9 (7.17)	25.9 (7.63)	25.4 (6.19)	25.9 (6.99)
Median	25.8	24.5	25.0	24.9
IQR	22.9, 30.4	20.9, 29.1	21.3, 28.2	21.3, 29.1
Min, max	13.9, 69.2	13.7, 64.4	12.9, 47.6	12.9, 69.2
Missing value	1	9	14	24
Country				
AUS	0	8 (5.1)	5 (3.0)	13 (3.2)
BEL	9 (11.1)	14 (8.9)	19 (11.3)	42 (10.3)
BGR	4 (4.9)	7 (4.5)	6 (3.6)	17 (4.2)
CAN	1 (1.2)	1 (<1)	3 (1.8)	5 (1.2)
CHN	0	6 (3.8)	5 (3.0)	11 (2.7)
COL	0	1 (<1)	0	1 (<1)
ESP	22 (27.2)	27 (17.2)	25 (14.9)	74 (18.2)
FRA	0	5 (3.2)	1 (<1)	6 (1.5)
GRC	6 (7.4)	12 (7.6)	19 (11.3)	37 (9.1)

Variable	Rezafungin 400/400 mg N=81	Rezafungin 400/200 mg N=157	Caspofungin N=168	Total N=406
HUN	2 (2.5)	0	0	2 (<1)
ISR	0	3 (1.9)	2 (1.2)	5 (1.2)
ITA	7 (8.6)	4 (2.5)	8 (4.8)	19 (4.7)
KOR	0	6 (3.8)	6 (3.6)	12 (3.0)
ROU	2 (2.5)	0	3 (1.8)	5 (1.2)
RUS	2 (2.5)	1 (<1)	0	3 (<1)
SGP	0	3 (1.9)	0	3 (<1)
THA	0	8 (5.1)	17 (10.1)	25 (6.2)
TWN	0	3 (1.9)	1 (<1)	4 (1.0)
USA	26 (32.1)	48 (30.6)	48 (28.6)	122 (30.0)
Geographic Region, n (%)				
Asia-Pacific (excluding China/Taiwan)	0	25 (15.9)	28 (16.7)	53 (13.1)
China/Taiwan	0	9 (5.7)	6 (3.6)	15 (3.7)
Europe/Israel/Turkey	54 (66.7)	73 (46.5)	83 (49.4)	210 (51.7)
North/South America	27 (33.3)	50 (31.8)	51 (30.4)	128 (31.5)
Diagnosis at randomization, n (%)				
Candidemia only	62 (76.5)	119 (75.8)	124 (73.8)	305 (75.1)
Invasive Candidiasis	19 (23.5)	38 (24.2)	44 (26.2)	101 (24.9)
Final diagnosis, n (%)				
Candidemia only	62 (76.5)	116 (73.9)	124 (73.8)	302 (74.4)
Invasive candidiasis	19 (23.5)	41 (26.1)	44 (26.2)	104 (25.6)
APACHE II Score				
Mean (SD)	13.4 (7.13)	13.1 (7.59)	13.4 (7.21)	13.3 (7.33)
Median	12.0	12.0	12.5	12.0
IQR	9.0, 17.0	8.0, 17.0	8.0, 18.0	8.0, 17.0
Min, max	2.0, 31.0	0.0, 40.0	0.0, 37.0	0.0, 40.0
Missing	2	3	6	11
APACHE II Score Group 1, n (%)				
<20	62 (76.5)	125 (79.6)	135 (80.4)	322 (79.3)
≥20	17 (21.0)	29 (18.5)	27 (16.1)	73 (18.0)
Missing	2 (2.5)	3 (1.9)	6 (3.6)	11 (2.7)
APACHE II Score Group 2, n (%)				
10 to 19	39 (48.1)	69 (43.9)	81 (48.2)	189 (46.6)
<10	23 (28.4)	56 (35.7)	54 (32.1)	133 (32.8)
≥20	17 (21.0)	29 (18.5)	27 (16.1)	73 (18.0)
Missing	2 (2.5)	3 (1.9)	6 (3.6)	11 (2.7)
ANC at randomization (cells/μL)				
Mean (SD)	9407.1 (8270.66)	8117.5 (6048.25)	8513.3 (5852.02)	8543.2 (6487.78)
Median	7300	7395	6961	7240
IQR	4397, 11411	4280.0, 10328	4870.0, 10800.0	4595.0, 10915.0
Min, max	1832.9, 61800	0, 41174	0, 37220	0, 61800
Missing	1	6	7	14
ANC at randomization (cells/μL), n (%)				
<500	0	9 (5.7)	6 (3.6)	15 (3.7)
≥500	80 (98.8)	142 (90.4)	155 (92.3)	377 (92.9)
Missing	1 (1.2)	6 (3.8)	7 (4.2)	14 (3.4)

Variable	Rezafungin 400/400 mg N=81	Rezafungin 400/200 mg N=157	Caspofungin N=168	Total N=406
Randomization strata, n (%)				
Candidemia only, APACHE II score <20 and ANC ≥500 cells/µL	45 (55.6)	82 (52.2)	94 (56.0)	221 (54.4)
Candidemia only, APACHE II score ≥20 or ANC <500 cells/µL	14 (17.3)	32 (20.4)	25 (14.9)	71 (17.5)
Invasive candidiasis, APACHE II score <20 and ANC ≥500 cells/µL	16 (19.8)	34 (21.7)	34 (20.2)	84 (20.7)
Invasive candidiasis, APACHE II score ≥20 or ANC <500 cells/µL	3 (3.7)	6 (3.8)	6 (3.6)	15 (3.7)
Missing	3 (3.7)	3 (1.9)	9 (5.4)	15 (3.7)
eCrCl at baseline (mL/min)				
Mean (SD)	100.0 (56.06)	88.6 (93.78)	87.2 (63.12)	90.4 (75.18)
Median	88.0	71.6	72.1	77.7
IQR	64.1, 142.0	38.8, 110.4	41.3, 115.0	41.1, 117.1
Min, max	6.7, 250.3	5.6, 949.6	0.4, 314.0	0.4, 949.6
Missing	2	13	16	31

Source: Statistical Reviewer's Analysis; adsl.xpt
In the two trials, about 90% and 95% of screened subjects were randomized in the Phase 3 and 2 trials.
Abbreviations: ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation II; AUS, Australia; BEL, Belgium; BGR, Bulgaria; BMI, body mass index; CAN, Canada; CHN, China; COL, Colombia; eCrCl, estimated creatinine clearance; ESP, Spain; FRA, France; GRC, Greece; HUN, Hungary; ISR, Israel; ITA, Italy; ITT, Intention-to-treat population; IQR, interquartile range; KOR, South Korea; ROU, Romania; RUS, Russia; SD, standard deviation; SGP, Singapore; THA, Thailand; TWN, Taiwan; USA, United States of America

In the two studies, about 90% and 95% of screened subjects were randomized in the phase 3 and 2 studies.

Table 167. Patient Screening and Enrollment, Pooled Analyses, Phase 2 and 3 Studies

Disposition	Phase 3 Study	Phase 2 Study
Patients screened	222	219[a]
Screening failures	23 (10.4%)	12 (5.5%)
Patients enrolled	199 (89.6%)	207 (94.5%)
Patients randomized	199 (89.6%)	207 (94.5%)

Source: Statistics Reviewer's analysis.
[a] Excluding one subject with a randomization error

Table 168. Patient Disposition, Pooled Analyses, Phase 2 and 3 Studies

Parameter, n (%)	Rezafungin 400/400 mg N=81	Rezafungin 400/200 mg N=157	Caspofungin N=168	Total N=406
ITT population	81 (100.0)	157 (100.0)	168 (100.0)	406 (100)
MITT population	76 (93.8)	139 (88.5)	155 (92.3)	370 (91.1)
End of study status				
Completed	56 (69.1)	101 (64.3)	109 (64.9)	266 (65.5)
Discontinued	25 (30.9)	56 (35.7)	59 (35.1)	140 (34.5)
Adverse event	2 (2.5)	0	4 (2.4)	6 (1.5)
Death	11 (13.6)	29 (18.5)	32 (19.0)	72 (17.7)
Lost to follow-up	4 (4.9)	7 (4.5)	6 (3.6)	17 (4.2)
Noncompliance with study	1 (1.2)	1 (<1)	0	2 (<1)
Other	1 (1.2)	10 (6.4)	6 (3.6)	17 (4.2)
Physician decision	2 (2.5)	0	1 (<1)	3 (<1)
Withdrawal by subject	4 (4.9)	9 (5.7)	10 (6.0)	23 (5.7)

Parameter, n (%)	Rezafungin 400/400 mg N=81	Rezafungin 400/200 mg N=157	Caspofungin N=168	Total N=406
End of treatment status				
Completed	58 (71.6)	104 (66.2)	119 (70.8)	281 (69.2)
Discontinued	23 (28.4)	53 (33.8)	49 (29.2)	125 (30.8)
Adverse event	3 (3.7)	9 (5.7)	11 (6.5)	23 (5.7)
Death	6 (7.4)	9 (5.7)	11 (6.5)	26 (6.4)
Diagnosis of other types of invasive candidiasis	3 (3.7)	2 (1.3)	4 (2.4)	9 (2.2)
Lack of efficacy	1 (1.2)	3 (1.9)	6 (3.6)	10 (2.5)
Lost to follow-up	0	3 (1.9)	1 (0.6)	4 (1.0)
Noncompliance	2 (2.5)	0	2 (1.2)	4 (1.0)
Other	2 (2.5)	14 (8.9)	2 (1.2)	18 (4.4)
Physician's decision	2 (2.5)	4 (2.5)	3 (1.8)	9 (2.2)
Screening blood culture negative for *Candida*	0	4 (2.5)	2 (1.2)	6 (1.5)
Subject never dosed with study drug	0	0	1 (<1)	1 (<1)
Withdrawal by subject	4 (4.9)	5 (3.2)	6 (3.6)	15 (3.7)

Source: Table 2 of the Summary of Clinical Efficacy and Statistics Reviewer's analysis
Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; N, number of patients in treatment arm; n, number of patients in specified population or group

All-Cause Mortality at Day 30 (-2 Days), mITT Population, Pooled Results

The following results are the Applicant's post hoc pooled analysis results for combined phase 2 and 3 studies. These results should be interpreted with caution. Refer to Section 6.3.1 for a discussion of regarding the interpretation of the pooled results.

Table 169. All-Cause Mortality at Day 30 Pooled Analysis From Applicant, Phase 2 and 3 Studies

	Phase 2 Study			Phase 3 Study		Pooled	
Variable	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: Table 8 of the Summary of Clinical Efficacy
Note: Percentages were calculated using the total number of subjects in each treatment arm (N) as the denominator.
[a] Subjects who died on or before Day 30, or with unknown survival status.
[b] Phase 2 STRIVE: Two-sided 95% confidence interval (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.
[c] 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.
[d] Pooled: Two-sided 95% CI for the weighted (by study and part 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.
Abbreviations: N, number of subjects; n, number of subjects in the category

17. Clinical Safety

17.1. Phase 1 Studies

As has been noted earlier, 8 phase 1 studies were conducted (Single Ascending Dose, Multiple Ascending Dose, QT, Phototoxicity, two DDI studies, absorption, distribution, metabolism, and excretion, and PK in Hepatic Impairment; see Table 32) in 179 subjects. These studies covered a dose range of 50 to 1,400 mg as a single dose or up to 4 weekly doses. Apart from subjects with hepatic impairment, subjects in the phase 1 studies were healthy volunteers. In these studies, there were no deaths or SAEs, and the findings were similar to the safety findings for the integrated summary of safety (ISS; infusion reactions, nausea, headache, constipation, diarrhea, abdominal pain were common AEs noted in subjects). Of note, there were no hepatotoxicity/hepatic impairment related adverse reactions in the phase 1 studies. One subject in the hepatic impairment study had an AE of "hepatic encephalopathy." However, this subject had severe hepatic impairment at baseline, and the AE happened 13 days after infusion and was considered unrelated. In phase 1 studies, infusion-related reactions generally occurred with the 400 mg dose. Note that the phase 1 Phototoxicity study only evaluated the 400 mg dose (four weekly doses). There was a single subject in the phase 1 studies who had an event of tremor; however, upon review of the case, the findings were more consistent with a transient infusion-related reaction (symptom happened during infusion along with anxiety and warmth and resolved spontaneously an hour after onset).

17.2. Phase 2 Study 400 mg/400 mg Cohort

Also as noted earlier, the phase 2 study featured a 400 mg/400 mg cohort which was ultimately not the dosing proposed by the Applicant for the candidemia/IC treatment indication. This cohort enrolled 81 subjects. From a safety perspective, there were no clear dose dependent findings related to treatment-emergent adverse events (TEAEs). When evaluating the phase 2 study data, only the General Disorders and Administration Site Conditions system organ class (particularly with regards to the TEAEs of fatigue, peripheral edema, and pyrexia) had an incidence rate in the 400 mg/400 mg cohort that was >10% more than the 400 mg/200 mg cohort incidence rate. No individual TEAE occurred in the 400 mg/400 mg cohort at a rate 10% greater than in the 400 mg/200 mg cohort. Notably, no TEAEs of tremor, peripheral neuropathy or ataxia occurred in the 400 mg/400 mg cohort. There was no clear dose-dependency for infusion -related reactions in the phase 2 study. Hepatic adverse events under the Group Query "Abnormal LFTs" were reported at a higher rate in the 400 mg/400 mg cohort (6/81; 7.4%) compared to the 400/200 mg cohort (1/53; 1.9%); however, when the transaminase results from the clinical safety laboratory data were reviewed the values were similar in the two dose cohorts. Patients Treated Under Expanded Access IND

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 ranged from 2 to 115 weeks (in some cases it was 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.

17.3. Blinded Safety Data From Ongoing 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 serious adverse event (SAE; gastric cancer), as well as one death (sudden cardiac arrest), were reported; no discontinuation from the study due to AEs were reported. The phase 3 ReSPECT prophylaxis study is ongoing, and 166 subjects have been 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.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

19.1. Antimicrobial Interaction With Rezafungin

The antimicrobial interaction of rezafungin was evaluated against some FDA-approved antifungal and antibacterial drugs (amphotericin B, fluconazole, posaconazole, flucytosine, colistin, ceftazidime, avibactam, imipenem, amikacin, ciprofloxacin, tigecycline, trimethoprim, sulfamethoxazole, erythromycin, linezolid, rifampicin, vancomycin, and daptomycin) in a checkerboard assay (Eliopoulos and Moellering 1991) to determine the potential of synergistic or antagonistic interactions.

The results show no antagonism of rezafungin with any of the antifungal agents tested. However, there were either synergistic, additive, or indifferent effects observed against all fungal isolates tested. The combination of either amphotericin B or posaconazole with rezafungin had an additive or indifferent effect against all *Candida* spp. tested. Fluconazole and flucytosine in combination with rezafungin had an additive or indifferent effect against all yeasts tested.

When tested in combination with antibacterial agents, synergy was observed for rezafungin in combination with colistin, tigecycline, and trimethoprim/sulfamethoxazole against *E. coli* ATCC

25922, and for rezafungin in combination with ceftazidime/avibactam and amikacin against *S. aureus* ATCC 29213. No antagonistic effects were observed in any tested combinations with rezafungin.

19.2. Mycological Data From Clinical Studies

Overview of the Rezafungin Clinical Program

The Applicant conducted a single phase 2 study (known as STRIVE) and a single phase 3 study (known as ReSTORE) for the treatment of candidemia and invasive candidiasis (C/IC) in adult patients using rezafungin as the study drug and caspofungin as the comparator. Data from both phase 2 and phase 3 studies were pooled to demonstrate the safety and efficacy of rezafungin. Although there were differences in the primary efficacy endpoints of both clinical studies, the evaluations of mycological eradication at Day 5, Day 14, and Day 30 were conducted as key clinical efficacy secondary endpoints. The primary endpoints for both studies are as follows (copied verbatim):

Phase 2 STRIVE Study: Evaluate the overall success based on mycological eradication and resolution of systemic signs attributable to candidemia and/or invasive candidiasis of rezafungin for injection at Day 14 (±1 day) in the mITT population.

Phase 3 ReSTORE Study: Demonstrate that rezafungin for injection is noninferior to caspofungin for ACM at Day 30 (-2 days) in the modified intent-to-treat (mITT) population (FDA).

Demonstrate that rezafungin for injection is noninferior to caspofungin for global cure (clinical cure as assessed by the Investigator, radiological cure [for qualifying invasive candidiasis subjects], and mycological eradication, as confirmed by the data review committee) at Day 14 (±1 day) in the mITT population (European Medicines Agency).

Clinical microbiology reviewer comments: Subjects in the mITT populations of the rezafungin-treated arm of both clinical studies received rezafungin for injection 400 mg in week 1 followed by 200 mg once-weekly for a total duration of therapy of two to four weeks. From a clinical microbiology perspective, pooled data from the phase 2 and 3 studies were utilized for the mycological efficacy analysis. In particular, the clinical microbiology team evaluated Day 14 data for the mycological responses, mycological eradication by baseline MICs of Candida species isolates, and for the Agency's rezafungin BPs recommendations. The Day 14 timepoint was most informative for evaluating mycological response since the Day 5 mycological response was considered to be premature for mycological assessments due to the underlying nature of the C/IC indication. We note that the primary efficacy endpoint of 30-day ACM was more informative for clinical assessments.

Microbiological Methods in Clinical Studies

The microbiological methods were generally similar for both clinical studies.

STRIVE/ Phase 2 Study (copied verbatim from the NDA submission)

As part of the standard of care for inclusion in the study, a culture was to have been obtained. To establish a mycological diagnosis of candidemia, sufficient for inclusion in the study, either ≥1 blood culture positive for yeast or *Candida*, or a Sponsor-approved rapid in vitro diagnostic test positive for *Candida* spp., or a positive Gram stain for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site from a sample taken ≤96 hours before randomization was required.

ReSTORE/ Phase 3 Study (copied verbatim from the NDA submission)

For study inclusion, a culture must have been obtained and a mycological diagnosis of candidemia or invasive candidiasis made from a sample collected ≤4 days (96 hours) before randomization. Mycological diagnoses for candidemia or invasive candidiasis were defined as follows:

- ≥1 blood culture positive for yeast or *Candida* spp.;
- A positive test for *Candida* from a Sponsor-approved rapid in vitro diagnostic;
- A positive Gram stain (or other method of direct microscopy) for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site.

As noted, rapid in vitro diagnostics were employed for identifying subjects with candidemia and/or invasive candidiasis; however, no subjects were enrolled based on in vitro diagnostic results.

Baseline Microbiology

Species Distribution Among Subjects at Baseline

Candida albicans were isolated at the highest frequency at baseline followed by *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*. Among the predominant *Candida* species, a total of 58 (41.7%) and 69 (44.5%) *C. albicans*, 38 (27.3%) and 35 (22.6%) *C. glabrata*, 27 (19.4%) and 22 (14.2%) *C. tropicalis*, 14 (10.1%) and 27 (17.4%) *C. parapsilosis*, and 5 (3.6%) and 3 (1.9%) *C. krusei* isolates were obtained at baseline from subjects in the rezafungin and caspofungin treatment arms, respectively. The distribution of *Candida* species among mITT populations at baseline using pooled data are summarized by treatment arm in Table 170.

Table 170. Summary of *Candida* spp. Isolated From Subjects at Baseline (mITT Population, Pooled Data)

Organism	N. America/S. America n (%; n/N)		Europe/Israel/Turkey n (%; n/N)		Asia/Pacific n (%; n/N)		Overall n (%; n/N)	
	RZF (N=43)	CAS (N=46)	RZF (N=67)	CAS (N=76)	RZF (N=29)	CAS (N=33)	RZF (N=139)	CAS (N=155)
C. albicans	19 (44.2)	24 (52.2)	32 (47.8)	31 (40.8)	7 (24.1)	14 (42.4)	58 (41.7)	69 (44.5)
C. glabrata	13 (30.2)	15 (32.6)	17 (25.4)	14 (18.4)	8 (27.6)	6 (18.2)	38 (27.3)	35 (22.6)
C. tropicalis	7 (16.3)	2 (4.3)	8 (11.9)	7 (9.2)	12 (41.4)	13 (39.4)	27 (19.4)	22 (14.2)
C. parapsilosis	1 (2.3)	4 (8.7)	11 (16.4)	20 (26.3)	2 (6.9)	3 (9.1)	14 (10.1)	27 (17.4)
C. krusei	2 (4.7)	-	2 (3.0)	3 (3.9)	1 (3.4)	-	5 (3.6)	3 (1.9)
C. dubliniensis	3 (7.0)	-	-	1 (1.3)	-	1 (3.4)	3 (2.2)	2 (1.3)
C. guilliermondii	-	-	1 (1.5)	-	1 (3.4)	-	2 (1.4)	-
C. lusitaniae	1 (2.3)	1 (2.2)	-	-	-	-	1 (0.7)	1 (0.6)
C. metapsilosis	2 (4.7)	0 (0.0)	1 (1.5)	-	-	-	3 (2.2)	-
C. kefyr	-	-	-	1 (1.3)	-	-	-	1 (0.6)
C. nivariensis	-	-	-	1 (1.3)	-	-	-	1 (0.6)

Source: ISE Tables 1.5.1.1 and 1.5.1.2
RZF, rezafungin 400/200 mg; CAS, caspofungin 70/50 mg; n, number of subjects with the specified species at baseline; N, number of subjects.
Abbreviations: mITT, modified intent-to-treat

Polymicrobial infections at baseline with more than one *Candida* spp. were isolated at a low frequency (25/294; 8.5%) from both treatment arms and are summarized in Table 171 below.

Table 171. Summary of Subjects With Multiple *Candida spp*. Isolated at Baseline (mITT Population, Pooled Data)

Organism	Overall - n (%; n/N)	
	RZF (N=139)	CAS (N=155)
C. albicans and *C. glabrata*	3 (2.2)	4 (2.6)
C. glabrata and *C. tropicalis*	5 (3.6)	3 (1.9)
C. albicans, *C. glabrata*, and *C. tropicalis*	-	1 (0.6)
C. albicans and *C. tropicalis*	1 (0.7)	3 (1.9)
C. parapsilosis and *C. tropicalis*	1 (0.7)	-
C. glabrata and *C. dubliniensis*	1 (0.7)	-
C. tropicalis and *C. guilliermondii*	1 (0.7)	-
C. albicans and *C. dubliniensis*	-	1 (0.6)
C. glabrata and *C. krusei*	-	1 (0.6)

Source: ERAID ad hoc analysis; ISE Table 1.5.1.1
RZF, rezafungin 400/200 mg; CAS, caspofungin 70/50 mg; n, number of subjects with the specified species at baseline; N, number of subjects.
Abbreviations: mITT, modified intent-to-treat

Summary of Rezafungin In Vitro Activity Against *Candida* spp. at Baseline

In vitro MIC data of rezafungin, including the range and $MIC_{50/90}$ by treatment group, geographic region and overall, against baseline isolates of *Candida* spp. from the mITT population are summarized in Table 172.

Table 172. Summary of Rezafungin Activity by MIC Against Baseline *Candida* spp. Overall by Treatment Group and by Region (mITT Population, Pooled Data)

Organism	Summary of Rezafungin Activity (µg/mL; Pooled)								
	Rezafungin 400/200 mg (N=139)			Caspofungin 70/50 mg (N=155)			Overall (N=294)		
	n	Range	$MIC_{50/90}$	n	Range	$MIC_{50/90}$	n	Range	$MIC_{50/90}$
C. albicans	58	0.008-0.12	0.03/0.12	69	0.004-0.12	0.03/0.06	127	0.004-0.12	0.03/0.06
C. glabrata	38	0.03-0.5	0.06/0.12	35	0.016-0.5	0.06/0.12	73	0.016-0.5	0.06/0.12
C. tropicalis	27	0.016-0.12	0.03/0.12	22	0.016-0.12	0.06/0.12	49	0.016-0.12	0.06/0.12
C. parapsilosis	14	0.5-2	1/2	27	0.5-2	1/2	41	0.5-2	1/2
C. krusei	5	0.03-0.06	-	3	0.03-0.06	-	8	0.03-0.06	-
C. dubliniensis	2	0.03-0.25	-	2	0.12	-	4	0.03-0.25	-
C. guilliermondii	2	1	-	-	-	-	2	1	-
C. lusitaniae	1	0.06	-	1	0.12	-	2	0.06-0.12	-
C. metapsilosis	3	0.12-0.5	-	-	-	-	3	0.12-0.5	-
C. nivariensis	-	-	-	1	0.03	-	1	0.03	-
C. kefyr	-	-	-	1	0.03	-	1	0.03	-

Organism	Summary of Rezafungin Activity (µg/mL; Pooled)								
	N. America/S. America (N=89)			Europe/Israel/Turkey (N=143)			Asia/Pacific (N=62)		
	n	Range	$MIC_{50/90}$	n	Range	$MIC_{50/90}$	n	Range	$MIC_{50/90}$
C. albicans	43	0.004-0.12	0.03/0.06	63	0.008-0.12	0.03/0.12	21	0.008-0.06	0.016/0.12
C. glabrata	28	0.03-0.12	0.06/0.12	31	0.03-0.5	0.06/0.12	14	0.016-0.12	0.06/0.12
C. tropicalis	9	0.016-0.12	-	15	0.016-0.12	0.06/0.06	25	0.016-0.12	0.06/0.12
C. parapsilosis	5	1-2	-	31	0.5-2	1/2	5	0.5-2	-
C. krusei	2	0.06	-	5	0.03-0.06	-	1	0.03	-
C. dubliniensis	2	0.03-0.25	-	1	0.12	-	1	0.12	-
C. guilliermondii	-	-	-	1	1	-	1	1	-
C. lusitaniae	2	0.06-0.12	-	-	-	-	-	-	-
C. metapsilosis	2	0.25-0.5	-	1	0.5	-	-	-	-
C. nivariensis	-	-	-	1	0.03	-	-	-	-
C. kefyr	-	-	-	1	0.03	-	-	-	-

Source: ISE Tables 1.5.4.1 and 1.5.4.2
n, number of subjects with the specified species at baseline; N, number of subjects.
Abbreviations: MIC, minimum inhibitory concentration; mITT, modified intent-to-treat

Clinical Microbiology Reviewer's Comments

(1) Against 58 C. albicans isolates from the rezafungin treatment arm, the MIC_{90} was 0.12 mcg/mL; and against 69 C. albicans isolates from the caspofungin treatment arm, the MIC_{90} was 0.06 mcg/mL. Against a combined total 127 C. albicans isolates from both treatment arms, the MIC_{90} was 0.06 mcg/mL.

(2) The MIC_{90} was 0.12 mcg/mL against 38 C. glabrata isolates in the rezafungin arm and 35 isolates in the caspofungin arm. Against a combined total 73 C. glabrata isolates from both treatment arms, the MIC_{90} was 0.12 mcg/mL.

(3) The MIC_{90} was 0.12 mcg/mL against 27 C. tropicalis isolates in the rezafungin arm and 22 isolates in the caspofungin arm. Against a combined total 49 C. tropicalis isolates from both treatment arms, the MIC_{90} was 0.12 mcg/mL.

(4) The MIC_{90} was 2.0 mcg/mL against 14 C. parapsilosis isolates in the rezafungin arm and 27 isolates in the caspofungin arm. Against a combined total 41 C. parapsilosis isolates from both treatment arms, the MIC_{90} was 2.0 mcg/mL.

(5) The MIC_{range} was 0.03 to 0.06 mcg/mL against 5 C. krusei isolates in the rezafungin arm and 3 isolates in the caspofungin arm. Against a combined total 8 C. krusei isolates from both treatment arms, the MIC_{range} was 0.03 to 0.06 mcg/mL.

Per-Pathogen Response

The 30-Day ACM outcomes were similar in both treatment arms for *C. albicans* and *C. glabrata*, but 14-Day mycological responses were slightly higher numerically for *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* in the rezafungin-treated arm. However, based on these small subsets of data presented in the NDA, we cannot make any conclusion on the mycological responses per pathogen between these two arms. A summary of the per-pathogen response for 30-Day ACM and 5- and 14-Day mycological response are presented in Table 173.

Table 173. Summary of Per-Pathogen Outcomes by Treatment Group (mITT Population, Pooled Data)

Organism	30-Day All-cause Mortality (Pooled - n/N1 [%])		5-Day Mycological Response (Pooled - n/N1 [%])		14-Day Mycological Response (Pooled - n/N1 [%])	
	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)
C. albicans	13/58 (22.4)	13/69 (18.8)	41/58 (70.7)	46/69 (66.7)	39/58 (67.2)	46/69 (66.7)
C. glabrata	6/38 (15.8)	4/35 (11.4)	29/38 (76.3)	21/35 (60.0)	32/38 (84.2)	22/35 (62.9)
C. tropicalis	5/27 (18.5)	7/22 (31.8)	22/27 (81.5)	12/22 (54.5)	20/27 (74.1)	14/22 (63.6)
C. parapsilosis	1/14 (7.1)	8/27 (29.6)	11/14 (78.6)	18/27 (66.7)	11/14 (78.6)	19/27 (70.4)
C. krusei	1/5 (20.0)	0/3 (0.0)	2/5 (40.0)	2/3 (66.7)	2/5 (40.0)	3/3 (100)
C. dubliniensis	0/3 (0.0)	0/2 (0.0)	3/3 (100)	2/2 (100)	3/3 (100)	2/2 (100)
C. guilliermondii	0/2 (0.0)	-	1/2 (50.0)	-	1/2 (50.0)	-
C. lusitaniae	0/1 (0.0)	0/1 (0.0)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
C. metapsilosis	0/3 (0.0)	-	3/3 (100)	-	3/3 (100)	-
C. kefyr	-	0/1 (0.0)	-	1/1 (100)	-	1/1 (100)
C. nivariensis	-	0/1 (0.0)	-	1/1 (100)	-	1/1 (100)

Source: ISE Table 2.1.13 and 2.2.12.1; n, number of subjects with the outcome; N1, number of subjects with the specified species per treatment group.

Abbreviations: mITT, modified intent-to-treat

Clinical Microbiology Reviewer's Comments

As mentioned earlier, the clinical microbiology reviewer relied on the pooled data for 14-Day mycological response as most of the subjects from the mITT population received at least two weekly doses of rezafungin. Subjects enrolled in both the phase 2 and phase 3 clinical studies received one 400-mg dose of rezafungin for injection on week 1 followed by a 200 mg once weekly dose for a total duration of therapy of two to four weeks.

Based on 14-day mycological response, the following rezafungin-treated subjects with predominant Candida species at baseline achieved mycological success:

(1) 39/58 (67.2%) subjects with C. albicans.
(2) 32/38 (84.2%) subjects with C. glabrata.
(3) 20/27 (74.1%) subjects with C. tropicalis.

(4) 11/14 (78.6%) subjects with C. parapsilosis.
(5) 2/5 (40%) subjects with C. krusei.

Although numerically higher clinical outcomes were observed for rezafungin-treated vs. caspofungin-treated subjects with more than one *Candida* spp. isolated at baseline, the clinical significance is unknown due to the small total number of subjects with polymicrobial infections. The responses for subjects with multiple *Candida* spp. at baseline are summarized in Table 174.

Table 174. Summary of Per-Pathogen Outcomes for Subjects With Multiple *Candida* spp. at Baseline (mITT Population, Pooled Data)

Organism (Polymicrobial)	30-Day All-cause Mortality (Pooled - n/N1 [%])		5-Day Mycological Response (Pooled - n/N1 [%])		14-Day Mycological Response (Pooled - n/N1 [%])	
	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)
C. albicans and *C. glabrata*	3/3 (100)	3/4 (75.0)	2/3 (66.7)	3/4 (75.0)	3/3 (100)	3/4 (75.0)
C. glabrata and *C. tropicalis*	5/5 (100)	1/3 (33.3)	5/5 (100)	1/3 (33.3)	5/5 (100)	1/3 (33.3)
C. albicans, *C. glabrata*, and *C. tropicalis*	-	1/1 (100)	-	1/1 (100)	-	1/1 (100)
C. albicans and *C. tropicalis*	1/1 (100)	3/3 (100)	1/1 (100)	0/3 (0.0)	1/1 (100)	1/3 (33.3)
C. parapsilosis and *C. tropicalis*	1/1 (100)	-	1/1 (100)	-	1/1 (100)	-
C. glabrata and *C. dubliniensis*	1/1 (100)	-	1/1 (100)	-	1/1 (100)	-
C. tropicalis and *C. guilliermondii*	1/1 (100)	-	1/1 (100)	-	1/1 (100)	-
C. albicans and *C. dubliniensis*	-	1/1 (100)	-	1/1 (100)	-	1/1 (100)
C. glabrata and *C. krusei*	-	1/1 (100)	-	1/1 (100)	-	1/1 (100)

Source: ERAID ad hoc analysis; n, number of subjects with the outcome; N1, number of subjects with the specified species per treatment group.
Abbreviations: mITT, modified intent-to-treat

Emergence of Resistance During Therapy (ReSTORE)

There were two occasions where MIC values increased at least 4-times higher than the baseline isolates during treatment with rezafungin and caspofungin in the clinical studies.

(1) There was a single instance among rezafungin-treated subjects, where the baseline rezafungin MIC value increased 8-fold during therapy. For subject ID# (b) (6), the *C. glabrata* baseline isolate had a rezafungin MIC of 0.06 mcg/mL. At Day 35, a *C. glabrata* isolate had a rezafungin MIC value of 0.5 mcg/mL and upon sequencing a mutation in FKS2 resulting in a S663P substitution was identified; this mutation was not present in the baseline isolate. This subject had a favorable outcome for the Day 30 ACM endpoint. The caspofungin MIC value for this post-baseline isolate was also elevated 4-fold relative to baseline (0.06 µg/mL to 0.25 µg/mL).

Clinical microbiology reviewer's comments: This is an observation of cross-resistance among the echinocandins due to the mutations in one of the hotspot regions of the fks gene. As seen in this case, the post-treatment rezafungin MIC was elevated 8-times higher than baseline for C. glabrata (0.06 mcg/mL to 0.5 mcg/mL). Although the subject was not treated with caspofungin, the post-treatment caspofungin MIC was also elevated 4-times higher than at baseline (0.25 µg/mL relative to baseline MIC of 0.06 µg/mL).

(1) There was also a single instance among caspofungin-treated subjects where the baseline MIC value increased 8-fold during therapy. One subject (ID# (b) (6)) was

identified that had *C. albicans* isolated at baseline and post baseline at Day 5. For this subject, the caspofungin MIC values increased from 0.008 to 0.06 µg/mL and concomitantly the rezafungin MIC value was found to be increased 4-fold from 0.03 µg/mL to 0.12 µg/mL. Sequencing revealed that both the baseline and the Day 5 isolates were free of FKS1 hot spot mutations. This patient died and was a failure for mycological response at both Day 5 and 14.

Clinical microbiology reviewer's comments: In this case, the baseline caspofungin MIC of 0.008 mcg/mL increased 8-fold to 0.06 mcg/mL at Day 5 but still remained below the FDA-recognized susceptible breakpoint (0.25 mcg/mL). Concomitantly, the rezafungin baseline MIC of 0.03 mcg/mL increased 4-fold to 0.12 mcg/mL but still remained below the proposed FDA susceptible breakpoint. However, the patient died and did not achieve mycological success at Day 5 or Day 14. There was no mutation identified in the fks gene. It is plausible that there might be some unidentified genetic change such as other mutations governing other cell wall structures that may have triggered the elevated MIC for both echinocandins.

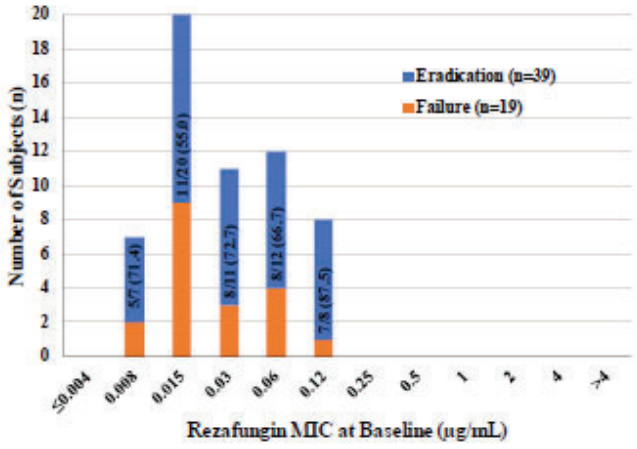
Correlation of Baseline Rezafungin MICs to Outcome

The Applicant submitted efficacy data correlating different MICs to outcome by target pathogens from rezafungin treated patients in the mITT population. For the primary efficacy endpoint, ACM at Day 30, outcomes are summarized as success (subject was alive at Day 30) or failure (subject died on or before Day 30 or had unknown survival status) and mycological response is summarized as eradication (which included presumed eradication) or failure (which included indeterminate and presumed persistence).

C. albicans

Based on the mycological responses at Day 14, *C. albicans* was eradicated or presumed eradicated in 67.2% (39/58) of rezafungin-treated subjects. The highest rezafungin MIC associated with a favorable response was 0.12 µg/mL; no isolates were available at ≥0.25 µg/mL. The correlation of rezafungin MIC value to the mycological response at Day 14 is shown in Figure 18 and Table 175.

Figure 18. Correlation of Rezafungin MIC to Mycological Response at Day 14 With *C. albicans* (mITT Population, Pooled Data)



Source: ISE Table 2.2.13

Abbreviations: MIC, minimum inhibitory concentration; mITT, modified intent-to-treat

Table 175. Correlation of MIC and Outcome - *C. albicans*

Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) [%; n1/n]									
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
30 Day all-cause mortality			6/7 (85.7)	14/20 (70.0)	8/11 (72.7)	10/12 (83.3)	7/8 (87.5)			
5 Day mycological response			4/7 (57.1)	13/20 (65.0)	7/11 (63.6)	10/12 (83.3)	7/8 (87.5)			
14 Day mycological response			5/7 (71.4)	11/20 (55.0)	8/11 (72.7)	8/12 (66.7)	7/8 (87.5)			

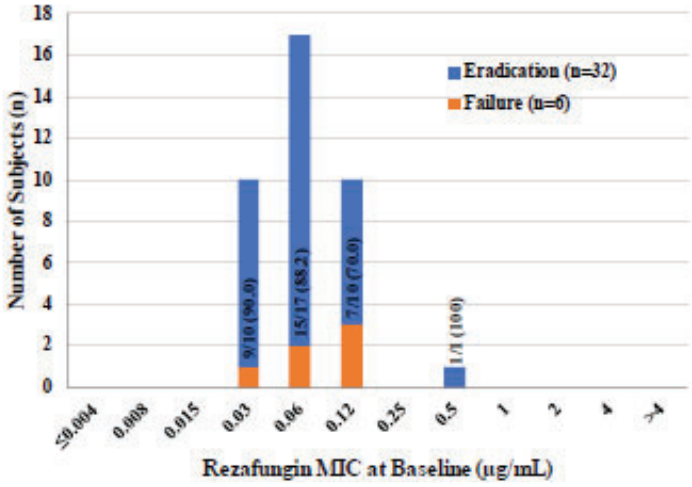
Source: ISE Tables 2.1.14 and 2.2.13

Abbreviations: MIC, minimum inhibitory concentration

C. glabrata

Based on the mycological responses at Day 14, *C. glabrata* was eradicated or presumed eradicated in 84.2% (32/38) of subjects. The highest rezafungin MIC associated with a favorable response was 0.5 µg/mL; no isolates were available at 0.25 µg/mL or ≥1 µg/mL. The correlation of rezafungin MIC value to the mycological response at Day 14 is shown in Figure 19 and Table 176.

Figure 19. Correlation of Rezafungin MIC to Mycological Response at Day 14 With *C. glabrata* (mITT Population, Pooled Data)



Source: ISE Table 2.2.13

Abbreviations: MIC, minimum inhibitory concentration; mITT, modified intent-to-treat

Table 176. Correlation of MIC and Outcome - *C. glabrata*

Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) [%; n1/n]									
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
30 Day all-cause mortality					9/10 (90.0)	14/17 (82.4)	8/10 (80.0)		1/1 (100)	
5 Day mycological response					8/10 (80.0)	16/17 (94.1)	5/10 (50.0)		0/1 (0.0)	
14 Day mycological response					9/10 (90.0)	15/17 (88.2)	7/10 (70.0)		1/1 (100)	

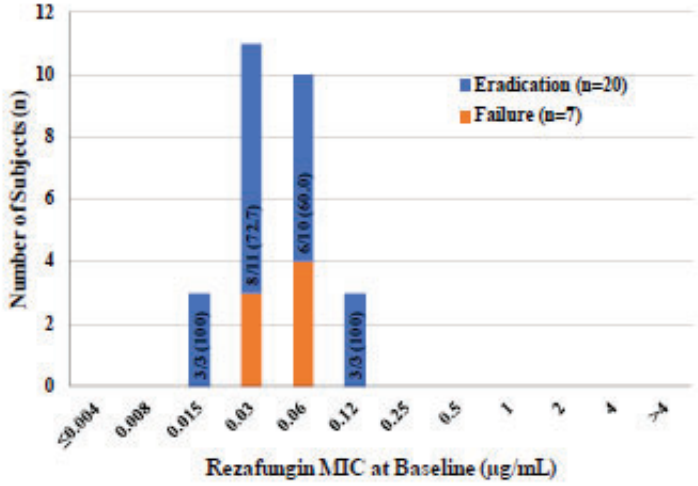
Source: ISE Tables 2.1.14 and 2.2.13

Abbreviations: MIC, minimum inhibitory concentration

C. tropicalis

Based on the mycological response at Day 14, *C. tropicalis* was eradicated or presumed eradicated in 74.1% (20/27) of subjects. The highest rezafungin MIC associated with a favorable response was 0.12 mcg/mL; no isolates were available at ≥0.25 µg/mL. The correlation of rezafungin MIC value to the mycological response at Day 14 is shown in Figure 20 and Table 177.

Figure 20. Correlation of Rezafungin MIC to Mycological Response at Day 14 With *C. tropicalis* (mITT Population, Pooled Data)



Source: ISE Table 2.2.13

Abbreviations: MIC, minimum inhibitory concentration; mITT, modified intent-to-treat

Table 177. Correlation of MIC and Outcome - *C. tropicalis*

Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) [%; n1/n]									
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
30 Day all-cause mortality				3/3 (100)	9/11 (81.8)	8/10 (80.0)	2/3 (66.7)			
5 Day mycological response				3/3 (100)	9/11 (81.8)	7/10 (70.0)	3/3 (100)			
14 Day mycological response				3/3 (100)	8/11 (72.7)	6/10 (60.0)	3/3 (100)			

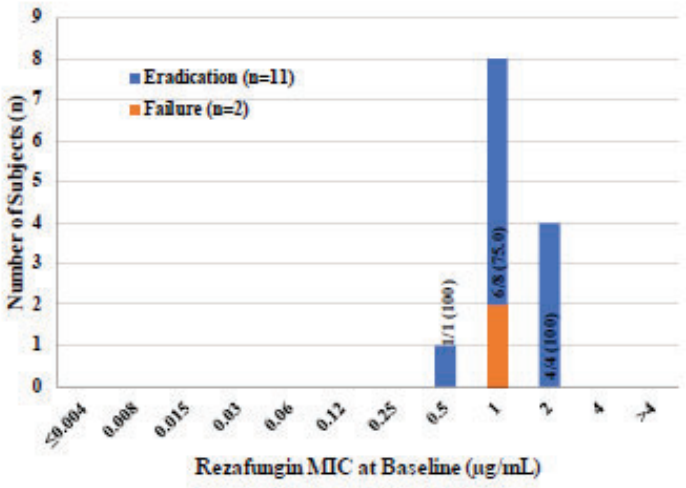
Source: ISE Tables 2.1.14 and 2.2.13

Abbreviations: MIC, minimum inhibitory concentration

C. parapsilosis

Based on the mycological response at Day 14, *C. parapsilosis* was eradicated or presumed eradicated in 84.6% (11/13) of subjects. The highest rezafungin MIC associated with a favorable response was 2 µg/mL; no isolates were available at ≥4 µg/mL. The correlation of rezafungin MIC value to the mycological response at Day 14 is shown in Figure 21 and Table 178.

Figure 21. Correlation of Rezafungin MIC to Mycological Response at Day 14 With *C. parapsilosis* (mITT Population, Pooled Data)



Source: ISE Table 2.2.13
Abbreviations: MIC, minimum inhibitory concentration; mITT, modified intent-to-treat

Table 178 Correlation of MIC and Outcome - *C. parapsilosis*

Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) [%; n1/n]									
	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	>4
30 Day all-cause mortality						1/1 (100)	7/8 (87.5)	4/4 (100)		
5 Day mycological response						0/1 (0.0)	7/8 (87.5)	4/4 (100)		
14 Day mycological response						1/1 (100)	6/8 (75.0)	4/4 (100)		

Source: ISE Tables 2.1.14 and 2.2.13
Abbreviations: MIC, minimum inhibitory concentration

19.3. Applicant-Proposed Interpretive Criteria

The Applicant has proposed MIC and disk diffusion rezafungin BPs against targeted fungal pathogens based on the following in vitro, in vivo, and clinical data:

(1) MIC frequency distributions from clinical study and surveillance isolates; and
(2) PK-PD information including Monte Carlo simulation and target attainment analysis (fAUC/MIC ratio target); and
(3) A summary of response rates based on MIC and zone diameter values; and
(4) A correlation between zone diameter and broth microdilution MIC values by scatterplot for profiling and clinical study isolates and error-rate bounding analysis for use in the generation of proposed disk diffusion interpretive criteria.

The Applicant proposed rezafungin MIC BPs are presented below in Table 179:

Table 179. Proposed Interpretive Criteria for Rezafungin

Organism	MIC (µg/mL)	Zone Diameter* (mm)
C. albicans	≤0.25 Susceptible	≥13 mm Susceptible
C. glabrata	≤0.5 Susceptible 1 Intermediate ≥2 Resistant	≥14 mm Susceptible 11-13 mm Intermediate ≤10 mm Resistant
C. tropicalis	≤0.25 Susceptible	≥13 mm Susceptible
C. parapsilosis	≤2 Susceptible	≥9 mm Susceptible
C. krusei	≤0.25 Susceptible	NA

MIC, minimum inhibitory concentration; NA, not applicable
*Determined with a 5 µg disk

Source: NDA submission (Table 74 of 2.7.2 Summary of Clinical Pharmacology 2.7.2.4 Special Studies)

The Applicant stated that a CLSI Rezafungin Breakpoint Working Group was formed that presented data and proposed BPs and epidemiological cutoff values (ECVs) at the June 2021 CLSI meeting. It was approved by the broader CLSI AFST (Antifungal Susceptibility Testing) Subcommittee (NC-216). CLSI-approved BPs (CLSI 2022b) (M27M44S) and ECVs (CLSI 2022a) (M57S-Ed4) for rezafungin against *Candida* species have been published and are presented in the following Table 180:

Table 180. CLSI Published BPs and ECVs for Rezafungin Against *Candida* species

	MIC BPs and Interpretive Categories (µg/mL)			ECV (µg/mL)
***Candida* species**	**Susceptible**	**Intermediate**	**Resistant**	
C. albicans	≤0.25	-	-	0.06
C. auris	≤0.5	-	-	0.5
C. dubliniensis	≤0.12	-	-	0.12
C. glabrata	≤0.5	-	-	0.12
C. krusei	≤0.25	-	-	0.12
C. parapsilosis	≤2	-	-	4
C. tropicalis	≤0.25	-	-	0.12

Source: (CLSI 2022b; CLSI 2022a) (M27M44S & M57S-Ed4)
MIC interpretive categories for rezafungin were adopted during a meeting with the Subcommittee on Antifungal Tests held in June 2021. The MICs are considered tentative for one year from the publication of M27M44S and are open for comment.
At this time, only suscept ble breakpoints have been set for rezafungin. Once more data are available, intermediate and resistant breakpoints will be added.
Abbreviations: BP, breakpoint; CLSI, Clinical and Laboratory Standards Institute; ECV, epidemiological cutoff value; MIC, minimum inh bitory concentration

The following data are presented in tables and figures for predominant *Candida* species in support of the Applicant's proposed MIC BPs in the NDA.

Candida albicans

MIC Distribution – Clinical Study versus Surveillance

- $MIC_{50/90}$ values of 0.03/0.06 µg/mL were observed for *C. albicans* for both surveillance isolates and pooled clinical study isolates (Table 181 and Figure 22).

- An ECV of 0.06 µg/mL was derived from an ECOFF finder analysis of data from 1,620 clinical isolates tested at the Jones Microbiology Institute Inc. (JMI) from nine studies.

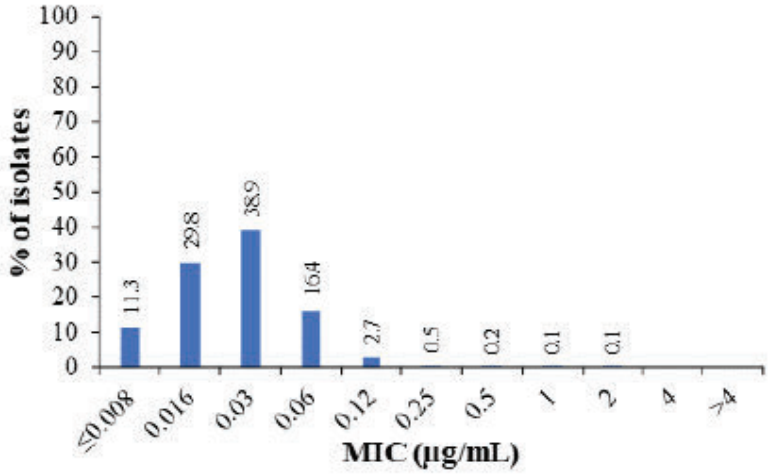
Table 181. Rezafungin MIC Distribution Against Clinical Study and Surveillance Isolates of *C. albicans*

Study	N		Number (n) of isolates with indicated rezafungin MIC (µg/mL)									
			≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
2018-2020 SURVEILLANCE (N=943)	943	n	12	8	86	255	364	196	20	2		
		%	1.3	0.8	9.1	27.0	38.6	20.8	2.1	0.2		
		cum. %	1.3	2.1	11.2	38.3	76.9	97.7	99.8	100.0		
POOLED (N=127)	127	n		2	15	41	30	28	11			
		%		1.6	11.8	32.3	23.6	22.0	8.7			
		cum. %		1.6	13.4	45.7	69.3	91.3	100.0			
Phase 2 STRIVE (N=83)	83	n		2	1	8	24	37	10	1		
		%		2.4	1.2	9.6	28.9	44.6	12.0	1.2		
		cum. %		2.4	3.6	13.3	42.2	86.7	98.8	100.0		
Phase 3 ReSTORE (N=78)	78	n			15	35	15	11	2			
		%			19.2	44.9	19.2	14.1	2.6			
		cum. %			19.2	64.1	83.3	97.4	100.0			

Source: ISE Table 1.5.2.1; ad hoc analysis of NC-188, NC-194, and NC-214
cum., cumulative.

Abbreviations: MIC, minimum inhibitory concentration

Figure 22. Overall Rezafungin MIC Distribution Against *C. albicans* (N=2,371)



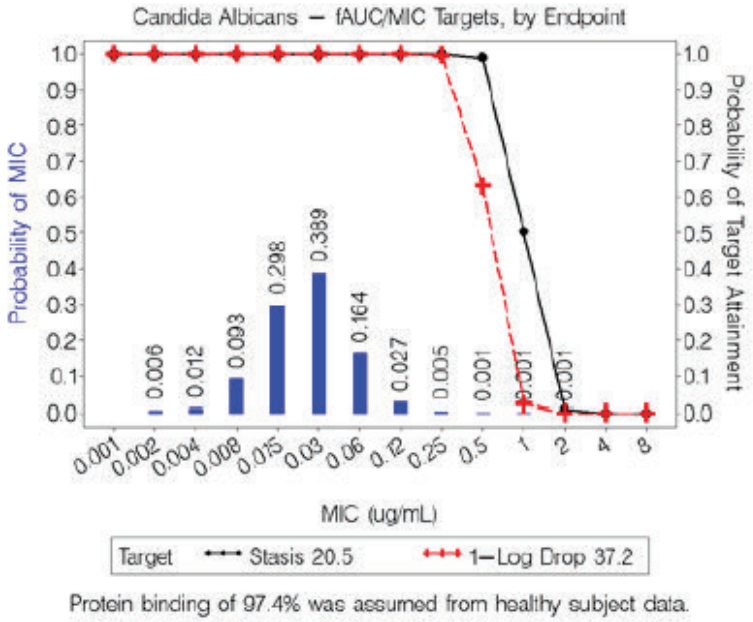
Source: NC-031, NC-039, NC-064, NC-073, NC-074, NC-110, NC-138, NC-163, NC-188, NC-194, NC-195, NC-214; ad hoc analysis Appendix 1
NOTE: 10 isolates from Study NC-039 had rezafungin MIC values ≤0.03 µg/mL; these are shown at an MIC of 0.03 µg/mL

Abbreviations: MIC, minimum inhibitory concentration

Target Attainment

Target attainment data from Monte Carlo simulations using MIC data gathered from surveillance studies (2018 to 2020) demonstrated greater than 99% target attainment for *C. albicans* with MIC values ≤0.25 µg/mL for a 1-log10 CFU reduction and ≤0.5 µg/mL for stasis (Figure 23).

Figure 23. Probability of Target Attainment for *C. albicans*



Source: NC-201
Abbreviations: fAUC, free area under the concentration-time curve; MIC, minimum inhibitory concentration

Correlation Between MIC and Clinical Outcome

Favorable outcomes were noted across all baseline rezafungin MIC values for *C. albicans*. The highest rezafungin MIC associated with a favorable response was 0.12 µg/mL (Table 182).

Table 182. Correlation of MIC and Outcome - *C. albicans*

Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) [%; n1/n]									
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
30 Day all-cause mortality			6/7 (85.7)	14/20 (70.0)	8/11 (72.7)	10/12 (83.3)	7/8 (87.5)			
5 Day mycological response			4/7 (57.1)	13/20 (65.0)	7/11 (63.6)	10/12 (83.3)	7/8 (87.5)			
14 Day mycological response			5/7 (71.4)	11/20 (55.0)	8/11 (72.7)	8/12 (66.7)	7/8 (87.5)			

Source: ISE Tables 2.1.14 and 2.2.13
Abbreviations: MIC, minimum inhibitory concentration

Candida glabrata

MIC Distribution – Clinical Study Versus Surveillance

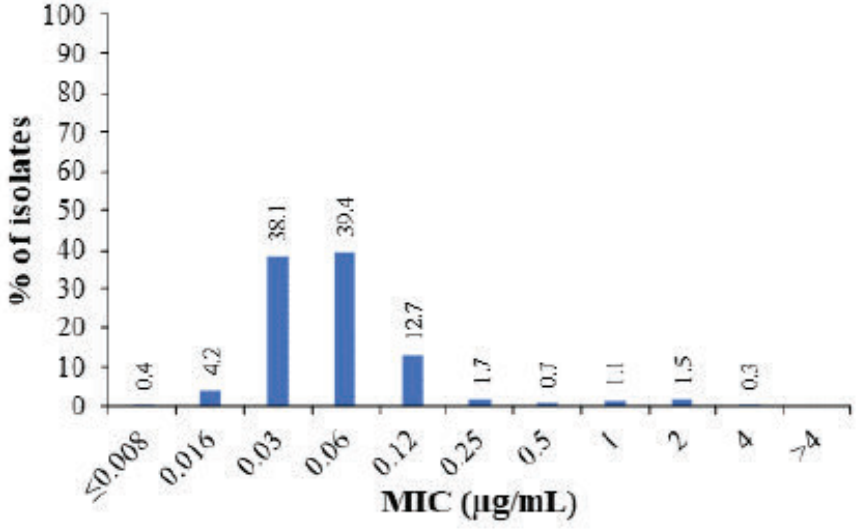
- $MIC_{50/90}$ values of 0.06/0.06 and 0.06/0.12 µg/mL were observed for *C. glabrata* surveillance isolates and pooled clinical study isolates, respectively (Table 183 and Figure 24).
- An ECV of 0.12 mcg/mL was derived from an ECOFF finder analysis.

Table 183. Rezafungin MIC Distribution Against Clinical Study and Surveillance Isolates of *C. glabrata*

Study	N		Number (n) of isolates with indicated rezafungin MIC (µg/mL)									
			≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	≥4
2018-2020 SURVEILLANCE (N=407)	407	n	2	8	170	200	15	4		2	6	
		%	0.5	2.0	41.8	49.1	3.7	1.0		0.5	1.5	
		cum. %	0.5	2.5	44.2	93.4	97.1	98.0		98.5	100.0	
POOLED (N=73)	73	n		1	22	33	15		2			
		%		1.4	30.1	45.2	20.5		2.7			
		cum. %		1.4	31.5	76.7	97.3		100.0			
Phase 2 STRIVE (N=37)	37	n			10	25	1		1			
		%			27.0	67.6	2.7		2.7			
		cum. %			27.0	94.6	97.3		100.0			
Phase 3 ReSTORE (N=49)	49	n		1	16	17	14		1			
		%		2.0	32.7	34.7	28.6		2.0			
		cum. %		2.0	34.7	69.4	98.0		100.0			

Source: ISE Table 1.5.2.1; ad hoc analysis of NC-188, NC-194, and NC-214
cum., cumulative.
Abbreviations: MIC, minimum inhibitory concentration

Figure 24. Overall Rezafungin MIC Distribution Against *C. glabrata* (N=1,131)

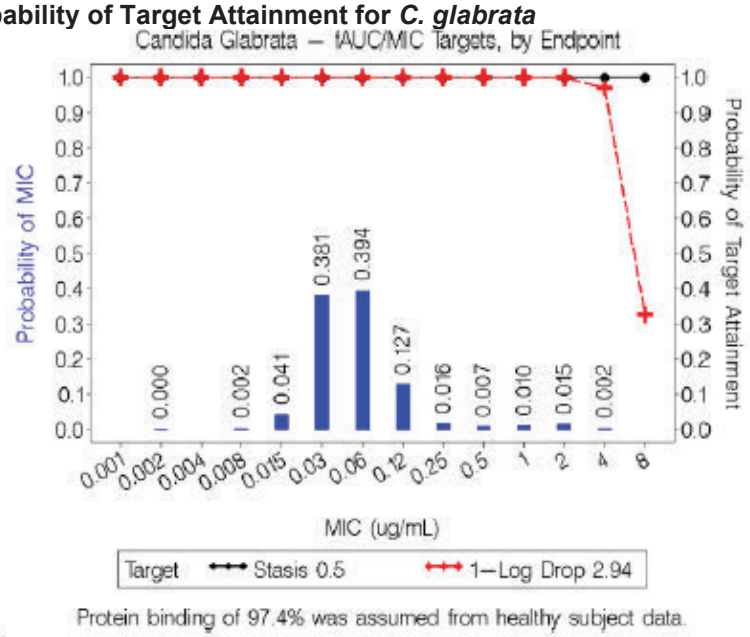


Source: NC-031, NC-039, NC-064, NC-073, NC-074, NC-110, NC-138, NC-163, NC-188, NC-194, NC-195, NC-214; ad hoc analysis Appendix 1
NOTE: 1 isolate from Study NC-039 had rezafungin MIC values ≤0.03 µg/mL; this isolate is shown at an MIC of 0.03 µg/mL
Abbreviations: MIC, minimum inhibitory concentration

Target Attainment

Target attainment data from Monte Carlo simulations using MIC data gathered from surveillance (2018 to 2020) demonstrate a greater than 97% target attainment for *C. glabrata* with MIC values ≤4 µg/mL for both a 1-$\log_{10}$ CFU reduction and for stasis (Figure 25). This threshold is above the provisional ECV (0.12 µg/mL) and proposed susceptible breakpoint (0.5 µg/mL) approved by CLSI and includes all clinical study isolates.

Figure 25. Probability of Target Attainment for *C. glabrata*



Source: NC-201

Abbreviations: fAUC, free area under the concentration-time curve; MIC, minimum inhibitory concentration

Correlation Between MIC and Clinical Outcome

The highest rezafungin MIC associated with favorable all-cause mortality and 14 Day mycological response was 0.5 µg/mL for *C. glabrata* (Table 184). However, there were no isolates available with MIC 0.25 µg/mL and clinical outcome was not 100% with isolates with MIC 0.12 µg/mL.

Table 184. Correlation of MIC and Outcome - *C. glabrata*

Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) [%; n1/n]									
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
30 Day all-cause mortality					9/10 (90.0)	14/17 (82.4)	8/10 (80.0)		1/1 (100)	
5 Day mycological response					8/10 (80.0)	16/17 (94.1)	5/10 (50.0)		0/1 (0.0)	
14 Day mycological response					9/10 (90.0)	15/17 (88.2)	7/10 (70.0)		1/1 (100)	

Source: ISE Tables 2.1.14 and 2.2.13

Abbreviations: MIC, minimum inhibitory concentration

Candida tropicalis

MIC Distribution – Clinical Study versus Surveillance

$MIC_{50/90}$ values of 0.03/0.06 and 0.06/0.12 µg/mL were observed for *C. tropicalis* surveillance isolates and pooled clinical study isolates, respectively (Table 185 and Figure 26). An ECV of 0.12 µg/mL derived from ECOFF finder analysis.

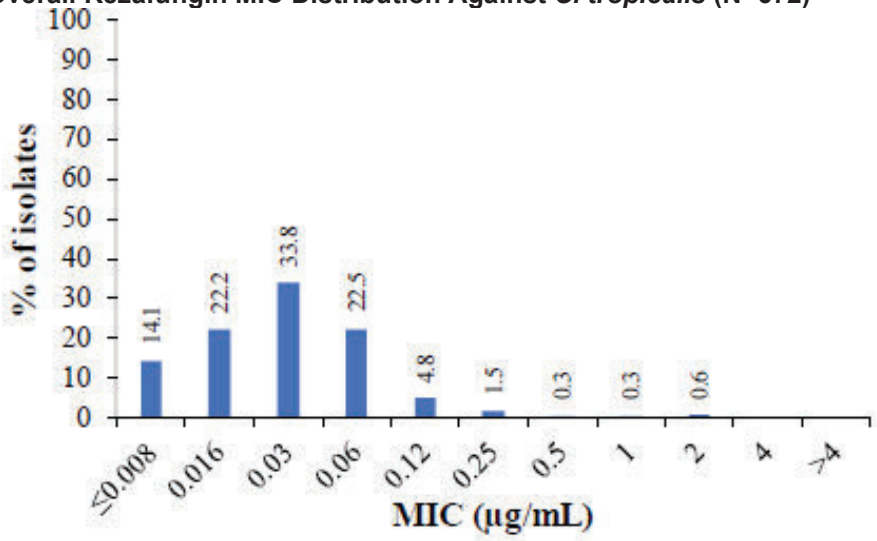
Table 185. Rezafungin MIC Distribution Against Clinical Study and Surveillance Isolates of *C. tropicalis*

Study	N		Number (n) of isolates with indicated rezafungin MIC (µg/mL)									
			≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
2018-2020 SURVEILLANCE (N=244)	244	n			21	49	97	63	12	2		
		%			8.6	20.1	39.8	25.8	4.9	0.8		
		cum. %			8.6	28.7	68.4	94.3	99.2	100.0		
POOLED (N=49)	49	n				6	16	20	7			
		%				12.2	32.7	40.8	14.3			
		cum. %				12.2	44.9	85.7	100.0			
Phase 2 STRIVE (N=22)	22	n				2	7	10	3			
		%				9.1	31.8	45.5	13.6			
		cum. %				9.1	40.9	86.4	100.0			
Phase 3 ReSTORE (N=36)	36	n				5	13	13	5			
		%				13.9	36.1	36.1	13.9			
		cum. %				13.9	50.0	86.1	100.0			

Source: ISE Table 1.5.2.1; ad hoc analysis of NC-188, NC-194, and NC-214
cum., cumulative.

Abbreviations: MIC, minimum inhibitory concentration

Figure 26. Overall Rezafungin MIC Distribution Against *C. tropicalis* (N=672)



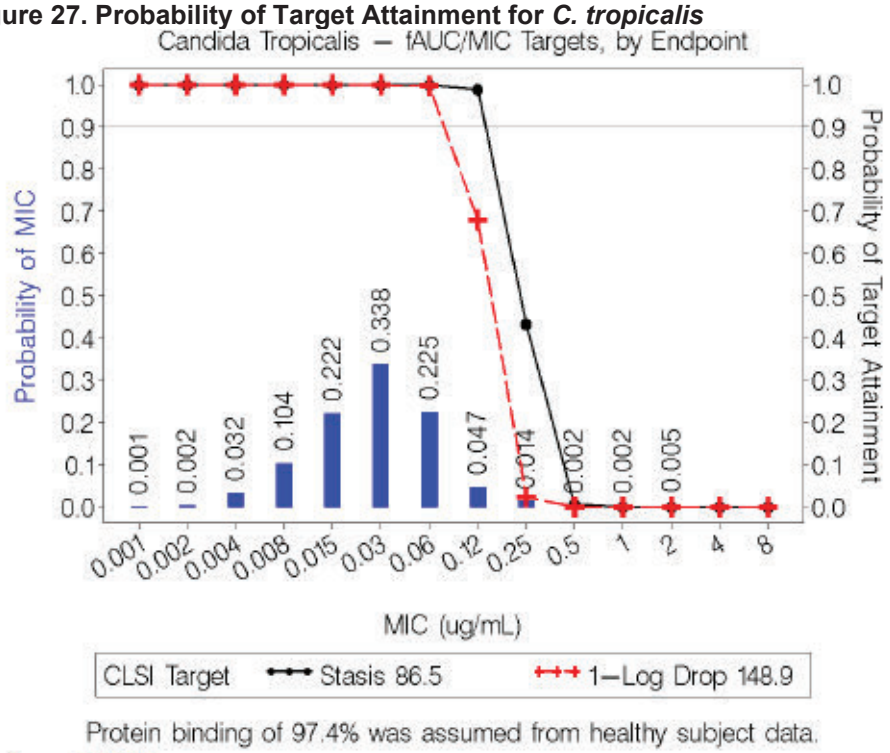
Source: NC-031, NC-039, NC-064, NC-073, NC-074, NC-110, NC-138, NC-163, NC-188, NC-194, NC-195, NC-214; ad hoc analysis Appendix 1
NOTE: 15 isolates from Study NC-039 had rezafungin MIC values ≤0.03 µg/mL; these isolates are shown at an MIC of 0.03 µg/mL

Abbreviations: MIC, minimum inhibitory concentration

Target Attainment

Target attainment data from Monte Carlo simulations using MIC data gathered from surveillance (2018 to 2020) demonstrated a greater than 98% target attainment for *C. tropicalis* with MIC values ≤0.06 µg/mL for a 1-$\log_{10}$ CFU reduction and ≤0.12 µg/mL for stasis (Figure 27)

Figure 27. Probability of Target Attainment for *C. tropicalis*



Source: NC-201

Abbreviations: fAUC, free area under the concentration-time curve; CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inh bitory concentration

Correlation Between MIC and Clinical Outcome

The highest rezafungin MIC associated with a favorable response was 0.12 µg/mL for *C. tropicalis* (Table 186).

Table 186. Correlation of MIC and Outcome - *C. tropicalis*

Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) [%; n1/n]									
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
30 Day all-cause mortality				3/3 (100)	9/11 (81.8)	8/10 (80.0)	2/3 (66.7)			
5 Day mycological response				3/3 (100)	9/11 (81.8)	7/10 (70.0)	3/3 (100)			
14 Day mycological response				3/3 (100)	8/11 (72.7)	6/10 (60.0)	3/3 (100)			

Source: ISE Tables 2.1.14 and 2.2.13

Abbreviations: MIC, minimum inhibitory concentration

Candida parapsilosis

MIC Distribution – Clinical Study versus Surveillance

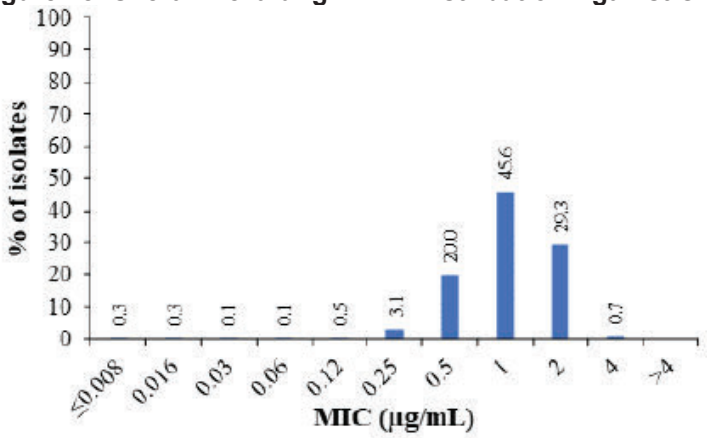
$MIC_{50/90}$ values of 1/2 µg/mL were observed for *C. parapsilosis* for both surveillance isolates and pooled clinical study isolates (Table 187 and Figure 28). An ECV of 4 µg/mL was derived from an ECOFF finder analysis.

Table 187. Rezafungin MIC Distribution Against Clinical Study and Surveillance Isolates of *C. parapsilosis*

Study	N		Number (n) of isolates with indicated rezafungin MIC (µg/mL)									
			≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	>4
2018-2020 SURVEILLANCE (N=356)	356	n		1		2	12	91	184	65	1	
		%		0.3		0.6	3.4	25.6	51.7	18.3	0.3	
		cum. %		0.3		0.8	4.2	29.8	81.5	99.7	100.0	
POOLED (N=41)	41	n						2	28	11		
		%						4.9	68.3	26.8		
		cum. %						4.9	73.2	100.0		
Phase 2 STRIVE (N=27)	27	n		1				1	18	7		
		%		3.7				3.7	66.7	25.9		
		cum. %		3.7				7.4	74.1	100.0		
Phase 3 ReSTORE (N=24)	24	n						1	16	7		
		%						4.2	66.7	29.2		
		cum. %						4.2	70.8	100.0		

Source: ISE Table 1.5.2.1; ad hoc analysis of NC-188, NC-194, and NC-214
cum., cumulative.
Abbreviations: MIC, minimum inhibitory concentration

Figure 28. Overall Rezafungin MIC Distribution Against *C. parapsilosis* (N=946)



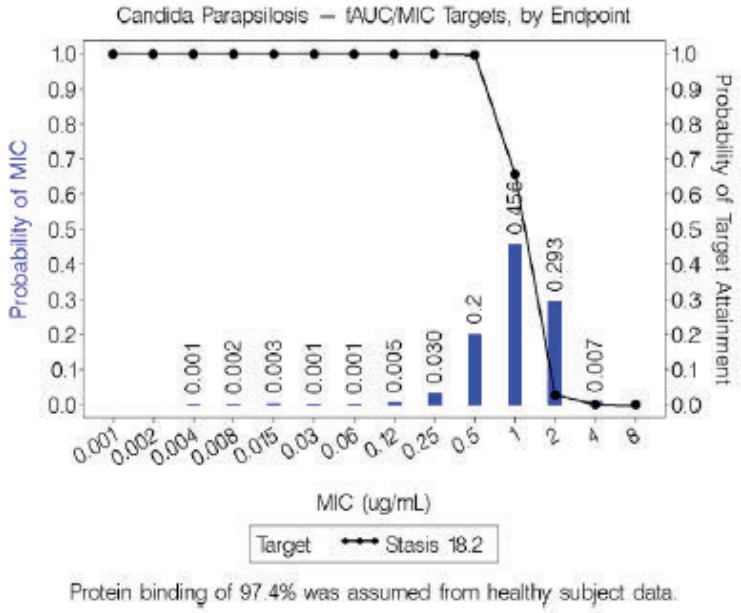
Source: NC-031, NC-039, NC-064, NC-073, NC-074, NC-110, NC-138, NC-163, NC-188, NC-194, NC-195, NC-214; ad hoc analysis Appendix 1
Abbreviations: MIC, minimum inhibitory concentration

Target Attainment

- Target attainment data from Monte Carlo simulations using MIC data gathered from surveillance (2018 to 2020) demonstrate a greater than 99% target attainment for *C. parapsilosis* with MIC values ≤0.5 µg/mL for stasis (Figure 29). This threshold for stasis is below the provisional ECV (4 µg/mL) and the proposed susceptible breakpoint (2 µg/mL).
- A 1-log_{10} CFU reduction was not achieved for this species in the neutropenic IC mouse model.

- The proposed BP of 2 µg/mL for rezafungin against *C. parapsilosis* isolates is 4 dilutions higher than 0.5 µg/mL at which 99% target attainment has been achieved for stasis.

Figure 29. Probability of Target Attainment for *C. parapsilosis*



Source: NC-201

Abbreviation: fAUC, free area under the concentration-time curve; MIC, minimum inhibitory concentration

Correlation Between MIC and Clinical Outcome

The highest rezafungin MIC associated with a favorable response was 2 µg/mL for *C. parapsilosis* (Table 188). However, the PK-PD target attainment data support only 0.5 µg/mL (99% target achieved) based on stasis and did not attain a 1-log kill in the nonclinical IC model in animals.

Table 188. Correlation of MIC and Outcome - *C. parapsilosis*

Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) [%; n1/n]									
	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	>4
30 Day all-cause mortality						1/1 (100)	7/8 (87.5)	4/4 (100)		
5 Day mycological response						0/1 (0.0)	7/8 (87.5)	4/4 (100)		
14 Day mycological response						1/1 (100)	6/8 (75.0)	4/4 (100)		

Source: ISE Tables 2.1.14 and 2.2.13

Abbreviations: MIC, minimum inhibitory concentration

Candida krusei

MIC Distribution – Clinical Study versus Surveillance

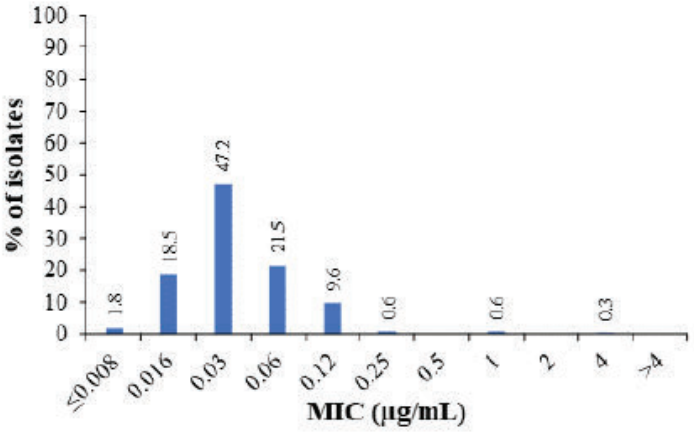
$MIC_{50/90}$ values of 0.03/0.06 and 0.06/0.06 µg/mL were observed for *C. krusei* surveillance isolates and pooled clinical study isolates, respectively (Table 189 and Figure 30). An ECV of 0.12 µg/mL was derived from an ECOFF finder analysis.

Table 189. Rezafungin MIC Distribution Against Clinical Study and Surveillance Isolates of *C. krusei*

Study	N		Number (n) of isolates with indicated rezafungin MIC (µg/mL)									
			≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
2014-2020 SURVEILLANCE (N=147)	147	n			1	38	76	24	8			
		%			0.7	25.9	51.7	16.3	5.4			
		cum. %			0.7	26.5	78.2	94.6	100.0			
POOLED (N=8)	8	n					3	5				
		%					37.5	62.5				
		cum. %					37.5	100.0				
STRIVE (N=5)	5	n					1	4				
		%					20.0	80.0				
		cum. %					20.0	100.0				
ReSTORE (N=4)	4	n					2	2				
		%					50.0	50.0				
		cum. %					50.0	100.0				

Source: ISE Table 1.5.2.1; ad hoc analysis of NC-074, NC-110, NC-138, NC-163, NC-188, NC-194, and NC-214
cum., cumulative.
Abbreviations: MIC, minimum inhibitory concentration

Figure 30. Overall Rezafungin MIC Distribution Against *C. krusei* (N=335)



Source: NC-031, NC-039, NC-064, NC-074, NC-110, NC-138, NC-163, NC-188, NC-194, NC-195, NC-214; ad hoc analysis Appendix 1
NOTE: 11 isolates from Study NC-039 had rezafungin MIC values ≤0.03 µg/mL; these isolates are shown at an MIC of 0.03 µg/mL

Abbreviations: MIC, minimum inhibitory concentration

Target Attainment

PK-PD and target attainment analysis was not conducted with *C. krusei*.

Correlation Between MIC and Clinical Outcome

- Only five patients with *C. krusei* were treated with rezafungin.
- Among the five rezafungin-treated patients, the highest rezafungin MIC associated with a favorable response was 0.06 µg/mL (Table 190).
- The proposed breakpoint of ≤0.25 µg/mL is based largely on the ECV.

Table 190. Correlation of MIC and Outcome - *C. krusei*

Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) [%; n1/n]									
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	>0.5
30 Day all-cause mortality					1/2 (50.0)	3/3 (100)				
5 Day mycological response					1/2 (50.0)	1/3 (33.3)				
14 Day mycological response					1/2 (50.0)	1/3 (33.3)				

Source: ISE Tables 2.1.14 and 2.2.13
Abbreviations: MIC, minimum inhibitory concentration

19.4. FDA Recommendations for Breakpoints or Susceptibility Test Interpretive Criteria for Rezafungin

The following is a summary of the Agency's STIC/BPs recommendations with our rationale for labeling recommendations on the first and the second list pathogens pertinent to section 12.4 Microbiology of the rezafungin USPI:

- **1st list pathogens/indicated pathogens for the candidemia//IC indication:** Rezafungin has been shown to be active against most isolates of the following *Candida* species, both in vitro and in clinical infections:
  - *C. albicans*
  - *C. glabrata*
  - *C. tropicalis*
  - *C. parapsilosis*
- **2nd list pathogens:** We do not recommend including *C. krusei* in the first list due to insufficient numbers (<10, n=5) of candidemia/IC clinical cases and insufficient data with respect to the mycological response at Day 14 (2/5; 40%) in clinical studies. However, we recommend including *C. krusei* along with other *Candida* species in the second list of pathogens.
  - *C. krusei*
  - *C. auris*
  - *C. dubliniensis*
  - *C. fabianii*
  - *C. guilliermondii*

- *C. inconspicua*
- *C. kefyr*
- *C. lusitaniae*
- *C. metapsilosis*
- *C. orthopsilosis*
- *C. pulcherrima*
- *C. rugosa*
- *C. sojae*

Agency's MIC STIC/BPs Recommendations With Rationales

The Applicant's proposed MIC BPs were revised for accuracy and clarity. The Agency's recommended MIC BPs for *Candida* species are listed in Table 191:

Table 191. Agency's Recommended MIC STIC/BPs for Rezafungin

	Minimum Inhibitory Concentrations (µg/mL)		
***Candida* species**	**Susceptible**	**Intermediate**	**Resistant**
C. albicans	≤0.12	---	---
C. glabrata	≤0.12	---	---
C. tropicalis	≤0.12	---	---
C. parapsilosis	≤2	---	---

Source: Clinical Microbiology Reviewer created Table based on data analysis presented in NDA-217417.
Note: The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.
Abbreviations: BP, breakpoint; MIC, minimum inhibitory concentration; STIC, suscept bility test interpretive criteria

The Agency's recommendation is based on MIC_{90} values of surveillance and clinical study isolates, epidemiological cutoff values (ECV/ ECOFF), and mycological eradication data from clinical studies. The rezafungin clinical development program provides limited information to allow the determination of concordance between PTA findings and clinical outcome. For other FDA approved echinocandins, PTA results based on nonclinical PK-PD targets do not always align with clinical outcomes. Therefore, the Agency relied primarily on clinical and mycological data as the primary evidence for recommending STIC values with species specific rationales as follows:

(1) ***C. albicans*:** We recommend a susceptible-only (S) BP of ≤0.12 µg/mL for *C. albicans* which covers 99.8%, and 100% of the isolates from 2018 to 2020 surveillance and pooled clinical studies, respectively. We do not agree with the Applicant-proposed susceptible-only (S) BP of ≤0.25 µg/mL. This proposed BP is solely based on the nonclinical PK-PD and PTA simulation data and is not supported by mycological eradication data from clinical studies, MIC_{90} data from the surveillance and the clinical study isolates, or an ECV/ECOFF value.

The Agency relied on the following data in support of the Agency's rezafungin BP recommendation:

- The maximum cumulative Day 14 mycological success rate of 67.2% (39/58) in the clinical studies was achieved at MIC ≤0.12 µg/mL. While 87.5% (7/8) mycological

success was achieved with isolates at MIC =0.12, no clinical *C. albicans* isolates were available with an MIC ≥0.25 µg/mL.
- The MIC_{90} value of ≤0.06 µg/mL was observed for both the surveillance and the pooled clinical study isolates of *C. albicans*.
- An ECV of 0.06 µg/mL has been derived from ECOFF finder analysis by using a large collection of *C. albicans* isolates.
- A unimodal distribution is prevalent among surveillance and clinical *C. albicans* isolates.

Therefore, we recommend a susceptible-only (S) BP of ≤0.12 µg/mL for *C. albicans*.

(2) ***C. glabrata*:** We recommend a susceptible-only (S) BP of ≤0.12 µg/mL for *C. glabrata* which covers 97.1%, and 97.3% of the isolates from 2018 to 2020 surveillance and pooled clinical studies, respectively. We do not agree with the Applicant's proposed Susceptible (S)/Intermediate (I)/Resistant (R) BPs of ≤0.5/1.0/≥2.0 µg/mL. The proposed S/I/R BPs are solely based on the Applicant's nonclinical PK-PD and PTA data.

The Agency primarily relied on the following data in support of the Agency's rezafungin BP recommendation:

- The maximum cumulative Day 14 mycological success rate of 81.6% (31/38) in the clinical studies was achieved at MIC ≤0.12 µg/mL. While 70% (7/10) mycological success was achieved with isolates at MIC =0.12, no clinical isolate was available at MIC 0.25 µg/mL; and only one clinical isolate with mycological success was available at MIC 0.5 µg/mL. However, no clinical *C. glabrata* isolate with an MIC >0.5 µg/mL was available.
- The MIC_{90} values of 0.06 µg/mL and 0.12 µg/mL were observed for the surveillance, and the pooled clinical study isolates, respectively.
- An ECV of 0.12 µg/mL has been derived from ECOFF finder analysis by using a collection of 742 clinical isolates.
- A unimodal distribution is prevalent among surveillance and clinical *C. glabrata* isolates.

Therefore, we recommend a susceptible-only (S) BP of ≤0.12 µg/mL for *C. glabrata*.

(3) ***C. tropicalis*:** We recommend a susceptible-only (S) BP of ≤0.12 µg/mL for *C. tropicalis* which covers 99.2%, and 100% of the isolates from 2018 to 2020 surveillance and pooled clinical studies, respectively. We do not agree with the Applicant's proposed susceptible-only (S) BP of ≤0.25 µg/mL. This proposed BP for *C. tropicalis* does not seem to be supported by the mycological eradication, MIC_{90} from the surveillance and the clinical study isolates, or ECV.

The Agency primarily relied on the following data in support of the Agency's rezafungin BP recommendation:

- The maximum cumulative Day 14 mycological success rate of 74% (20/27) in the clinical studies was achieved at MIC ≤0.12 µg/mL. While a mycological success rate of 100% (3/3) was achieved with isolates at MIC =0.12, no clinical isolates were available at MIC ≥0.25 µg/mL.
- The MIC_{90} values of 0.06 µg/mL and 0.12 µg/mL were observed for the surveillance, and the pooled clinical study isolates, respectively.
- An ECV of 0.12 mcg/mL has been derived from ECOFF finder analysis by using 406 clinical *C. tropicalis* isolates.
- A unimodal distribution is prevalent among surveillance and clinical *C. tropicalis* isolates.

Therefore, we recommend a susceptible-only (S) BP of ≤0.12 µg/mL for *C. tropicalis*.

(4) ***C. parapsilosis*:** We agree with the Applicant's proposed susceptible-only (S) BP of ≤2 µg/mL and the supporting rationale. The proposed susceptible-only (S) BP of ≤2 µg/mL for *C. parapsilosis* covers 99.7%, and 100% of the isolates from 2018 to 2020 surveillance and pooled clinical studies, respectively.

The Applicant and the Agency relied on the following data in support of the BP recommendation for *C. parapsilosis*:

- The maximum cumulative Day 14 mycological success rate of 84.6% (11/13) was achieved at MIC ≤2 µg/mL. While a mycological success rate of 100% (4/4) was achieved with isolates at MIC =2 µg/mL, no clinical isolates were available at MIC ≥4 µg/mL.
- The MIC_{90} value of ≤2 µg/mL was observed for both the surveillance and the pooled clinical study isolates of *C. parapsilosis*.
- An ECV of 4 mcg/mL has been derived from ECOFF finder analysis by using 707 clinical *C. parapsilosis* isolates. Only one isolate was available at MIC of 4 µg/mL from 2018 to 2020 surveillance study.
- A unimodal distribution is prevalent among surveillance and clinical *C. parapsilosis* isolates.
- We also recognize the reduced susceptibility of echinocandins to *C. parapsilosis* isolates due to the naturally occurring proline-to-alanine substitution (P660A) to the highly conserved hot spot 1 region of FKS1 protein.

Therefore, we agree with the Applicant's proposed susceptible-only (S) BP of ≤2 µg/mL for *C. parapsilosis.*

MIC-Disk Correlation and Disk Diffusion BPs

The Agency's disk diffusion BPs were determined based on the correlation of the disk diffusion diameter to the Agency's recommended MIC BPs for the proposed pathogens. The re-analysis of the disk diffusion BPs was done using the data submitted in the NDA and by following the CLSI guidelines for 'Without Intermediate Range' (Table 192).

Table 192. CLSI Guideline Acceptable Discrepancy Rate (Without Intermediate Range)

MIC Range	Discrepancy Rates		
No Intermediate Range	Very Major	Major	Minor
≥NS +1	<2%	NA	-----
NS+S	<10%	<10%	-----
≤S-1	NA	<2%	-----

Source: (CLSI 2018)
Note: If there are no intermediate ranges for both disk diffusion and dilution testing, minor discrepancies are not a consideration. R is the resistant breakpoint MIC; S is the susceptible breakpoint MIC.
Abbreviations: CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inh bitory concentration; NA, not applicable; NS, not susceptible; S, susceptible

The Agency's proposed disk diffusion susceptibility interpretive criteria are listed in Table 193.

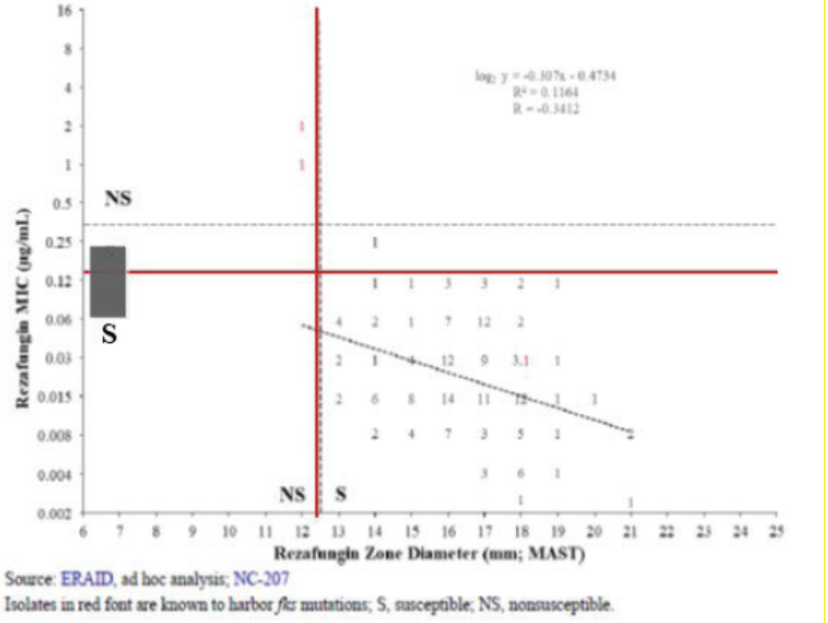
Table 193. Agency's Proposed Disk Diffusion BPs for Rezafungin

	Disk Diffusion (Zone Diameter in mm)		
***Candida* Species**	**Susceptible**	**Intermediate**	**Resistant**
C. albicans	≥13	---	---
C. glabrata	≥15	---	---
C. tropicalis	≥14	---	---
C. parapsilosis	≥09	---	---

Source: Clinical Microbiology Reviewer created Table based on data analysis presented in NDA-217417.
Note: The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.
Abbreviations: BP, breakpoint

C. albicans: We agree with the Applicant's proposal and recommend a susceptible (S) ≥13 mm and a nonsusceptible (NS) ≤12 mm disk diffusion BPs for *C. albicans* from error-rate bounding analysis of 166 isolates. No 'very major' or 'major' discrepancy rates existed among 166 total *C. albicans* isolates analyzed (Figure 31 and Table 194).

Figure 31. Broth MIC vs. Disk Diffusion Correlation for *C. albicans* (N=166)



Source: ERAID, ad hoc analysis; NC-207
Isolates in red font are known to harbor *fks* mutations; S, susceptible; NS, nonsusceptible.

Abbreviations: MIC, minimum inhibitory concentration

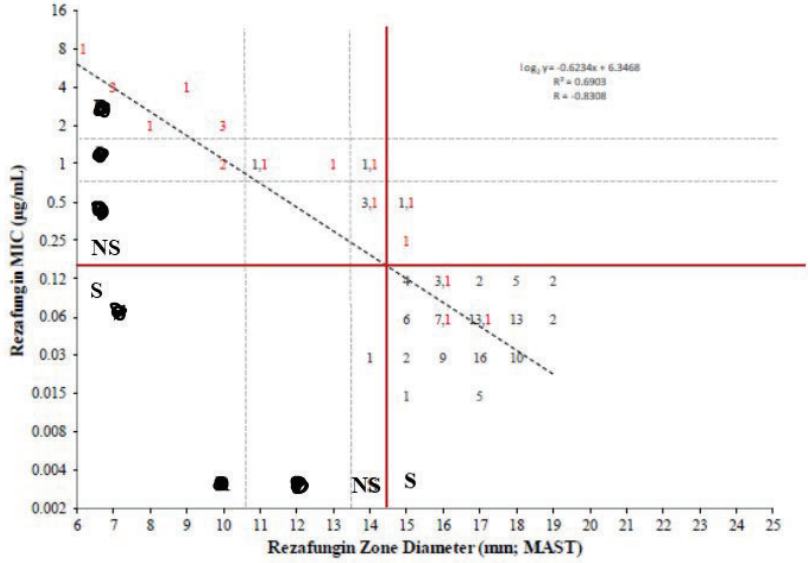
Table 194. Error-Rate Bounded Analysis - *C. albicans*

MIC Range	Discrepancy Rates		
	Total isolates, N	Very Major, n (%)	Major, n (%)
≥NS + 1	2	0 (0.0)	NA
NS to S	12	0 (0.0)	0 (0.0)
≤S - 1	152	NA	0 (0.0)
TOTAL	166	0 (0.0)	0 (0.0)
Recommended disk diffusion BPs	Susceptible ≥13 mm; and non-susceptible ≤12 mm		

Source: ERAID, ad hoc analysis; NC-207
Abbreviations: BP, breakpoint; MIC, minimum inhibitory concentration; N, number of isolates at indicated MIC range; n, number of isolates with indicated discrepancy; NA, not applicable; NS, nonsusceptible; S, susceptible

C. glabrata: We recommend a susceptible (S) ≥15 mm and an NS ≤14 mm disk diffusion BPs for *C. glabrata* from error-rate bounding analysis of 126 isolates. We do not agree with the Applicant's proposed disk diffusion Susceptible (S)/ Intermediate (I)/ Resistant (R) BPs of ≥14/11 to 13/≤10 mm. A higher 'very major' discrepancy rate of 9.1% was observed compared to the acceptable rate of <2% among 22 isolates of ≥ NS +1 category; however, this error rate was the lowest considering all other choices. Discrepancy rates were within acceptable ranges in all other categories (Figure 32 and Table 195).

Figure 32. Broth MIC vs. Disk Diffusion Correlation for *C. glabrata* (N=126)



Source: ERAID, ad hoc analysis; NC-207
Isolates in red font are known to harbor *fks* mutations; S, susceptible; NS, nonsusceptible.

Abbreviations: MIC, minimum inhibitory concentration

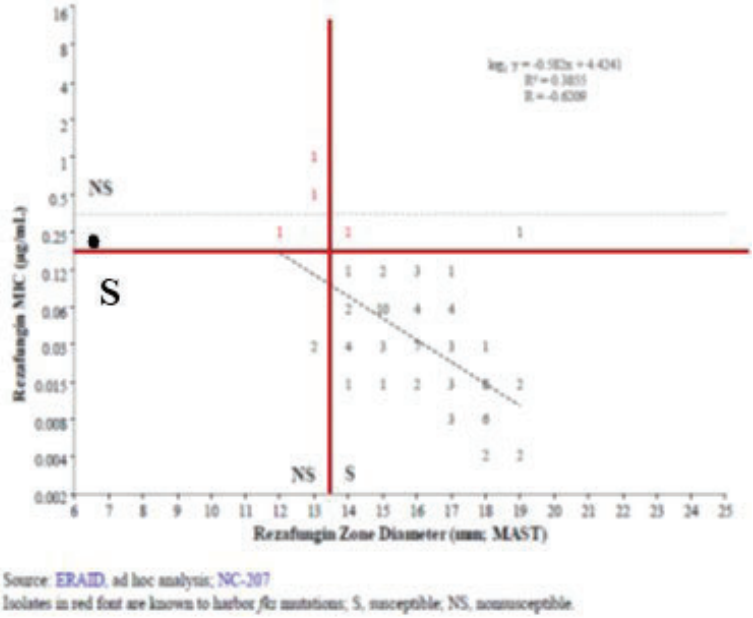
Table 195. Error-Rate Bounded Analysis - *C. glabrata*

MIC Range	Discrepancy Rates		
	Total isolates, N	Very Major, n (%)	Major, n (%)
≥NS + 1	22	2 (9.1)	NA
NS to S	18	1 (5.6)	0 (0.0)
≤S - 1	86	NA	1 (1.2)
TOTAL	126	3 (2.4)	1 (0.8)
Recommended disk diffusion BPs	Susceptible ≥15 mm; and non-susceptible ≤14 mm		

Source: ERAID, ad hoc analysis; NC-207
Abbreviations: BP, breakpoint; MIC, minimum inhibitory concentration; N, number of isolates at indicated MIC range; n, number of isolates with indicated discrepancy; NA, not applicable; NS, nonsusceptible; S, susceptible

C. tropicalis: We agree with the Applicant's proposal and recommend a susceptible (S) ≥14 mm and an NS ≤13 mm disk diffusion BPs for *C. tropicalis* from error-rate bounding analysis of 82 isolates. A higher 'very major' discrepancy rate of 20% was observed compared to the acceptable rate of <10% among 10 isolates in NS to S category. We found this error rate was the lowest considering all other choices. Discrepancy rate for 'major' error was little higher at 2.9% than acceptable range of <2.0% among 70 isolates in ≤ S-1category (Figure 33 and Table 196).

Figure 33. Broth MIC vs. Disk Diffusion Correlation for *C. tropicalis* (N=126)



Source: ERAID, ad hoc analysis; NC-207
Isolates in red font are known to harbor *fks* mutations; S, susceptible; NS, nonsusceptible

Abbreviations: MIC, minimum inhibitory concentration

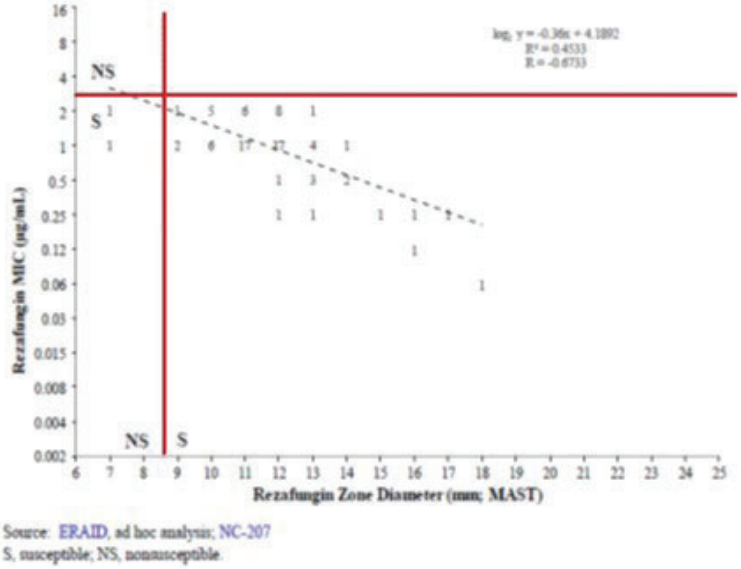
Table 196. Error-Rate Bounded Analysis – *C. tropicalis*

MIC Range	Discrepancy Rates		
	Total isolates, N	Very Major, n (%)	Major, n (%)
≥NS + 1	2	0 (0.0)	NA
NS to S	10	2 (20.0)	0 (0.0)
≤S - 1	70	NA	2 (2.9)
TOTAL	82	2 (2.4)	2 (2.4)
Recommended disk diffusion BPs	Susceptible ≥14 mm; and non-susceptible ≤13 mm		

Source: ERAID, ad hoc analysis; NC-207
Red font indicates an error-rate above that deemed acceptable by CLSI
Abbreviations: BP, breakpoint; MIC, minimum inhibitory concentration; N, number of isolates at indicated MIC range; n, number of isolates with indicated discrepancy; NA, not applicable; NS, nonsusceptible; S, susceptible

C. parapsilosis: We agree with the Applicant's proposal and recommend a susceptible (S) ≥9 mm and an NS ≤8 mm disk diffusion BPs for *C. parapsilosis* from error-rate bounding analysis of 83 isolates. Discrepancy rates were present in two categories but within acceptable ranges (Figure 34 and Table 197).

Figure 34. Broth MIC vs. Disk Diffusion Correlation for *C. parapsilosis* (N=83)



Abbreviations: MIC, minimum inhibitory concentration

Table 197. Error-Rate Bounded Analysis - *C. parapsilosis*

MIC Range	Discrepancy Rates		
	Total isolates, N	Very Major, n (%)	Major, n (%)
≥NS + 1	0	0 (0.0)	NA
NS to S	22	0 (0.0)	1 (4.5)
≤S - 1	61	NA	1 (1.6)
TOTAL	83	0 (0.0)	2 (2.4)
Recommended disk diffusion BPs	Susceptible ≥09 mm; and non-susceptible ≤08 mm		

Source: ERAID, ad hoc analysis; NC-207
Abbreviations: BP, breakpoint; MIC, minimum inhibitory concentration; N, number of isolates at indicated MIC range; n, number of isolates with indicated discrepancy; NA, not applicable; NS, nonsusceptible; S, susceptible

20. Mechanism of Action/Drug Resistance

Mechanism of Action

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) 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.

Resistance

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 values. There are two highly conserved 'hot spot' regions (HS1 and HS2) in both FKS1 and FKS2 among *Candida* spp (Garcia-Effron et al. 2011). Mutations in these two regions of *fks* typically confer echinocandin resistance. These mutations influence glucan biosynthesis, thereby altering cell-wall components.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Between [redacted] (b) (4) OSIS conducted a remote regulatory assessment of the 26-week monkey study (contract research organization study #00148558, Cidara study # NC-190) conducted at [redacted] (b) (4) The inspectors observed the following objectionable conditions during the remote regulatory assessment. The catheters became dislodged for several animals during the infusion of the test systems from May 26, 2020, through November 10, 2020. The events were documented with additional comments on the Treatment Rate Sheets indicating "Undetermined amount of test article dosed outside of the vein." The firm acknowledged the observation and stated that the unanticipated dosing events were sufficiently documented, reported, and assessed for impact on the study by the Study Director.

The Office of Study Integrity and Surveillance did not consider the firm's response to be adequate since the study protocol indicated that the vehicle or test article formulations will be administered via intravenous infusion. The response from the firm acknowledged that an undetermined amount of volume was delivered perivascularly; however, deviation reports were not generated for the study director to assess the impact of these dosing irregularities. The inspectors noted that this observation may have an impact on data quality and integrity as the actual dosing volumes were not accurate. Despite these errors, pharmacokinetics evaluations confirmed exposure to rezafungin at doses up to 5-fold the clinical exposure based on AUC comparisons.

Due to the unusually high incidence of tremors, even in control animals, the study director was asked about the availability of historical data for tremors in NHP infusion studies. The study director assessment and the vet staff communications indicated that the tremors were largely shivering/behavior because of prolonged restraint and infusion of NHPs for up to 60 minutes with a solution equilibrated to room temperature for 45 minutes prior to administration. Per a study communication, the term "tremors" was being used for documenting instances of animals shivering during infusion which implies a different mechanism and cause than a general "tremor." The firm did discuss the possibility of amending the study 00148558 final report to clarify this issue when made aware of the concerns from the Agency. Despite the increase in background tremors in control animals, a rezafungin-related increase in moderate, severe, whole body, locomotor and hindlimb tremors was detected (see neurotoxicity review issue discussion in Section 7.6.1).

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes in the finalized PI as compared to the Applicant's draft PI submitted on July 22, 2022. The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent

(if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 198. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
BOXED WARNING	N/A
1 INDICATIONS AND USAGE	The indication was revised to reflect approval for a limited use indication in patients 18 years of age or older who have limited or no alternative options for the treatment of candidemia/IC and a statement was added to inform providers that approval of this indication is based on limited clinical safety and efficacy data for REZZAYO (see IAMA Section 2.2). This labeling language was based on the recommendations of page 14 of the Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases-Questions and Answers (Revision 1) guidance (May 2022). A limitation of use statement was added to inform providers that rezafungin has not been studied in patients with endocarditis, osteomyelitis, and meningitis due to *Candida* since these patients were not included in the clinical trials (see IAMA Section 15.2.1). This limitation of use statement is also included in the PIs of other echinocandins.
2 DOSAGE AND ADMINISTRATION	Given the association observed between the duration of rezafungin dosing and the neurotoxicity findings in nonhuman primates studies and the fact that the safety database in the NDA is limited to patients receiving a maximum of 4 weekly doses, the recommended dosage statement was revised to note that the safety of rezafungin has not been established beyond 4 weekly doses (see IAMA Section 7.4). A missed doses section was added to advise administration of the missed dose as soon as possible. The Applicant proposed a 3-Day missed dose window, i.e., maintain schedule if a patient receives a missed dose within 3 days of assigned schedule. The simulated rezafungin AUC and C_{max} estimates following two 200 mg doses four days apart are within those seen with the initial 400 mg loading dose (STRIVE and ReSTORE), as well as 400 mg once-weekly regimen (STRIVE) and higher doses evaluated in Phase 1 studies. We agree with the Applicant's proposal based on the available safety findings from phase 1, STRIVE, and ReSTORE studies (see IAMA Section II.7 and 16.3).
4 CONTRAINDICATIONS	A statement was added that rezafungin is contraindicated in patients with known hypersensitivity to rezafungin or other echinocandins because hypersensitivity reactions have been demonstrated with other echinocandins and cross-sensitivity within the class has been recognized.
5 WARNINGS AND PRECAUTIONS	*5.1 Infusion-Related Reactions* was revised to add a recommendation to restart the infusion at a lower rate, with a

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	cross-reference to *Dosage and Administration (2.3)* for infusion rate details. *5.3 Hepatic Adverse Reactions* was added since hepatic adverse reactions were observed in clinical trials of rezafungin and hepatic adverse reactions are included as warnings for other drugs in the echinocandin class (see IAMA Section 7.5.1.7)
6 ADVERSE REACTIONS	The description of the trial population for the phase 2 and phase 3 studies was updated to note that the maximum duration of rezafungin dosing was 4 weekly doses (see Section 7.4) and that patients with a history (or presenting with significant symptoms) of severe ataxia, tremor, or neuropathy or a diagnosis of multiple sclerosis or a movement disorder (including Parkinson's Disease or Huntington's Disease) or currently taking a severe neurotoxic medication were excluded from the phase 3 study (see IAMA Section 7.6.1). Based on the reviewer's analysis of TEAEs, the following adverse reactions occurring in <5% patients in the phase 2 and phase 3 studies at the proposed clinical dose were added to the subsection *Less Common Adverse Reactions in Patients with Candidemia and Invasive Candidiasis*: tremor, disseminated intravascular coagulation, dysphagia, gastrointestinal hemorrhage, fluid overload, insomnia, erythema, headache, dizziness, acute kidney injury, abnormal liver tests (includes hypertransaminasemia and increased gamma-glutamyltransferase), peripheral neuropathy (includes neuropathy peripheral, polyneuropathy, and peroneal nerve palsy). A commentary on tremors was added to this section to further clarify the clinical significance of the findings (see IAMA Section 7.5).
7 DRUG INTERACTIONS	Per 21 CFR 201.56(d)(4), the entire DRUG INTERACTIONS section or required content within this section was omitted since there are no clinically significant DDIs (see IAMA Section 8.2).
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	*8.1* No adverse embryofetal outcomes were observed when rezafungin was dosed intravenously to pregnant rabbits during the period of organogenesis up to 35 mg/kg, approximately 3 times the clinical exposure based on AUC comparison (see IAMA Section 8.4). *8.2 Lactation* was revised to include a statement that when a drug is present in animal milk, it is likely that the drug will be present in human milk, (b) (4) has been deleted. *8.3 Females and Males of Reproductive Potential* section was drafted to describe drug-related findings on sperm from animal studies and a statement was added to reflect that the effect on human male fertility is unknown (see IAMA Section 8.4). *8.4 Pediatric Use* section was drafted to state that the safety and effectiveness of rezafungin have not been established in pediatric patients based on the recommendations in the Pediatric

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	Information Incorporated Into Human Prescription Drug and Biological Product Labeling guidance (March 2019). *8.5 Geriatric Use* section was drafted to describe the geriatric study population evaluated in phase 2 and 3 trials. A statement was included to note that these trials did not include sufficient numbers of older adult patients to determine if patients 65 years and older respond differently than younger adult patients. This labeling language was based on the recommendations in the Geriatric Information in Human Prescription Drug and Biological Product Labeling guidance (September 2020).
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	Information [redacted] was removed [redacted]
12 CLINICAL PHARMACOLOGY	*12.2 Pharmacodynamics* was revised to state [redacted] *12.3 Pharmacokinetics* was edited for clarity and a table added to consolidate information into a single table summarizing PK parameters for the approved dosing. To improve readability, the following summary statement was added: No clinically relevant effects on the pharmacokinetics of rezafungin were observed based on age, sex, race, weight, or hepatic impairment (Child Pugh Class B or C). No clinically relevant effect in the pharmacokinetics of rezafungin was observed based on renal impairment (creatinine clearance: [redacted] mL/min to above 120 mL/min) and no effect is expected in patients undergoing hemodialysis [redacted] *12.4 Microbiology* was revised to clarify that the clinical significance of the in vitro fungicidal activity of rezafungin is unknown and *C. krusei* was [redacted] added to the second list of pathogens (see IAMA Section 19).
13 NONCLINICAL TOXICOLOGY	*13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility* was revised to include findings of decreased sperm motility, hypospermia, and abnormal sperm morphology in rats dosed with rezafungin at approximately [redacted] times the clinical exposure based on AUC and normal sperm findings in nonhuman primates dosed with

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	rezafungin at approximately 6 times the clinical exposure based on AUC (see IAMA Section 13.2.1). *13.2 Animal Toxicology and/or Pharmacology* was revised to include the neurological findings of tremors, axonal degeneration, demyelination and increased cellularity/hyperplasia of Schwann cells in the nonhuman primate studies and axonal degeneration observed in rats (see IAMA Section 7.6.1).
14 CLINICAL STUDIES	The description of the phase 3 trial was updated to add the clinical conditions excluded from the trial [septic arthritis in a prosthetic joint, osteomyelitis, endocarditis or myocarditis, meningitis, endophthalmitis, chorioretinitis, or any central nervous system infection, chronic disseminated candidiasis, or urinary tract candidiasis due to ascending Candida infection secondary to obstruction] (see IAMA Section 6.2.2). In the efficacy results table, (b) (4) was deleted because (b) (4) was not agreed to with FDA. (b) (4) deleted and replaced with a brief description of the study because (b) (4)
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Minor changes were made to the product quality sections of the prescribing information. Refer to the Integrated Quality Assessment.

[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): AUC, area under the concentration-time curve; AUC_{0-168}, area under the concentration-time curve from 0 to 168 hours; DDI, drug-drug interaction; IC, invasive candidiasis; N/A, not applicable; PI, Prescribing Information; PK, pharmacokinetic; TEAE, treatment-emergent adverse event

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Carton labeling
- Container label
- Prescribing information

24. Postmarketing Requirements and Commitments

There are two postmarketing requirements:

1. Long term microbiologic surveillance data are needed to monitor changes in susceptibility to rezafungin against *Candida* species specific to the candidemia/IC indication. From a clinical microbiology perspective, the following postmarketing requirement will be communicated to the Applicant:

   Conduct a United States surveillance study for a five-year period after the introduction of rezafungin to the market to monitor changes in susceptibility of Candida species to rezafungin.

2. The information provided in NDA 217417 is not sufficient to assess the mutagenic potential of rezafungin. Cytotoxicity (i.e., reduction in the background lawn and/or mean number of revertant colonies) was observed at ≥50 µg/plate in TA1537 without metabolic activation, ≥100 µg/plate in TA1537 with metabolic activation, ≥250 µg/plate in TA98, TA1535, and WP2 uvrA without metabolic activation and TA100 with and without metabolic activation, and at ≥500 µg/plate in TA98, TA1535, and WP2 uvrA with metabolic activation. The antibacterial properties of CD101 (rezafungin) significantly limited doses that could be evaluated in the Ames test. Since this test is for risk identification, and often requires higher concentrations to identify an effect, the recommendation is to test higher doses up to and including 5000 mcg/plate, if possible. Additionally, the bacteria must survive in order to express the mutation and to be recognized as a positive result, therefore compounds that are too toxic to the bacteria cannot be tested in a valid assay using these organisms. The Applicant was referred to ICH Guidance S2(R1) Note 2, and OECD guidelines for testing of chemicals (Test 471). Both referenced documents indicate that an in vitro test in mammalian cells for mutagenicity is indicated for compounds toxic to the test bacteria (although an initial Ames test is still recommended regardless).

   The in vitro bacterial reverse mutation (Ames) test is the primary in vitro gene mutation assay used in the testing of investigational drugs for human use. The most appropriate follow-up test for an investigational drug in the in vitro bacterial reverse mutation test would be the MLA (Mouse Lymphoma Assay) or HPRT (Hypoxanthine Phosphoribosyl Transferase Forward Mutation Assay) that assesses a similar endpoint (mutation, small scale DNA damage). The in vitro metaphase chromosome aberration test does not measure gene mutations. It measures clastogenicity (large scale DNA damage). Thus, the in vitro metaphase chromosome aberration test is generally not a suitable follow-up for the in vitro Ames test as it measures a different endpoint.

   The in vitro micronucleus assay can detect cytogenetic damage resulting from DNA fragments or whole chromosomes (clastogenicity [and aneugenicity]). This is large scale DNA damage. In general, the in vitro micronucleus does not assess an endpoint similar to what is detected in the in vitro bacterial reverse mutation (Ames) test (mutation, small scale DNA damage).

   The Division has consulted with the Agency's experts on genetic toxicology and they have agreed with the Division's recommendation. In addition, the required follow-up in vitro mutagenicity test in mammalian cells to confirm the negative mutagenic potential of rezafungin should be conducted GLP in compliance with 21 CFR (Part 58). From a

clinical Pharmacology/Toxicology perspective, the following postmarketing requirement will be communicated to the Applicant:

C*onduct a mouse lymphoma TK assay (MLA) or hypoxanthine phosphorybosyl transferase (HPRT) forward mutation assay to assess the mutagenic potential of rezafungin*

There is one post-marketing commitment:

During the NDA review, the drug product specification was amended with two additional tests such as assay/gross content and assay of the drug product reconstituted solution. It was agreed that qualification and validation data for these additional tests would be provided via a postmarketing commitment (PMC). The following CMC PMC between OPQ and the Applicant should be included in the action letter.

Complete necessary qualification and validation studies of the current assay high-performance liquid chromatography analytical procedure to be used for the gross content and assay of reconstituted solution tests in the drug product specification. Update the relevant sections of Module 3 accordingly.

25. Financial Disclosure

Table 199. Covered Clinical Studies: CD101.IV.2.03 (Phase 2) and CD101.IV.3.05 (Phase 3)

Was a list of clinical investigators provided:			Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 45 for Phase 2 study;71 for Phase 3			
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): None			
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None			
	If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.			
Is an attachment provided with details of the disclosable financial interests/arrangements:		NA	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:		NA	Yes ☐	No ☐ (Request information from Applicant)
	Number of investigators with certification of due diligence (Form FDA 3454, box 3): NA			
Is an attachment provided with the reason:		NA	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Literature

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Guidance for Industry

Guidance for Industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020a)

Guidance for Industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020b)

Guidance for Industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice* (March 2019)

Draft Guidance for Industry *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers (Revision 1)* (May 2022)

Guidance for Industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019)

Guidance for Industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022)

Guidance for Industry *Geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry* (September 2020)

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27. Review Team

Table 200. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Eva Zuffova
Chief Project Management Staff	Gregory DiBernardo
Pharmacology-Toxicology Reviewer	Owen McMaster
Pharmacology-Toxicology Deputy Division Director	Terry Miller
Office of Clinical Pharmacology (OCP) Reviewer	Timothy Bensman
OCP Team Leader (Acting)	Abhay Joshi
OCP Pharmacometrics Reviewer	Jiajun Liu
OCP Pharmacometrics Team Leader	Justin Earp
Clinical Microbiology Reviewer	Jalal Sheikh
Clinical Microbiology Team Leader	Avery Goodwin
Clinical Reviewer	Shrimant Mishra
Clinical Team Leader	Heidi Smith
Biometrics Reviewer(s)	Xianbin Li; Cheryl Dixon
Biometrics Team Leader	Daniel Rubin
Cross-Disciplinary Team Leader	Heidi Smith
OCP Pharmacometrics Division Director	Hao Zhu
Pharmacology-Toxicology Division Director	Hanan Ghantous
OCP Deputy Division Director	Zhixia (Grace) Yan Danielsen
Director Project Management Staff	Maureen Dillon-Parker
Associate Director of Labeling	Abimbola Adebowale
Deputy Division Director (Clinical)	Dmitri Iarikov
Division Director (Clinical)	Peter Kim
Office Director (or designated signatory authority)	John Farley

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 201. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Dorota Matecka, Molly Lee, David Claffey, Karina Zuck, Katherine Windsor, Caryn McNab, Anh-Thy Ly; Paresma Patel, Golam Kibria, James Norman, Shannon Heine, Erica Pfeiler
OPDP	Wendy Lubarsky
OSI	Cheryl Grandinetti, Phillip Kronstein
OSE/DEPI	Hannah Day, Natasha Pratt
OSE/DMEPA	Deborah Myers, Valerie Vaughan
OSE/DRISK	Celeste Karpow, Naomi Boston
Other	Aleksander Winiarski (OSE); Amy Chung (OSE), Neha Gada (OSE), Christos Mastroyannis (DPMH), Tamara Johnson (DPMH)

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; DPMH, Division of Pediatric and Maternal Health

27.1. Reviewer Signatures

See next page.

Table 202. Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Primary Reviewer	Shrimant Mishra, MD OND/OID/DAI	☒ Benefit-Risk Assessment Interdisciplinary Assessment x Additional Information and Analyses Sections: 17, 23-25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp:	Shrimant Mishra -S Digitally signed by Shrimant Mishra -S Date: 2023.03.22 09:44:03 -04'00'				
Clinical Cross-Disciplinary Team Lead	Heidi Smith, MD PhD OND/OID/DAI	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12-25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp:	Heidi L. Smith -S Digitally signed by Heidi L. Smith -S Date: 2023.03.22 08:08:38 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Pharmacology/ Toxicology Primary Reviewer	Owen McMaster, PhD OND/OID/DPT-ID	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 7, 8, 12, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Owen G. Mcmaster -S Digitally signed by Owen G. Mcmaster -S Date: 2023.03.22 14:20:47 -04'00'					
Pharmacology/ Toxicology Deputy Division Director	Terry Miller, PhD OND/OID/DPT-ID	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 7, 8, 12, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Terry J. Miller -S Digitally signed by Terry J. Miller -S Date: 2023.03.22 11:14:36 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Pharmacology/ Toxicology Division Director	Hanan Ghantous, PhD, DABT OND/OID/DPT-ID	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 7, 8, 12, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Terry J. Miller -S Digitally signed by Terry J. Miller -S Date: 2023.03.22 11:15:53 -04'00'					
Biometrics Primary Reviewer	Xianbin Li, PhD OTS/OB/DBIV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2, 6.3.1, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Xianbin Li -S Digitally signed by Xianbin Li -S Date: 2023.03.22 08:54:46 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Biometrics Secondary Reviewer	Cheryl Dixon, PhD OTS/OB/DBIV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2, 6.3.1, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Cheryl A. Dixon -S Digitally signed by Cheryl A. Dixon -S Date: 2023.03.22 10:57:03 -04'00'					
Biometrics Team Leader	Daniel Rubin, PhD OTS/OB/DBIV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2, 6.3.1, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Daniel Rubin -S Digitally signed by Daniel Rubin -S Date: 2023.03.22 09:54:26 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Reviewer	Timothy Bensman, Pharm.D., PhD OTS/OCP/DIDP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Timothy J. Bensman -S Digitally signed by Timothy J. Bensman -S Date: 2023.03.22 10:33:33 -04'00'					
Clinical Pharmacology Team Leader (acting)	Abhay Joshi, PhD OTS/OCP/DIDP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Abhay Joshi -S Digitally signed by Abhay Joshi -S Date: 2023.03.22 10:08:16 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Deputy Division Director	Zhixia (Grace) Yan Danielsen, PhD OTS/OCP/DIDP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Zhixia Y. Danielsen -S Digitally signed by Zhixia Y. Danielsen -S Date: 2023.03.22 09:18:47 -04'00'					
Clinical Pharmacology/ Pharmacometrics Primary Reviewer	Jiajun Liu, PharmD, MSc OTS/OCP/DPM	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jiajun Liu -S Digitally signed by Jiajun Liu -S Date: 2023.03.22 13:15:29 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology/ Pharmacometrics Team Leader	Justin C. Earp, PhD OTS/OCP/DPM	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Hao Zhu -S Digitally signed by Hao Zhu -S Date: 2023.03.22 14:51:18 -04'00'					
Clinical Pharmacology/ Pharmacometrics Division Director	Hao Zhu, PhD OTS/OCP/DPM	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Hao Zhu -S Digitally signed by Hao Zhu -S Date: 2023.03.22 12:44:48 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Microbiology Primary Reviewer	Jalal Sheikh, PhD OND/OID/DAI	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.3.2, 19, 20, 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jalal U. Sheikh -S Digitally signed by Jalal U. Sheikh -S Date: 2023.03.22 13:01:16 -04'00'					
Clinical Microbiology Primary Reviewer	Avery Goodwin, PhD OND/OID/DAI	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.3.2, 19, 20, 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Avery C. Goodwin -S Digitally signed by Avery C. Goodwin -S Date: 2023.03.22 08:30:10 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Product Quality Team Leader	Dorota Matecka, PhD OPQ	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☐ Yes ☒ No
Signature/date/time stamp: Dorota M. Matecka -S Digitally signed by Dorota M. Matecka -S Date: 2023.03.22 11:48:28 -04'00'					
Regulatory Project Management Project Manager	Eva Zuffova, PhD, MS DRO/ID	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12, 27	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.		☐ Yes ☒ No
Signature/date/time stamp: Eva Zuffova -S Digitally signed by Eva Zuffova -S Date: 2023.03.22 13:21:37 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Regulatory Project Management Chief Project Management Staff	Gregory DiBernardo DRO/ID	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Gregory Dibernardo -S Digitally signed by Gregory Dibernardo -S Date: 2023.03.22 12:35:22 -04'00'					
Regulatory Project Management Director, Project Management	Maureen Dillon-Parker, MS, RAC DRO/ID	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Maureen P. Dillon Parker -S Digitally signed by Maureen P. Dillon Parker -S Date: 2023.03.22 13:32:38 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Labeling Associate Director for Labeling	Adebowale Abimbola, PhD, MS OND/OID/DAI	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 23,	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Abimbola O. Adebowale -S Digitally signed by Abimbola O. Adebowale -S Date: 2023.03.22 12:15:01 -04'00'					
Clinical Deputy Director	Dmitri Iarikov, MD, PhD OND/OID/DAI	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1-27	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Dmitri E. Iarikov -S Digitally signed by Dmitri E. Iarikov -S Date: 2023.03.22 14:09:54 -04'00'					

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Director	Peter Kim, MD, MS OND/OID/DAI	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1-27	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Peter W. Kim -S Digitally signed by Peter W. Kim -S Date: 2023.03.22 14:37:35 -04'00'					
Clinical Office Director	John Farley, MD, MPH OND/OID	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1-27	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp:					

Abbreviations: IA, Interdisciplinary Assessment

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EVA ZUFFOVA
03/22/2023 03:04:32 PM

JOHN J FARLEY
03/22/2023 03:13:15 PM