Statistical Analysis Plan

Title: 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)

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STATISTICAL ANALYSIS PLAN

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)

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Methodology:	Multicenter, randomized, double-blind
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APPROVAL SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACM	all-cause mortality
AE	adverse event
AESI	adverse event of special interest
ADaM	Analysis Data Model
ADaM IG	Analysis Data Model Implementation Guide
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APACHE II	Acute Physiology and Chronic Health Evaluation
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
C	Celsius
CE	clinically evaluable
CH	Potentially Clinically Significant High
CI	Confidence Interval
CL	Potentially Clinically Significant Low
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of AIDs
DILI	Drug Induced Liver Injury
DMID	Division of Microbiology and Infectious Diseases
DRC	Data Review Committee
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCrCL	estimated creatinine clearance
eCRF	electronic case report form
EMA	European Medicines Agency
EOI	End of infusion
EOT	End-of-Treatment
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
F	Fahrenheit
FDA	Food and Drug Administration
FU	Follow-up
IC	Invasive Candidiasis
ICE	Intercurrent event
ICH	International Conference on Harmonisation

Abbreviation	Definition
ICU	Intensive Care Unit
IRT	interactive response technology
ITT	intent-to-treat
IV	Intravenous(ly)
IVD	in vitro diagnostic
kg	kilogram
KM	Kaplan Meier
LFT	liver function test
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimal inhibitory concentration
MIC50	minimal inhibitory concentration required to inhibit the growth of 50% of the isolates
MIC90	minimal inhibitory concentration required to inhibit the growth of 90% of the isolates
mg	milligram
mITT	Modified Intent-to-treat
NI	non-inferiority
NLM	National Library of Medicine
PCS	potentially clinically significant
PI	Principal Investigator
PICC	Peripherally Inserted Central Catheter
PK	pharmacokinetic
PT	Preferred Term
PT/INR	Prothrombin time or International Normalized Ratio
QLQ-CIPN20	Chemotherapy-Induced Peripheral Neuropathy questionnaire
QTcF	QT interval corrected using Fridericia's formula
RR	respiratory rate
SAE	serious treatment-emergent adverse event
SAP	statistical analysis plan
SARA	Scale for the Assessment and Rating of Ataxia
SD	standard deviation
SI	Systeme Internationale
SOC	system organ class
SMQ	Standardized MedDRA query
spp.	species
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

Abbreviation	Definition
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

This Statistical Analysis Plan (SAP) provides the framework for the summarization and analysis of the clinical data from the study, "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)". Changes made to the SAP after it has been signed but prior to database lock will be documented in a SAP amendment. Changes made to the analyses after database lock will be described in the clinical study report (CSR). Pharmacokinetic (PK) analyses except for the analyses based on the concentration described in Section 4.6 will not be included in this SAP. Additional supportive/exploratory analyses might be added once subject data is available. Table shells and data set specifications will be prepared on the basis of this document.

1.1.2. Study Objectives

Per regulatory authority's expectations, the primary objectives of the study are separate for the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) as follows:

- Demonstrate that Rezafungin for Injection is non-inferior to caspofungin in terms of all-cause mortality (ACM) at Day 30 (-2 days) in the modified intent-to-treat (mITT) population (FDA primary objective)

- Demonstrate that Rezafungin for Injection is non-inferior to caspofungin in terms of 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 [DRC]) at Day 14 (±1 day) in the mITT population (EMA primary objective)

The secondary objectives of this study are to:

- Compare global cure (clinical cure as assessed by the Investigator, radiological cure [for qualifying invasive candidiasis subjects], and mycological eradication, as confirmed by the DRC) for subjects receiving Rezafungin for Injection and caspofungin at Day 5, Day 30 (-2 days), End of Treatment (EOT) (≤2 days of last dose), and Follow-up (Days 52-59) in the mITT population

- Compare mycological eradication for subjects receiving Rezafungin for Injection and caspofungin at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52-59) in the mITT population

- Compare clinical cure as assessed by the Investigator for subjects receiving Rezafungin for Injection and caspofungin at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52-59) in the mITT population

- Compare radiological cure for invasive candidiasis subjects receiving Rezafungin for Injection and caspofungin at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59) in the mITT population

- Compare the safety and tolerability for subjects receiving Rezafungin for Injection and caspofungin in the safety population

- Evaluate the pharmacokinetics of Rezafungin for Injection

An exploratory objective of this study is to:

- Compare resolution of systemic signs attributable to candidemia and/or invasive candidiasis for subjects receiving of Rezafungin for Injection and caspofungin at Day 5, Day 14 (±1 day), Day 30 (-2 days) and Follow-up (Days 52-59) in the mITT population.

1.2. Synopsis of Study Design

This is a Phase 3, multicenter, prospective, randomized, double-blind, efficacy and safety study of intravenous (IV) Rezafungin for Injection (laboratory code: CD101) versus an active comparator regimen of caspofungin (IV) followed by optional oral fluconazole step-down therapy in subjects with candidemia and/or invasive candidiasis (IC). Subjects will receive either IV Rezafungin for Injection or IV caspofungin, randomized in a 1:1 ratio. Subjects can be switched to oral step-down treatment by the Investigator after ≥3 days of IV treatment (or the minimum duration of IV therapy advised by the site's national/regional/local guidelines, whichever is greater) if they meet the oral step-down therapy criteria (as described in the Protocol Section 8.2.3.2).

Subjects randomized to receive Rezafungin for Injection:

> Subjects will receive a loading dose of Rezafungin for Injection 400 milligram (mg) in Week 1, followed by 200 mg once weekly for a total of 2 to 4 doses. To maintain the blind, subjects will also receive placebo for caspofungin IV, which will be administered on Days 2-7, Days 9-14 and during the optional dosing period on Days 16-21 and Days 23-28, or will receive daily placebo for oral step-down therapy (first eligibility on Day 4 or later as advised by a site's national/regional/local guidelines), which will be administered every day including rezafungin infusion days.

Subjects randomized to caspofungin:

> Subjects will receive a total treatment of ≥14 days beginning with a single caspofungin 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 advised by the site's national/regional/local guidelines, whichever is greater) of caspofungin treatment, subjects who meet the step-down therapy eligibility criteria may

be switched to oral fluconazole at a dose of 6 mg/kilogram (kg) (rounded to the nearest 200 mg increment) with a maximum dose of 800 mg (e.g., a subject weighing 73 kg would receive fluconazole 400 mg dose [2 capsules of 200 mg each] based on a 6 mg/kg target dose of 438 mg based on weight [73 kg × 6 mg/kg = 438 mg). NOTE: Refer to dosing section of protocol for alternative regimens of fluconazole in subjects with renal impairment). To maintain the blind, subjects in the caspofungin treatment group who have switched to oral step-down therapy will receive placebo for Rezafungin for Injection IV once weekly on the days of scheduled Rezafungin for Injection doses until study drug is stopped (on Day 8, Day 15 and Day 22 [if applicable]).

Subjects will complete an End of Treatment visit within 2 calendar days after the last dose of study drug and a Follow-up visit within the Day 52-59 period. Subjects who stop study drug prior to Day 22 and are considered clinical failures (i.e., require a change in antifungal therapy to treat candidemia and/or invasive candidiasis) may have their Follow-up visit earlier but the visit must still be ≥30 days following the last once weekly infusion of Rezafungin for Injection/placebo.

The study design diagram is provided in Appendix 1 (Section 5.1). The schedule of Assessments and procedures for the required treatment, End of Treatment, and Follow-up periods can be found in Appendix 2 (Section 5.2). The schedule of assessments and procedures for the optional treatment period dosing schedule is shown in Appendix 3 (Section 5.3). The dosing schedule by day can be found in Appendix 4 (Section 5.4).

Alternative caspofungin regimens and guidance for special populations (moderate hepatic impairment; subjects weighing >80 kg or on concomitant rifampin, nevirapine, efavirenz, phenytoin, dexamethasone, or carbamazepine; use of concomitant cyclosporine; or renal impairment) can be found in the protocol.

1.2.1. Randomization and Blinding

After informed consent has been obtained, subjects will be screened for study eligibility before randomization.

Subjects will be assigned a subject number and randomized (1:1) to receive either IV Rezafungin for Injection or IV caspofungin. The randomization will be stratified based on the following factors at Screening:

- diagnosis (candidemia only; invasive candidiasis) and
- 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 has a positive result for both blood culture/rapid in vitro diagnostic (IVD) and culture specimen obtained from a normally sterile site, the subject will be randomized to the invasive candidiasis stratum.

The study site's pharmacist (or pharmacist designee) will obtain the study drug assignment via an Interactive Response Technology (IRT). Randomized subjects will be assigned the study drug corresponding to the next available randomization number in the respective stratum from the computer-generated randomization schedule. A subject is considered randomized when the randomization transaction is recorded in the IRT.

All study personnel, including the Sponsor, Principal Investigator (PI), and site personnel involved in study conduct, and subjects will remain blinded to study medication assignment until the study is completed and the database is locked, except for the pharmacy monitor, unblinded program manager, clinical supplies, document manager, and quality (additional details are presented in the Sponsor Blinding Plan). The Pharmacy Monitor will monitor drug preparation and drug accountability during the study and cases in which unblinding is required due to a safety or tolerability issue. The Data and Safety Monitoring Board (DSMB) will be unblinded to safety data for safety reviews as defined in the DSMB Charter.

1.2.2. **Unblinding**

This study is a double-blind design. The PI, study personnel, and subjects will not make any effort to determine which study drug treatment is being received. Unblinded pharmacy personnel and an independent unblinded statistician for preparation of the DSMB report will be utilized in this study.

Unblinded data will be provided to the DSMB for the interim analyses of safety as detailed in the DSMB Charter. No interim unblinded data will be provided to the Sponsor. Only in the case of an emergency, when knowledge of the study drug treatment is essential for the clinical management or welfare of a specific subject, may the PI unblind a subject's study drug assignment. As soon as possible and without revealing the subject's study drug assignment (unless important to the safety of subjects remaining in the study), the PI must notify the Sponsor if the blind is broken for any reason. The PI will record in source documentation the date and reason for revealing the blinded study drug assignment for that subject.

As detailed in the country specific protocol amendment (A5-CN, 29Jan2021), there will be two database locks. The first database lock will occur after approximately 184 subjects in the mITT population have been randomized and completed the study (primary enrollment). The randomization of the last patient for the first database lock (for primary enrollment) occurred on Aug 16, 2021. After the database is locked and the SAP is final (for primary enrollment), the study blind codes for only subjects who were randomized on or prior to Aug 16, 2021 will be broken for completion of analysis and reporting. The Clinical Study Report (CSR) will be completed based on these data and analyses. Enrollment will be extended only in China and the second database lock will occur when recruitment and follow-up from this extended enrollment is complete. A SAP addendum will be completed and separate CSR for these subjects (from both primary and extended enrollment) will be written and will include separate analyses of subjects from China.

2. DEFINITIONS OF OUTCOME MEASURES

2.1. Primary Efficacy Outcome Measures

The primary efficacy outcome (for the FDA) is all-cause mortality (ACM) at Day 30 (-2 days), assessed for the mITT population. Subjects will be considered as meeting the ACM FDA endpoint at Day 30 if they have:

- a non-missing death date on the electronic case report form (eCRF), and
- study day for date of death is less than or equal to 30 days. Study Day 1 is defined as the first day of study drug administration. Subsequent study days are counted as the number of consecutive calendar days thereafter.

All attempts will be made to determine survival status at Day 30 and the Follow-up visit; subjects who complete Day 30 assessments on Day 28 or Day 29 (within the -2 days period) without further information thereafter will be considered alive at Day 30. If their status was "alive" on Day 28 or 29, and died at Day 30 their status will be "died". However, if it is unknown whether a subject is alive or deceased (and, subsequently, a death date is also not available), the subject will be considered deceased for the primary efficacy outcome. If it is known that the subject is deceased but only a partial death date is known, imputation rules for death date as outlined in Section 3.7 of this document will be followed. For the mITT population, the primary endpoint is calculated as the percentage of subjects that died out of the total number of subjects in the mITT population.

The primary efficacy outcome (for the EMA) is 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) in the mITT population. A DRC that is external to the sponsor will adjudicate global response. The committee will be comprised of physicians who will determine the outcomes of each subject in a blinded fashion. The DRC determination will be utilized to determine the primary efficacy outcome.

The DRC will assess global response and determine the responses as cure, failure and indeterminate. Subjects with missing data such that a response cannot be determined will be considered an indeterminate response. Since indeterminates are included in the denominator of the calculation of global cure success, these subjects are essentially failures. For the mITT population, the proportion of mITT subjects with a global cure success is defined using the following formula:

$$\frac{\text{Number of subjects with DRC global response = cure}}{\text{(Number of subjects with DRC global response = failure + DRC global response = indeterminate + DRC global response = cure)}}$$

All-cause mortality at Day 30 (-2 days) is a secondary outcome for the EMA and global cure at Day 14 (±1 day) as confirmed by DRC is a secondary outcome for the FDA.

2.1.1. Estimand Framework

An addendum to ICH E9 introduces the concept of an estimand which translates the trial objective into a precise definition of the treatment effect that is to be estimated. The description of the estimand includes four attributes: the population, the variable (or endpoint) to be obtained for each patient, the specification of how to account for intercurrent events (ICE), and the population-level summary for the variable. These attributes are described below for the FDA and EMA primary efficacy outcomes.

Table 2-1: Estimand Attributes

	ACM at Day 30 (FDA)	Global Response at Day 14 (EMA)
Population	mITT Population (see Section 2.6)	mITT Population (see Section 2.6)
Variable/Endpoint	Deceased by Day 30	DRC global response of cure
Handling of intercurrent events	Treatment policy estimand as measured irrespective of any ICE • Missing data considered deceased	Composite estimand as the following ICE's are incorporated into the variable/endpoint: • Death (failure) • Receipt of rescue therapy (failure) • Discontinuation of study drug due to an adverse event (failure) • Missing data (classified as indeterminate but analyzed as a failure)
Population-level summary	Difference between treatment groups in percentage of subjects who died	Difference between treatment groups in percentage of subjects with a DRC global response of cure

2.2. Secondary Efficacy Outcomes

All-cause mortality at Day 30 (-2 days) in the mITT population is a secondary outcome for the EMA, and global cure at Day 14 (± 1 day) in the mITT population is a secondary outcome for the FDA. Additional secondary efficacy outcome measures will be assessed in the mITT population and will include:

- **Global cure** (based on clinical cure as assessed by the Investigator, radiological response (for those subjects with invasive candidiasis documented by radiologic/imaging evidence

at baseline), and mycological eradication) at Day 5, Day 30 (-2 days), End of Treatment (≤2 days of last dose), and Follow-up (Days 52-59), confirmed by the DRC

- **Mycological eradication (programmatically derived)** at Day 5, Day 14 (±1 day), Day 30 (-2 days), End of Treatment (≤2 days of last dose), and Follow-up (Days 52-59)

- **Clinical cure as assessed by the Investigator** at Day 5, Day 14 (±1 day), Day 30 (-2 days), End of Treatment (≤2 days of last dose), and Follow-up (Days 52-59)

- **Radiological cure as assessed by the Investigator for invasive candidiasis subjects** at Day 5, Day 14 (±1 day), Day 30 (-2 days), End of Treatment (≤2 days of last dose), and Follow-up (Days 52–59)

2.2.1. Global Response

Global response is determined from the clinical response as assessed by the Investigator, radiological response (for those subjects with invasive candidiasis documented by radiologic/imaging evidence at baseline), and mycological response at Day 5, Day 14 (±1 day), Day 30 (-2 days), End of Treatment (≤2 days of last dose) and Follow-up (Days 52-59) as in **Table 2-2** and confirmed by the DRC. An independent blinded DRC will review subject data and confirm the determination of global response. The global response as determined by the DRC will be used for analysis. The role of the DRC and procedures for outcome determination are described in the DRC Charter.

Definitions for clinical response as assessed by the Investigator, mycological response and radiological response are included below in Section 2.2.3, Section 2.2.2 and Section 2.2.4 respectively.

Table 2-2: Global Response Categories

Global Response	Definition		
	Mycological Response	**Clinical Response as assessed by the Investigator**	**Radiological Response****
Cure	Eradication/Presumed Eradication*	Cure	Cure
Failure	Eradication/Presumed Eradication *	Cure	Failure
	Eradication/Presumed Eradication *	Failure	Cure, Failure or Indeterminate
	Eradication/Presumed Eradication *	Indeterminate	Failure
	Failure	Cure, Failure or Indeterminate	Cure, Failure or Indeterminate
	Indeterminate	Failure	Cure, Failure or Indeterminate
	Indeterminate	Cure	Failure
	Indeterminate	Indeterminate	Failure
Indeterminate	Eradication/Presumed Eradication *	Cure	Indeterminate
	Eradication/Presumed Eradication *	Indeterminate	Cure or Indeterminate
	Indeterminate	Cure	Cure or Indeterminate
	Indeterminate	Indeterminate	Cure or Indeterminate

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

** For those subjects with invasive candidiasis documented by radiologic/imaging evidence at baseline.

The global cure is the proportion of subjects with cure out of the total number of subjects in the specified analysis population.

If a subject discontinued the study medication prior to Day 14 and the global response at the EOT visit is failure, the global response at Day 14 for that subject is failure. If study drug was stopped early because the PI thought the subject was a clinical cure, the subject must be assessed during the Day 14 window. If the subject did not have the assessment, the global response for that subject at Day 14 is indeterminate.

2.2.2. Mycological response

Mycological response will be programmatically determined from the electronic case report form (eCRF) and central mycology data (or local mycology data if central is not available) at Day 5, Day 14 (±1 day), Day 30 (-2 days), End of Treatment, and Follow-up (Days 52-59), according to the definitions in Table 2-3.

Table 2-3: Mycological Response Definitions**

Mycological Response	Definition
Eradication*	• If positive blood culture at baseline: o The last blood culture drawn following the first dose of study drug on or prior to the day of assessments is negative • If positive culture from a normally sterile site at baseline (other than blood): o *Documented* mycological eradication: most recent culture on or prior to the day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is negative and culture was obtained after the initiation of study drug OR o *Presumed* mycological eradication: follow-up culture from all normally sterile sites of baseline *Candida* infection is not available (eg, 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 is positive, in a subject with a successful clinical outcome as assessed by the Investigator (ie, did not receive rescue antifungal treatment and has resolution of systemic signs and symptoms of invasive candidiasis that were present at baseline) **and** the subject has 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 is not lost to follow up on the day of assessment.

Mycological Response	**Definition**
Failure	• If positive blood culture at baseline: o The last blood culture drawn on or prior to the day of assessment is positive for *Candida* spp from a sample drawn following the first dose of study drug, OR • If positive culture from a normally sterile site at baseline: o *Documented* mycological persistence: culture on the day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is positive, OR o *Presumed* mycological persistence: follow-up culture from all normally sterile sites of baseline *Candida* infection is not available (eg, 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 is 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 requires a change of antifungal therapy to treat candidemia and/or invasive candidiasis***, OR • The subject dies of any cause prior to or on the day of assessment.
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • If positive blood culture at baseline: A post-baseline blood specimen was not available to culture or the result was not available. • If positive culture from a normally sterile site at baseline: A sterile site/fluid post-baseline specimen was not available to culture or the result was not available AND an assessment clinical response by the Investigator was not available or radiographic assessments are not available. • Subject is lost to follow-up on the day of assessment.

* Presumed eradication is defined only for a culture from a normally sterile site and is not defined for a blood culture.
**Table includes clarifications that are not in the protocol.
*** Defined as receipt of an antifungal with an indication of Candidemia/invasive candidiasis, Candida endophthalmitis/chorioretinitis or Candida endocarditis which started on or prior to the day of assessment or started on EOT (+ 1 day).

Documented evidence of IC at baseline is defined as having a radiologic test prior to the first dose of study drug that indicates new radiologic evidence of IC. Subjects who are diagnosed with IC by tissue/fluid culture whose first radiologic test is after the first dose of study drug are considered not to have a baseline radiologic test. In these subjects, radiology is not used to determine response.

Subjects who are diagnosed with candidemia at baseline (ie, prior to initiation of study drug) and progress to IC based on radiographic evidence or a tissue/fluid culture are considered to have IC for subsequent outcome assessments. The radiograph or tissue/fluid culture used to document progression is considered the baseline radiograph or tissue/fluid culture for outcome assessment.

The mycological eradication rate is the proportion of subjects with success (eradication/presumed eradication) out of the total number of subjects in the specified analysis population.

2.2.3. Investigator's Assessment of Clinical Response

The Investigator will make a determination of clinical cure at Day 5, Day 14 (±1 day), Day 30 (-2 days), End of Treatment (≤2 days of last dose), and Follow Up (Days 52-59) according to the definitions in **Table 2-4**.

Subjects whose disease is progressing or who receive rescue antifungal therapy for candidemia/IC prior to an assessment time point will be considered a clinical failure at the assessment time point and all subsequent time points. Subjects who do not have resolution of systemic signs and symptoms but are improving at the day of assessment are considered a clinical failure. As long as no rescue antifungal therapy for candidemia/IC was received, the subject may still qualify as a cure at future visits as long as they meet the criteria of clinical cure at those visits. For example, at Day 14 (±1 day) and Day 30 (-2 days), a subject who is on study drug can be a clinical cure if no rescue antifungal therapy for candidemia/IC was received and the subject meets the criteria of clinical cure even if they were assessed as a clinical failure at the Day 5 visit.

Table 2-4: 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 is alive.
Failure	• Progression or recurrence of attributable systemic signs or symptoms of candidemia and/or invasive candidiasis, OR • Lack of resolution of attributable systemic signs or symptoms of candidemia and/or invasive candidiasis, OR • Requirement for new systemic antifungal or prolonged therapy to treat candidemia and/or invasive candidiasis *, OR • An AE requires 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 are not available for the evaluation of efficacy for any reason including: o Lost to follow-up, o Withdrawal of consent, o Extenuating circumstances that preclude the classification of clinical outcome of candidemia and/or invasive candidiasis, o Assessment not done.

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

The clinical cure as assessed by the Investigator rate is the proportion of subjects with a cure out of the total number of subjects in the specified analysis population.

If a subject discontinued the study medication prior to Day 14 and the Investigator assessed response at the EOT visit is failure, the response at Day 14 for that subject is failure. If study drug was stopped early because the Investigator thought the subject was a clinical cure, the subject must be assessed during the Day 14 window. If the subject did not have the assessment, the response for that subject at Day 14 is indeterminate.

2.2.4. Radiological Response

Radiological response is defined in **Table 2-5**. Only subjects with invasive candidiasis, with radiologic or other imaging studies at baseline that demonstrate evidence of invasive candidiasis, should be assessed for this outcome. The radiologic response as assessed by investigator will be summarized.

Table 2-5: 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 is 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: o Lost to follow-up, o Withdrawal of consent, o Radiology/Imaging not completed o Extenuating circumstances that preclude the classification of a radiological outcome of invasive candidiasis

[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 documents evidence of invasive candidiasis.

The radiological cure rate as assessed by the Investigator is the proportion of subjects with a cure out of the total number of subjects with invasive candidiasis documented by radiologic/imaging evidence at baseline in the specified analysis population.

2.3. Exploratory Efficacy Outcomes

2.3.1. Resolution of Attributable Systemic Signs of Candidemia and/or Invasive Candidiasis that were Present at Baseline

It is a requirement that at least 1 systemic sign attributable to candidemia and/or IC be present at Screening for the subject to be eligible for enrollment. The Screening period for assessing systemic signs for inclusion in the study may include the 12 hours prior to the drawing of the qualifying positive culture (when systemic signs of infection resulted in obtaining blood cultures), qualifying positive culture from a sterile site, or qualifying rapid in vitro diagnostic, through enrollment. The possible signs of infection that might be attributable to candidemia and/or IC at baseline include fever, hypothermia, hypotension, tachycardia, tachypnea, and local signs of inflammation.

For the listed systemic signs of candidemia, the qualifying parameters are listed below:

Fever: Oral or axillary temperature ≥38°Celsius (C) [100.4°Fahrenheit (F)] or a tympanic, temporal, rectal, or core body temperature ≥38.3°C [101°F]

Hypothermia: Tympanic, temporal, rectal, or core body temperature ≤35°C [95.2°F]

Hypotension: Systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg with a normovolemic or hypervolemic status

Tachycardia: Heart rate >100 beats per minute with a normovolemic or hypervolemic status

Tachypnea: Respiratory rate >20 breaths per minute

Local signs of inflammation: Erythema, edema, heat and pain at the site of the qualifying culture

Resolutions of systemic signs will be programmatically categorized as follows:

- Yes (resolution): Resolution of all attributable systemic signs of candidemia and/or invasive candidiasis that were present at baseline and no new attributable systemic signs that were not present at baseline
- No (not resolved): New attributable systemic signs that were not present at baseline or lack of resolution of any attributable systemic signs of candidemia and/or invasive candidiasis that were present at baseline

Subjects whose assessment of systemic signs was not completed at a visit or at baseline for any reason (including death) will not be included in the analysis.

Resolution of systemic signs attributable to candidemia and/or invasive candidiasis for subjects receiving Rezafungin for Injection and caspofungin will be assessed at Day 5, Day 14 (±1 day), Day 30 (-2 days) and Follow-up (Days 52-59) in the mITT population.

2.3.2. All-Cause Mortality (ACM) through the FU Visit

All-cause mortality through the FU Visit (Day 59) is defined as death due to any cause from the date and time of first dose of treatment through the FU Visit. Subjects who did not die or died after Day 59 or are lost to follow-up will be censored in the analysis at the last date known to be alive or Day 59, whichever is earlier.

2.3.3. Time to First Negative Blood Culture

Time to first negative blood culture is defined in hours from the first dose of study drug to the first negative blood culture without subsequent positive cultures following the first pre-treatment blood culture confirmed positive for any *Candida* species. Blood culture results from both location 1 and location 2 need to be negative if the samples were taken from 2 locations on the same day. Subjects will be censored at the earliest start date and time of receipt of a new antifungal (i.e., other than study drug) for the treatment of candidemia received any time on/after the date and time of the first dose of study drug if it was used prior to having a negative blood culture. If a subject is lost to follow-up or died prior to having a negative blood culture, the subject will be censored at the date of the last blood culture. The details about the censoring rules under different scenarios are shown in the following table:

Blood Culture Result	Antifungal Use	Event (Negative Culture) or Censor	Event or Censoring Date
Negative blood culture without subsequent positive cultures	Not used or used after negative blood culture	Event	Earliest blood culture date with negative result
Negative blood culture obtained prior to first dose date and no subsequent positive cultures	Not used or used after negative blood culture	Censor	First dose date
No negative blood culture	Not used	Censor	Last blood culture date
No negative blood culture	Used	Censor	Earlier date between the last blood culture date and the antifungal start date

The number and percentage of subjects with a negative blood culture at 24 and 48 hours post first dose will also be provided by treatment group. The denominator will include subjects who were either not censored in the time to negative blood culture analysis or who were censored after 24 or 48 hours, respectively.

2.3.4. Clinical Outcomes by Baseline *Candida* species

The number and percentage of subjects who died by Day 30 (-2), were a global cure (as confirmed by the DRC) at Day 14 (±1), were a mycological eradication at Day 14 (±1 days),

were a radiological response (for subjects with invasive candidiasis documented by radiologic/imaging evidence) at Day 14 (±1 days) and were a clinical cure at Day 14 (±1 day) will be summarized by baseline *Candida* spp. and treatment group for subjects in the mITT population.

Mortality (Day 30 [-2]), global cure, mycological eradication, radiologic cure (for subjects with invasive candidiasis documented by radiologic/imaging evidence) and clinical cure by baseline *Candida* spp. and minimal inhibitory concentration (MIC) distribution for Rezafungin for Injection, caspofungin and fluconazole at Day 14 (-2) will be summarized by treatment group for subjects in the mITT population.

2.4. Health Outcome Measures

For subjects admitted to the Intensive Care Unit (ICU) on or after Study Day 1, the number of ICU admissions, the time to discharge for each admission and the total length of stay in the ICU across all admissions will be summarized by treatment group. The number and percentage of subjects re-admitted after discharge by Day 30 (-2 days) and by Follow-up (Days 52-59) will be presented by treatment group in the mITT population for all re-admissions, for re-admissions related to infectious disease and again for re-admissions related to Candidiasis.

2.5. Safety Outcome Measures

Safety will be assessed through the evaluation of adverse events (AEs), vital signs (temperature, heart rate, blood pressure, and respiratory rate), physical examinations (including neurological examinations), ECGs and clinical laboratory evaluations (hematology evaluations, chemistry panel, and urinalyses). Subjects will also be assessed at Screening and at the EOT visit, prior to Rezafungin for Injection dosing, with a thorough neurologic evaluation to assess for signs and symptoms of tremor, ataxia, and peripheral neuropathy. Adverse events will be graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) system version 5.0.

2.6. Population Definitions

The following analysis populations will be evaluated and used for presentation and analysis of the data:

- The intent-to-treat (ITT) population will include all randomized subjects.
- The safety population will include all subjects who received any amount of the study drug. Safety assessments will be performed on the safety population. Subjects who receive the wrong study drug for their entire course of study drug will be analyzed in the treatment group based on the drug received. Subjects who receive the wrong study drug for part of their course of study drug will be analyzed in the treatment group based on majority of (i.e., most frequent) doses received.
- The mITT population will include 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.

- The clinically evaluable (CE) population will include all subjects in the mITT population who also met inclusion criterion #4, did not meet exclusion criteria #1, #2, and #5, had a response other than indeterminate for both mycological and clinical response as assessed by DRC at Day 14 in the protocol specified window of Day 14 ± 1 day (subjects with invasive candidiasis documented by radiologic/imaging evidence also must have a radiological response by DRC other than indeterminate), and did not receive a concomitant antifungal that could confound the assessment of the global response at Day 14.

- The Pharmacokinetic (PK) population will include all subjects who received any amount of study drug and have at least one blood sample with measurable concentrations.

2.7. Protocol Deviations

Protocol deviations are collected from time of informed consent until the last study visit. Protocol deviations are defined as any variation from the protocol, including enrollment of a subject who did not meet all inclusion and exclusion criteria and failure to perform the assessments and procedures within the required time frame. Protocol deviations will be categorized into types of deviations (concomitant medication, inclusion/exclusion, informed consent, procedures/assessments, randomization, serious adverse event reporting and adverse events of special interest, study treatment administration/dispensing/compliance, and study visits) and classified as major or minor.

The Sponsor or designee will be responsible for producing the final protocol deviation file.

2.8. Subgroup analyses

Subgroup analyses will be conducted for the FDA and EMA primary efficacy endpoints. The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors. Additional subgroup analyses may be also be conducted.

The list of subgroups will be finalized prior to database lock but will include:

- Sex (male versus female)

- Race (white versus non-white and Asian versus non-Asian)

- Age category (<65 years versus ≥65 years)

- Geographic region (United States/South America, Europe/Israel/Turkey, Asia-Pacific (excluding China/Taiwan), China/Taiwan)

- Diagnosis at randomization (candidemia only versus IC)

- Final Diagnosis (candidemia only versus IC: progression from candidemia only to IC will be determined based on the radiological and/or tissue/fluid culture assessment through Day 14)

- APACHE II score/ANC at Screening (APACHE II score ≥20 OR ANC<500 cells/μL versus APACHE II score <20 AND ANC≥500 cells/μL)

- APACHE II score at Screening (≥20, <20, 10-19, <10)

- ANC at Screening (<500 cells/μL versus ≥500 cells/μL)

- Timing of culture used to document the *Candida* infection:

    - Positive culture at randomization definition 1: Subjects with a culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization, OR a culture from another normally sterile site obtained within 48 hours prior to randomization or within 72 hours after randomization; and

    - Positive culture at randomization definition 2: Subjects with a culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization, OR a culture from another normally sterile site obtained within 96 hours prior to randomization or within 72 hours after randomization

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The study is designed to show non-inferiority (NI) in the primary efficacy outcome of ACM at Day 30 (FDA) in the mITT population and global cure rate (EMA) at Day 14 following the first dose of test article in the mITT population. An NI margin of 20% will be used for the primary analyses. The NI margin was based on an analysis of studies where patients received no treatment or inadequate treatment, and the high unmet medical need in patients with candidemia and/or IC.

Sample size justification for the Primary Efficacy Outcome FDA (Day 30 ACM): For the FDA endpoint of ACM, assuming 85% of subjects will be evaluable for the mITT population, using a 20% NI margin, one-sided alpha of 0.025, an ACM rate of 20% in both treatment groups, 1:1 randomization, and the sample size methodology based on a continuity corrected Z-statistic, a total of 184 subjects in the mITT population provides 89.7% power to show NI.

Sample size justification for the Primary Efficacy Outcome EMA (Global cure): Using a 20% NI margin, one-sided alpha of 0.025, 80% power, 1:1 randomization, a global cure rate of 70% in both the Rezafungin for Injection and caspofungin groups, and the sample size methodology based on a continuity corrected Z-statistic, a total of 184 subjects (92 subjects in each treatment

group) are required in the mITT population. Assuming 85% of subjects will be evaluable for the mITT population, a total of approximately 218 subjects will be randomized.

Thus, a total of 218 randomized subjects provide sufficient power for the primary efficacy analyses for both the FDA and the EMA in the mITT population. A summary of the sample size calculations and assumptions is provided in the **Table 3-1** below:

Table 3-1: **Sample Size and Power Calculations**

	Primary Efficacy Outcome FDA (Day 30 ACM)	Primary Efficacy Outcome EMA (Global Cure)
Population	mITT	mITT
Outcome Rate	20%	70%
NI Margin	20%	20%
One-sided alpha	0.025	0.025
Power	89.7%	80%
Evaluability Rate	85%	85%
N	218	218

EMA = European Medicines Agency; FDA = United States Food and Drug Administration; mITT = modified intent-to-treat; N = total sample size.

3.2. General Methods

All tables, figures, and listings will be presented in landscape orientation in Courier New, 8-point font or higher, and will be incorporated into Microsoft Word, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Categorical parameters will be summarized using frequencies and percentages, while mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be used for continuous parameters.

Decimal precision will be as follows:

- Mean will contain one more decimal place than actual values.
- Median will contain one more decimal place than actual values.
- Standard deviation will contain two more decimal places than the actual values.
- 25th and 75th percentiles, minimum, and maximum will have the same precision as the actual values.

All statistical testing will be 2-sided and performed at the 0.05 level unless otherwise noted. Since no inferential testing will be conducted for secondary efficacy outcome measures, no adjustment is needed for multiplicity.

The first day of study drug administration will be Study Day 1. Subsequent study days are counted as the number of consecutive calendar days thereafter.

Individual subject listings of all data represented on the eCRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters. All data listings and tables displaying by-subject data that contain an evaluation date will display study day (Study Day).

If a safety laboratory result is reported relative to a lower/upper range of detection for an assay, for example "<10", the numeric portion of the result (10) will be used for statistical analyses and the full result, including any symbols, will be provided in the subject listings.

Sample sizes shown with summary statistics are the number of subjects with non-missing values. Where individual data points are missing, categorical data will be summarized based on reduced denominators (ie, only subjects with available data will be included in the denominators), unless otherwise specified.

Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The Kaplan-Meier curves will be presented by treatment group. The number of subjects at risk and number died in each treatment group will be displayed below the x-axis at day=0, 5, 14, 30, 55.

3.3. Computing Environment

All statistical analyses will be performed using SAS statistical software v9.4 or higher, unless otherwise noted.

The Analysis Data Model Version 2.1 (ADaM v2.1) and the ADaM Implementation Guide, Version 1.1 (ADaM IG v1.1) will be used for data standardization.

Medical history, concomitant procedures and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 21.0 or higher.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary March 2017 or higher.

3.4. Methods of Pooling Data

Data will be pooled across sites for all analyses.

3.5. Multiple Comparisons/Multiplicity

No adjustment for multiple comparison/multiplicity are to be used.

3.6. Withdrawals, Dropouts, Loss to Follow-up

Randomized subjects who are withdrawn or discontinue from the study will not be replaced.

3.7. Missing, Unused, and Spurious Data

The following rules for missing data will be followed:

- For the primary efficacy outcome measure of all-cause mortality for the FDA, subjects with a missing death date on the eCRF will be considered to have died. The subject's vital status will be determined using available sources such as the subject, the subject's contacts, hospital and other medical records and public records.
- For the primary efficacy outcome measure of global response for the EMA, subjects with a missing response are considered an indeterminate response and are included in the denominator for analyses in the mITT population.
- Adverse Event, Death Date and Prior/Concomitant Medication Date Imputations will follow the rules described in Appendix 7 Adverse Event and Prior/Concomitant Medication Date Imputations.
- The CTCAE grade and causality assessment for adverse events should not be missing (except in the case of a death reported only on the Survival Status eCRF which should be considered an adverse event of Death NOS) and will be queried for a value. Should there be missing data for adverse events other than Death NOS, adverse events with missing severity will be considered severe (Grade 3) and adverse events with missing causality will be considered related to study drug. For deaths from the Survival Status eCRF (and not on the Adverse Event eCRF), missing severity will be considered Grade 5 (death) and missing causality will be considered not related to study
- Unless otherwise specified, missing values for other individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentation.

3.8. Visit Windows

Study procedures should be completed within the windows provided in the Schedule of Assessments and Procedures in Appendix 2. Summaries of efficacy will be based on the nominal visits. Refer to Section 4.3 for the details.

Summaries of safety outcomes will be provided by Study Day based on the visit windows as specified in the protocol. The safety measurements taken outside the protocol specified visit windows will be considered as unscheduled visit measurements and will not be included in by-visit summaries but will be included in overall worst post-baseline summaries. If more than 1 measurement is available within the visit window, the following rules will be used:

- If there are measurements from both scheduled and unscheduled visits, the measurement taken on the scheduled visit will be used.
- If no scheduled visit is available, the earliest measurement in the window will be used.

Summaries of PK concentrations will be provided by nominal time points. For the "10 minutes prior to end of infusion" time point, this time point will be summarized if it is within -30 minutes prior to end of infusion and 10 minutes after end of infusion. No other time point windows will apply.

3.9. Interim Analyses

No interim analysis except for the safety data review by DSMB as stated below is planned.

3.9.1. Data and Safety Monitoring Board

An independent external DSMB will be established to review safety data. The DSMB will review safety data once when approximately 50% of subjects are randomized and as required for AEs of special interest while the study is ongoing as provided in the DSMB Charter. The DSMB will be comprised of clinicians and a statistician who are experienced in studies of fungal infections. A detailed charter will be developed, compliant with guidelines of the FDA and ICH that describes the roles and responsibilities of the DSMB, the timing of the meetings, as well as the data to be provided for review.

4. STATISTICAL ANALYSIS

4.1. Study Population

4.1.1. Analysis Populations and Subject Disposition

Each subject providing informed consent in the study will be accounted for. The number and percentage of subjects in each of the analysis populations will be summarized overall and by treatment group. The number and percentage of subjects prematurely withdrawing from the study and the primary reason for premature withdrawal (including withdrawal due to COVID-19) will be summarized overall and by treatment group for the ITT and mITT populations as will the number and percentage of subjects prematurely discontinuing treatment regimen and the primary reason for premature discontinuation (including withdrawal due to COVID-19). A separate listing will be provided for those subjects who sign informed consent but are not randomized (screen failures), including their specific reason for exclusion. The number and percentage of randomized subjects identified as failing to meet at least 1 inclusion criterion or meeting at least 1 exclusion criterion, and the specific inclusion criterion not met/exclusion criterion met, will be summarized by treatment group and overall, for the ITT population. A supportive by-subject listing will be generated for all inclusion criteria not met and exclusion criteria met.

Number of subjects in the mITT, and Safety populations will be summarized. A supportive by-subject listing will be generated for all randomized subjects indicating all analysis population assignments and any reason for exclusion from analysis populations (wherever applicable). Inclusions and exclusions from analysis populations will be finalized prior to Database lock and unblinding.

4.1.2. Protocol Deviations

The number and percentage of subjects with at least one, at least one minor and at least one major protocol deviation will be presented by treatment group and overall for the ITT population. The number and percentage of subjects with at least one major protocol deviation by type of deviation will be presented by treatment group and overall. A by-subject listing of all protocol deviations in the ITT population, with a flag for minor and major deviations by treatment group will be produced. All missed visits due to COVID-19 will be noted as protocol deviations and presented in the listing.

4.1.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics information including:

- sex, race, ethnicity, age at time of informed consent, female of child-bearing potential, age category (<65 year, ≥65 years)
- diagnosis at randomization (candidemia only, IC) and final diagnosis (candidemia only vs IC)
- Modified APACHE II score (≥20, <20, and within <20: 10-19, <10)
- diagnostic methodology used ≤96 hours before randomization (for positive *Candida* from blood culture, rapid IVD, gram stain positive for yeast from a specimen obtained from a normally sterile site, and culture specimen obtained from a normally sterile site)
- absolute neutrophil count at Baseline (<500/μL, ≥500/μL)
- absolute neutrophil count, modified APACHE II score and diagnosis at randomization (candidemia only, APACHE II ≥20 or ANC <500/μL; candidemia only, APACHE II score <20 and ANC ≥500/μL; IC, APACHE II ≥20 or ANC <500/μL; and IC, APACHE II score <20 and ANC ≥500/μL)
- height, weight, body mass index (BMI)
- estimated creatinine clearance (eCrCl, based on Cockcroft-Gault formula)
- Child-Pugh score category (<7, 7-9, and no history of liver disease)
- Geographic region (United States, Europe/Israel/Turkey, Asia-Pacific (excluding China/Taiwan), China/Taiwan, South America)

will be summarized by treatment group and overall in the ITT and mITT populations.

BMI (kg/m^2), calculated by dividing weight (kg) by height (m^2) will be captured in the eCRF.

The Cockcroft-Gault formula for eCrCl is:

$$eCrCl = \frac{[140 - Age\ (years)] \times [AIBW\ (kg)] \times [0.85\ if\ Female]}{72 \times [Serum\ Creatinine\ (mg/dL)]}$$

where AIBW (adjusted ideal body weight) = ideal weight + [0.4 x (actual weight (kg) – ideal weight]; ideal weight = [height (cm) – 152.4] x 0.9 + 45.5 + 4.5 (if male)

4.1.4. Medical and Surgical History

Medical and surgical history, including procedures recorded at screening and subjects diagnosed with COVID-19 at screening will be summarized by treatment group, system organ class (SOC), and preferred term (PT) using the latest version of MedDRA in the Safety and mITT populations. For this summary, subjects with more than 1 medical/surgical history within the same SOC or PT will be counted only once for that SOC or PT.

4.1.5. Candida Risk Factors

The number and percentage of subjects with each of the following risk factors at Screening will be summarized by treatment group in the ITT and mITT populations.

Risk factors for candidemia and IC include (but are not limited to):

- Central venous catheter
- PICC (Peripherally Inserted Central Catheter)
- Active malignancy
- Broad-spectrum antibiotic therapy
- Diabetes mellitus
- Immunosuppression
- Major surgery
- Total parenteral nutrition
- Transplant recipient
- Trauma
- End stage renal disease/ dialysis
- Burns

- Pancreatitis
- Other

For subjects who had a catheter and positive blood culture at Screening, a summary of the number and percentage of subjects by type of catheter will be provided. Descriptive statistics for the durations of catheter placement (any catheter and by type of catheter) since the catheter placement and since diagnosis (the first positive blood culture) will also be provided. The durations are defined as the number of days since the catheter placement or the number of hours since the first positive blood culture (if catheter was already in place prior to the first positive blood culture) to the catheter removal date and time. The catheters that were removed prior to the first positive blood culture are not included in the summary. If there is more than one catheter placed across multiple locations, the one with the longest duration is summarized. The number and percent of subjects who had their catheter removed within 48 hours after diagnosis with candidemia and subjects who did not have their catheter withdrawn will be summarized by treatment group in the mITT population. This analysis will be repeated for the subjects diagnosed with candidemia only in the mITT population.

4.1.6. Systemic Signs of Candidemia and/or IC

The number and percentage of subjects with each systemic sign at Screening determined to be attributed to candidemia and/or IC by the PI will be summarized by treatment group for subjects in the ITT and mITT populations. Signs include fever, hypothermia, hypotension, tachycardia, tachypnea, and local signs of inflammation. Symptoms include fatigue, pain and myalgia. If there are multiple assessments during Screening, the worst value for each sign or symptom will be used. A by-subject listing of systemic signs and symptoms assessed at Screening, Day 5, Day 14 (±1), Day 30 (-2), and the Follow-up visit, including the other clinical signs and symptoms reported on the eCRFs, and the PI determination of whether or not the sign/symptom is attributable to candidemia will also be provided.

4.1.7. Baseline Candida Pathogens

The number and percentage of subjects with blood or normally sterile tissue/fluid samples collected for culture ≤ 96 hours before randomization will be summarized by treatment group in the ITT population. The draw location and the result (growth of *Candida* or no growth of *Candida,* mutually exclusive) and timing of the most recent positive culture prior to randomization will be summarized by treatment group in the ITT population. The genus and species of *Candida* pathogens identified from baseline blood and sterile site cultures (all unique *Candida* species from the cultures collected within 96 hours before randomization or prior to the first dose of study drug after randomization) will be summarized by treatment group for subjects in the mITT population.

The number and percentage of subjects with the rapid diagnostic test performed will be summarized by treatment group in the ITT population, as well as the type of test, the results (positive or negative) and the *Candida* species.

For each baseline *Candida* species (defined as all unique *Candida* species from the cultures collected within 96 hours before randomization or prior to the first dose of study drug after randomization), a summary of the distribution of minimum inhibitory concentration (MIC) results from the central lab (or if not available, from the local lab) will be presented both by treatment group and for treatment groups combined for subjects in the mITT population in separate tables for each of Rezafungin for Injection, caspofungin, anidulafungin, micafungin, and fluconazole. In addition, for each baseline *Candida* species, the MIC_{50}, MIC_{90}, and MIC_{Range} for Rezafungin for Injection, caspofungin, fluconazole, anidulafungin, and micafungin will be summarized (MIC_{50} and MIC_{90} are presented only where there are at least 10 of a particular *Candida* species with susceptibility data available from the central mycology laboratory in each treatment group), will be summarized both by treatment group and for treatment groups combined for subjects in the mITT population. If there is more than 1 isolate of the same *Candida* species prior to first dose, the isolate that has the highest MIC to study drug received (i.e., the highest MIC to rezafungin for Rezafungin for Injection group, the highest MIC to caspofungin for Caspofungin group) is considered the baseline isolate.

A by-subject listing will be provided displaying all MIC results for any baseline *Candida* species that is resistant to echinocandins; a separate by-subject listing will be provided displaying all MIC and disk diffusion zone diameter results for any baseline *Candida* species that is resistant to fluconazole.

4.2. Extent of Exposure and Concomitant Procedures

4.2.1. Study Drug Exposure

Descriptive statistics for the duration of study drug therapy (IV and oral, and separately for IV therapy and oral therapy) will be summarized by treatment group for the mITT, and Safety populations.

Study drug duration is defined as the

date of the last dose of study drug - first dose of study drug + 1.

The number and percentage of subjects with 1–7, 8-14, 15-28 and >28 days of exposure as defined above will be presented for IV and IV and oral therapy combined. The number and percentage of subjects with 1–3, 4-7, 8-14, 15-28 and >28 days of exposure as defined above will be presented for oral therapy. Descriptive statistics will also be provided separately for the duration of IV therapy and the duration of oral therapy. The number and percentage of subjects switching to oral study drug therapy and a frequency distribution of the day of oral switch will be summarized by treatment group for the Safety and mITT populations.

A by-subject listing of all IV doses over time and a separate by-subject listing of the start and stop dates for oral therapy will be provided.

4.2.2. Prior and Concomitant Medications

The number and percentage of subjects who received prior and concomitant medications will be summarized by WHO drug anatomical therapeutic chemical (ATC) classification level 3 and PT.

Medications are considered prior if they are received prior to the first dose of study drug (start date and time [if applicable] is prior to the first dose of study drug) or if the start date is unknown. Medications are considered concomitant if they are received on or after the first dose of study drug (start date and time [if applicable] is on or after the first dose of study drug, stop date and time [if applicable] is after the first dose of study drug), or if the stop date is unknown or continuing. If the stop date is the same as the first dose date of study drug and the stop time is unknown, it will be assumed that the medication stopped prior to the first dose of study drug unless the medication start time is after first dose of study drug time. Date imputations will follow the rules described in Appendix 8 (Section 5.8).

The number and percentage of subjects who receive the following categories of prior and concomitant medications will be summarized by treatment group:

- Systemic antifungal medications received prior to the first dose of study drug (mITT population)
- Systemic antifungal medications (excluding study drug) received on/after the first dose of study drug through the Follow-up visit (mITT population)
- Non-antifungal medications received prior to the first dose of study drug (Safety population)
- Non-antifungal medications received on/after the first dose of study drug through the Follow-up visit (Safety population).

By-subject listings for non-antifungal medications and antifungal medications received prior to the first dose or administered after the first dose of study drug through the FU visit will be provided separately for the Safety population.

4.2.3. Concomitant Procedures

Concomitant procedures will be summarized by treatment group, SOC, and PT using the latest version of MedDRA in the mITT population. If the same procedure (based on PT) is reported for the same subject more than once, the procedure is counted only once for that PT. Procedures are considered concomitant if they are performed on or after the first dose of study drug (start date and time [if applicable] is on or after the first dose of study drug, stop date and time [if applicable] is after the first dose of study drug), or if the stop date is unknown or continuing.

A by-subject listing will display procedures on/after the first dose of study drug through the FU visit and will include the verbatim description of the procedure, MedDRA PT, reason for the procedure, and date and time of the procedure.

By-subject listings for transfusions and hemodialysis received prior to the first dose or after the first dose of study drug through the FU visit will be provided separately for the Safety population.

4.3. Analysis of Efficacy

Unless otherwise stated, all efficacy analyses will be conducted in the mITT population. Subjects will be analyzed in the treatment group to which they were randomized.

By subject listings of the primary and secondary efficacy outcomes will be provided.

4.3.1. Primary Efficacy Analysis

The analysis of the **primary efficacy outcome for the FDA** will be based on the mITT population.

The non-inferiority test will be a one-sided hypothesis test performed at the 2.5% level of significance. This non-inferiority test will be based on the upper limit of the two-sided 95% confidence interval (CI). The primary efficacy outcome is the percentage of subjects that died at Day 30.

The number and percentage of subjects in each treatment group that are alive and deceased (or with missing data) at Day 30 (-2 days) will be tabulated.

The null and alternative hypotheses are as follows:

$$H_0: p_1 - p_2 \geq \Delta, \text{ and}$$

$$H_1: p_1 - p_2 < \Delta,$$

where p_1 is the all-cause mortality rate at Day 30 (-2 days) in the Rezafungin for Injection treatment group, p_2 is the primary ACM at Day 30 (-2 days) rate in the caspofungin treatment group, and Δ is the non-inferiority margin of 20%.

To test the null hypothesis, a two-sided 95% CI for the observed difference in primary outcome rates (Rezafungin for Injection treatment group minus caspofungin treatment group) will be calculated for the mITT population using the unadjusted methodology of Miettinen and Nurminen (Miettinen and Nurminen, 1985). If the upper limit of the 95% CI for the difference in the mITT population is lower than 20%, then the null hypothesis will be rejected and non-inferiority of Rezafungin for Injection versus caspofungin will be declared.

To control the overall alpha level, superiority of rezafungin for ACM at Day 30 will be tested in the following order:

- If NI is declared for ACM at Day 30 in the mITT population and the rate of ACM at Day 30 in the rezafungin treatment group is lower than the caspofungin treatment group, the

difference between the treatment groups will be tested for superiority. If the upper bound of the 95% CI is less than 0, superiority of rezafungin will be concluded.

- For the subgroup of subjects with invasive candidiasis (final diagnosis), a two-sided 95% CI for the observed difference in the rate of ACM at Day 30 will be calculated using the unadjusted methodology of Miettinen and Nurminen. If superiority is declared in the mITT population for ACM at Day 30 and the rate of ACM at Day 30 in the rezafungin treatment group is lower than the caspofungin group for invasive candidiasis subjects, superiority of rezafungin will be tested. If the upper bound of the 95% CI is less than 0, superiority of rezafungin will be concluded.

The analysis of the **primary efficacy outcome for the EMA** will be based on the mITT population. The non-inferiority test will be a one-sided hypothesis test performed at the 2.5% level of significance. This non-inferiority test will be based on the lower limit of the two-sided 95% confidence interval (CI). The primary efficacy outcome is the percentage of subjects that have a global response of cure at Day 14 (±1 day) as confirmed by the DRC.

The number and percentage of subjects in each treatment group defined as global cure, failure and indeterminate will be tabulated, as will the overall category combining Failure and Indeterminate.

The null and alternative hypotheses are as follows:

$$H_0: p_1 - p_2 \leq -\Delta, \text{ and}$$

$$H_1: p_1 - p_2 > -\Delta,$$

where p_1 is the primary efficacy outcome rate in the Rezafungin for Injection treatment group, p_2 is the primary efficacy outcome rate in the caspofungin treatment group, and Δ is the non-inferiority margin of 20%.

To test the null hypothesis, a two-sided 95% CI for the observed difference in primary outcome rates (Rezafungin for Injection treatment group minus caspofungin treatment group) will be calculated for the mITT population. If the lower limit of the 95% CI for the difference in the mITT population exceeds –20%, then the null hypothesis will be rejected and the non-inferiority of Rezafungin for Injection to caspofungin will be declared.

To control the overall alpha level, superiority of rezafungin for global response will be tested in the following order:

- If NI is declared and the percentage of subjects that have a global response of cure at Day 14 (±1 day) as confirmed by the DRC in the rezafungin treatment group is higher than the caspofungin treatment group, the difference between the treatment groups will be tested for superiority. If the lower bound of the 95% CI is greater than 0, superiority of rezafungin will be concluded.

- For the subgroup of subjects with invasive candidiasis (final diagnosis), a two-sided 95% CI for the observed difference in global cure at Day 14 for the mITT population will be calculated using the unadjusted methodology of Miettinen and Nurminen. If superiority is declared for the EMA primary efficacy outcome of global response at Day 14 in the mITT population, and the global cure rate in the rezafungin treatment group is higher than the caspofungin group for invasive candidiasis subjects, superiority of rezafungin will be tested. If the lower bound of the 95% CI is greater than 0, superiority of rezafungin will be concluded.

A stratified 95% CI will be determined based on the two randomization strata: diagnosis (candidemia only; invasive candidiasis) and APACHE II score/ANC (APACHE II score ≥20 OR ANC<500 cells/µL; APACHE II score <20 AND ANC≥500 cells/µL) at Screening. If there are <5 subjects within a stratum and treatment group, or there is a 0 count within a stratum for a treatment group the categories will be combined. The 95% CI interval will be computed using the stratified methodology of Miettinen and Nurminen. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI as follows, where n_{1i} = number of subjects in Rezafungin for Injection treatment group in the ith stratum; n_{2i} = number of subjects in caspofungin treatment in the ith stratum:

$$W_i = \frac{n_{1i} n_{2i}}{n_{1i} + n_{2i}}.$$

The reasons for having a global response of failure or indeterminate at Day 14 (±1 day) will be presented using the number and percentage of subjects displayed by treatment group in the mITT population. Subjects who miss the efficacy assessment due to COVID-19 will have an indeterminate response and the number and percentage of subjects with an indeterminate response due to COVID-19 will be summarized.

Other subgroup analyses, including analyses by the pre-, peri- and post-COVID-19 period, will be conducted for descriptive purposes. Depending on the number of subjects in the study diagnosed with COVID-19, ACM at Day 30 and global response may be analyzed in patients with and without COVID-19.

4.3.1.1. Additional Analyses of the Primary Efficacy Outcomes

Sensitivity analyses of the primary outcome for FDA include:

- The first sensitivity analysis will exclude subjects whose survival status is not known (these subjects are considered deaths in the primary analysis).
- The second sensitivity analysis will calculate an adjusted (for the randomization stratification factors) 95% CI interval using the stratified methodology of Miettinen and Nurminen. As noted above, Cochran Mantel Haenszel weights will be used for the stratum weights in the calculation of the CI.
- The third sensitivity analysis will be conducted using multiple imputation for missing data. Missing primary outcome data will be imputed with multiple imputation. Fifty data sets will be created by treatment group using a logistic regression in which the randomization stratification factors of diagnosis (candidemia only; invasive candidiasis)

and APACHE II score/ ANC (APACHE II score ≥20 OR ANC<500 cells/μL; APACHE II score <20 AND ANC≥500 cells/μL) at Screening are included as predictive variables. The seed number of 101305 will be used. The difference in mortality rate is calculated per each imputed dataset and the risk differences are combined using proc mianalyze.

Sensitivity analyses of the primary outcome for EMA include:

- The first sensitivity analysis will consider indeterminate responses as successes.
- The second sensitivity analysis will present an unadjusted two-sided 95% CI for the observed difference in primary outcome rates (Rezafungin for Injection treatment group minus caspofungin treatment group) using the methodology of Miettinen and Nurminen.
- The third sensitivity analysis will analyze the primary outcome for the EMA in the CE population. The number and percentage of subjects with a global response of cure and failure will be provided along with an adjusted (for the randomization stratification factors) two-sided 95% CI for the difference in global cure rates.

4.3.2. Secondary Efficacy Outcomes

The secondary efficacy endpoints of clinical response as assessed by Investigator, mycological response (programmatically derived), radiological response (for subjects with invasive candidiasis documented by radiologic/imaging evidence at baseline) will be presented using the number and percentage of subjects with a response of cure (eradication for mycological response), failure, or indeterminate, displayed by treatment group in the mITT population at Day 5, Day 14 (±1 day), Day 30 (-2 days), End of Treatment (≤2 days of last dose), and Follow-up (Days 52-59).

The number and percentage of subjects with a global response of cure, failure, or indeterminate (confirmed by the DRC) will be presented by treatment group in the mITT population at Day 5, Day 30 (-2 days), EOT (≤2 days of last dose) and Follow-up (Days 52–59). 95% CIs for the treatment differences in global cure will be determined.

Treatment differences in secondary efficacy endpoints will be assessed using 95% CIs calculated at Day 5, Day 14 (±1 day), Day 30 (-2 days), End of Treatment (≤2 days of last dose), and Follow-up (Days 52-59). Two-sided 95% CIs will be constructed for the observed differences in the global cure, mycological eradication, radiologic cure and clinical cure rates using the method of Miettinen and Nurminen without stratification. The 95% CIs are for descriptive purposes only.

Analyses by diagnosis (candidemia only; invasive candidiasis) and APACHE II score/ ANC (APACHE II score ≥20 OR ANC<500 cells/μL; APACHE II score <20 AND ANC≥500 cells/μL) at Screening will also be provided.

4.3.3. Subgroup Analyses of the Primary Outcomes

Subgroup analyses of mortality through 30 days (-2 days) and global response at Day 14 (±1 day) will be performed to investigate the consistency of the treatment effects for different groups of subjects. Forest plots will be presented to visually assess the presence of treatment by subgroup interactions. All-cause mortality and global response at Day 14 (±1 day) will be assessed separately within the following subgroups in the mITT population: sex (male versus

female), race (white versus non-white and Asian versus non-Asian), age category (<65 years versus ≥65 years), geographic region (United States/South America, Europe/Israel/Turkey, Asia-Pacific (excluding China/Taiwan), China/Taiwan), final diagnosis (candidemia only versus IC), and APACHE II score/ANC at Screening (APACHE II score ≥20 OR ANC<500 cells/μL versus APACHE II score <20 AND ANC≥500 cells/μL), APACHE II score at Screening (≥20, <20, 10-19, <10), ANC at Screening (<500 cells/μL versus ≥500 cells/μL). All-cause mortality through 30 days (-2 days) and global response at Day 14 (±1 day) will also be summarized in the subgroups defined by timing of the culture used to document the *Candida* infection (positive culture at randomization definitions 1 and 2). This subgroup will not be included in the Forest plots.

For each subgroup, the number and percentage of subjects alive and deceased at Day 30 and the number and percentage of subjects with a global cure, failure and indeterminate response at Day 14 (±1 day) will be determined by treatment group. Two-sided 95% CIs for the observed difference in mortality rates and global cure rates will be calculated in the mITT population, using the unadjusted methodology of Miettinen and Nurminen.

4.3.4. Additional Efficacy Outcomes

Analyses for the additional efficacy endpoints will be performed using the mITT population.

Resolution of all systemic signs attributable at baseline to candidemia and/or invasive candidiasis for subjects receiving of Rezafungin for Injection and caspofungin at Day 5, Day 14 (±1 day), Day 30 (-2 days) and Follow-up (Days 52-59) will be presented by treatment group. This analysis will be repeated for subjects additionally with mycological eradication.

All-cause mortality at Follow-up will be presented for the mITT population by treatment group using frequencies and percentage of subjects that were alive and deceased at Follow-up. In addition, Kaplan-Meier (KM) methods will be utilized to analyze survival time in the mITT and ITT populations. The probability of being alive at Day 5, Day 14, Day 30, and Day 55 will be determined by treatment group. In addition, the 25^{th}, 50^{th} (median), and 75^{th} percentiles will be provided by treatment group. The number and percentage of subjects censored will be provided. KM survival curves will be provided. The number of subjects at risk and number died in each treatment group will be displayed below the x-axis at day= 0, 5, 14, 30, 55. Survival status will be provided in a by-subject listing.

The time to the first negative blood culture without subsequent positive culture from a sample drawn following the first dose of study drug will be summarized using KM methods for mITT population. The calculation will be in reference to the first dose date. For subjects who have negative blood culture prior to the first dose of study drug without subsequent positive culture, the time to the first negative blood culture will be set to zero. A log-rank test will be performed to test for differences in survival curves between treatment groups. Subjects will be censored if they receive an alternative antifungal (i.e., other than study drug) for the treatment of the candidemia, died or were lost to follow up prior to having the negative blood culture (see Section 2.3.3). KM survival curves will be provided. The 25^{th}, 75^{th} percentiles and the median survival time and 95% CIs will be determined by treatment group. This analysis will be repeated for the following subsets among the subjects with any post-baseline blood cultures: 1) Subjects with

positive culture at randomization definition 1 (defined in Section 2.8), 2) Subjects who did not receive systemic antifungal therapy prior to the first dose of study drug, 3) Subjects diagnosed with Candidemia only, and 4) Subjects diagnosed with Candidemia only with timing of positive culture at randomization definition 1 (defined in Section 2.8).

Results of blood culture, tissue/fluid culture from a normally sterile site, rapid diagnostic and radiological (and other imaging) testing will be provided in by-subject listings.

4.4. Analysis of Health Outcomes

The number and percentage of subjects admitted to the Intensive Care Unit (ICU) on or after Study Day 1 will be summarized by treatment group in the mITT population. For those subjects who did not die before hospital/ICU discharge, the time to discharge for each admission to hospital and to ICU will be generated and the longest length of stay for each subject will be summarized using descriptive statistics by treatment group in the mITT population. For subjects admitted to the hospital and to the ICU, the number of hospital/ICU admissions will be determined and the number and the percentage of the subjects with no ICU admission, 1 ICU admission, and 2 ICU admissions will be presented. In addition, for those subjects who did not die before hospital/ICU discharge, the total number of days in hospital, in ICU, and in general ward across all admissions will be determined. The total number of days in hospital is defined as the total number of days in hospital during the study period (i.e., if admission date is earlier than the first dose date, the number of days is defined as discharge date – first dose date +1; if admission date is on or later than first dose date, the number of days is defined as discharge date – admission date +1). The number of days from the initial admission and the one from re-admission (if applicable) will be summed to get the total number of days. For the subjects with missing hospital discharge date, the end of study date or the ICU discharge date, whichever is later, will be used for the discharge date. Descriptive statistics will be used to summarize the total number of days in hospital, in general ward, and for those admitted to the ICU, the total number of days in ICU, by treatment group in the mITT population. Similarly, the total number of days in hospital, in ICU, and in general ward at time of enrollment (defined as randomization date – admission date +1) will be summarized.

The number and percentage of subjects re-admitted to hospital and to ICU (re-admitted to ICU during initial hospitalization) after discharge by Day 30 (-2 days) and by Follow-up (Days 52-59) will be presented by treatment group for all subjects in the mITT population who were discharged from hospital, where the initial discharge date was on or after Study Day 1. Descriptive statistics will be used to summarize the time to first re-admission from the previous discharge date. The analysis will be repeated for re-admissions related to infectious disease and for re-admissions related to Candidiasis. Hospital admissions and re-admissions will be provided in by-subject listings

4.5. Analysis of Safety Data

All safety analyses will be conducted in the Safety population. Subjects who receive the wrong study drug for their entire course of study drug will be analyzed in the treatment group based on the drug received. Subjects who receive the wrong study drug for part of their course of study

drug will be analyzed in the treatment group based on majority of (i.e., most frequent) doses received.

4.5.1. Adverse Events

Verbatim descriptions of AEs will be coded using the latest MedDRA version (version 23.0 or higher). Summary tables will be provided for all treatment-emergent adverse events (TEAEs). A TEAE is defined as an AE that occurs during or after study drug administration and up through the Follow Up visit (Days 52-59). An AE is programmatically defined as treatment emergent if the start date and time is on or after the start date and time of the first dose of study drug. If the time of an AE is missing, it is considered treatment emergent if it starts on the same date as the first dose of study drug. Date Imputations will follow the rules described in Appendix 8 (Section 5.8).

Deaths obtained only through the Survival Status eCRF will not be recorded on the AE eCRF, but will be programmed as an AE with SOC and PT of "Death NOS" and analyzed as an AE/SAE with outcome of fatal.

An overall summary of AEs and TEAEs will include the number and percentage of subjects in each treatment group who experienced at least 1 AE/TEAE in the following categories: any AE, any TEAE, any TEAE up through Day 7, any study drug-related TEAE, any grade 4/5 TEAE, any serious AE (SAE), any study drug-related SAE, any SAE leading to death (that includes SAE started during study with an outcome of death that occurred after the Follow-up Visit), any study drug-related SAE leading to death, any TEAE resulting in interruption of administration of study drug, any TEAE leading to discontinuation of study drug, and any TEAE resulting in study discontinuation. The overall summary of AEs will be repeated for the high risk subgroups defined in Table 4-1.

Subjects with multiple events will be counted only once within each category. CTCAE grade (version 5.0) and relationship will be counted using the maximum grade and the strongest relationship respectively for a subject with multiple TEAEs.

The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by SOC and PT; by SOC, PT, and maximum CTCAE grade (1, 2, 3, 4, or 5); and by SOC, PT, and relationship (unrelated or related) to study drug. The incidence of TEAEs in each treatment group that occur up through Day 7 will be summarized by SOC and PT. The incidence of all TEAEs and all non-serious TEAEs that occur in at least 5% of subjects in the Rezafungin for Injection or caspofungin groups will be summarized separately by PT and treatment group, sorted by decreasing frequency in the Rezafungin for Injection group. The incidence of all TEAEs by SOC and PT will be also summarized by diagnosis (candidemia only versus IC) and by high risk subgroups defined in Table 4-1. For all analyses of TEAEs, if the same TEAE (based on PT) is reported for the same subject more than once, the TEAE is counted only once for that PT and at the highest grade and strongest relationship to study drug.

The number and percentage of subjects in each treatment group reporting a SAE, reporting a study drug-related SAE, reporting a TEAE resulting in interruption of study drug administration,

reporting a TEAE leading to discontinuation of study drug, and reporting a fatal SAE will be summarized by SOC and PT. In addition to a listing of all reported AEs, by-subject listings of all SAEs (including any SAEs with an outcome of death), AEs of special interest, and all TEAEs resulting in the alteration of or leading to discontinuation of study drug will be provided.

The number and percentage of subjects in each treatment group reporting a potential Drug Induced Liver Injury Adverse Events (DILI, Hepatic transaminase and Bilirubin elevations) will be presented. The following combination of Standardized MedDRA query (SMQ)/PTs will be used: Cholestasis and jaundice of hepatic origin (SMQ, broad), Liver related investigations, signs and symptoms (SMQ, broad), Liver-related coagulation and bleeding disturbances (SMQ, broad), Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ, broad), Hepatitis, non-infectious (SMQ, broad), Bilirubin conjugated (PT), Bilirubin urine (PT), Bilirubinuria (PT), Blood bilirubin (PT), Urobilinogen urine (PT), Urobilinogen faeces abnormal (PT), Urobilinogen faeces increased (PT), Urobilinogen faeces (PT).

Adverse Events of Special Interest (AESI)

All AEs will be reported, but certain adverse events of special interest will be specifically evaluated including but not limited to

- IV Infusion Intolerability Adverse Experiences
- Phototoxicity
- Ataxia, Neuropathy and Tremors (ataxia, axonal neuropathy, hypoesthesia, paresthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathies, peripheral sensorimotor neuropathy, polyneuropathy, toxic neuropathy, and tremors)

The number and percentage of subjects in each treatment group reporting AESI in the categories above will be reported. Additional analyses by higher risk subgroups might be considered. Higher risk subgroups that will be considered include but are not limited to:

Table 4-1: Higher Risk Subgroups

Elderly	≥65 years (yes/no)
Moderate hepatic impairment	Child-Pugh score of 7-9 (yes/no)
Higher weight	Baseline weight >80 kg (yes/no)
Neutropenia	(ANC<500, ANC≥500)
APACHE II score	(≥20, <20, 10-19, <10)
Diagnosis at Randomization	(candidemia only versus IC)

Subjects Diagnosed with COVID-19

Subjects diagnosed with COVID prior to entry into the study (based on medical history) or after the first dose of study drug (TEAE) will be presented in a listing with date of COVID-19 infection and outcome.

A table of TEAEs of coronavirus infection will be presented by PT and a listing of all TEAEs in subjects with diagnosed COVID-19 will be provided. Depending upon the number of subjects diagnosed with COVID-19, a summary of TEAEs by SOC and PT may be provided.

4.5.2. Clinical Laboratory Data

Several analyses of clinical laboratory data will be presented. For descriptive statistics of actual values and the change from baseline, values will be normalized against normal ranges from a common source (US National Library of Medicine [NLM], MedlinePlus) according to the following Scale Model formula (Karvanen, 2003): $s = x (U_s/U_x)$, where s = the individual laboratory value normalized against the laboratory normal range from the common source; x = the original individual laboratory value; U_x is the upper limit of the normal range for an individual laboratory parameter; U_s is the upper limit of the laboratory normal range for that laboratory parameter from the common source. WBC differentials in percent that are derived from the absolute counts will not be normalized because of the missing upper limit of the normal range in percent. For WBC differentials in percent with the non-missing upper limit, the maximum of the normalized values will be limited to 100%. Coagulation lab tests and urinalysis tests will not be normalized.

Descriptive statistics (based on Systeme Internationale [SI] units) for chemistry and hematology parameters, as well as the change from baseline, will be summarized by treatment group for all study visits and for the worst overall post-baseline value. The directionality for determining the worst overall post-baseline value is provided in Section 5.5. Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus the baseline value. If multiple values are obtained during the Screening period, the last non-missing values collected prior to the first dose of study drug will be used for the baseline.

The laboratory values will be graded using the CTCAE version 5.0. If no CTCAE grade is available, Division of Microbiology and Infectious Disease (DMID) or Division of AIDS (DAIDS) will be used for grading. Shift tables will be presented to show the number of subjects with each toxicity grade (1,2,3, or 4/5) at baseline versus each post-baseline visit and the worst post-baseline grade (including any unscheduled visits). For those laboratory parameters for which high toxicity grades are specified for both low and high values (e.g., sodium, potassium), shifts in toxicity will be presented for high and low toxicities separately. The percentages will be based on the number of subjects with both a baseline and post-baseline (at the specified visit) assessment of the specific laboratory parameter. The number and percentage of subjects with at least a 2-grade increase from baseline at any post-baseline study visit, including unscheduled visits, will be summarized by laboratory parameter and treatment group. Percentages for each lab test will be based on the number of subjects with both a baseline and a post-baseline evaluation of the particular laboratory test. A listing will be provided which provides all results for a given laboratory test for subjects who have at least one 2-grade increase from baseline.

Detailed subject listings of all laboratory data (including coagulation and urinalysis results) collected during the study will be provided. Laboratory values outside normal limits will be identified in the subject data listings. A column will display any applicable toxicity grading of the laboratory value. The results from pregnancy tests will also be listed.

Hepatic Safety Data

Hepatic effects (liver function test (LFT) abnormality) will be identified with selected adverse events (as defined in Section 4.5.1 [Adverse Events of Special Interest]), and the laboratory parameters: AST (aspartate aminotransferase), ALT (alanine aminotransferase), ALP (alkaline phosphatase) and TBL (total bilirubin).

Threshold values of interest for liver function tests are given below in **Table** 4-2: Criterion-based hepatic events

. The laboratory results meeting specified criteria standard table will be used to provide the number and percentage of patients having AST, ALT > 3, 5, 8, 10 x upper limit of normal (ULN) or TBL >1.5, 2 x ULN or ALP > 2, 3 x ULN and any other criteria specified in **Table** 4-2: Criterion-based hepatic events

at any time post-baseline regardless of their baseline value. For a combined criterion to be fulfilled, all conditions must be fulfilled on the same lab measurement.

The number and percentage of potential Hy's Law cases will be presented by treatment group. The criteria for Hy's law is: (ALT or AST) >3 ×ULN, ALP ≤2.0 ×ULN, and total bilirubin >2 ×ULN. A listing of subjects who meet either laboratory criteria for Hy's law will also be provided. Subjects meeting either criteria based on any combination of post-baseline laboratory results, irrespective of their temporal association, as well as subjects meeting the criteria at the same time point, will be listed. All laboratory results for the parameters included in the criteria will be presented by visit for all subjects who meet the criteria.

Table 4-2: Criterion-based hepatic events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN; >10xULN
AST	>3xULN; >5xULN; >8xULN; >10xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN
TBL	>1.5xULN; >2xULN
ALP	>2xULN; >3xULN
(ALT or AST) & TBL	ALT or AST >3xULN & TBL >2xULN ALT or AST >5xULN & TBL >2xULN ALT or AST >8x ULN &TBL >2xULN ALT or AST >10xULN & TBL >2xULN
(ALT or AST) & TBL & ALP	ALT or AST >3xULN & TBL > 2.0xULN & ALP <=2xULN (potential Hy's Law)

AST = Aspartate aminotransferase; also known as SGOT, ALT = Alanine aminotransferase; also known as SGPT, ALP = Alkaline phosphatase, TBL = Total bilirubin.

Nephrotoxicity

To evaluate the effect of Rezafungin for Injection on renal function, nephrotoxicity is defined as doubling of serum creatinine relative to baseline or an increase of ≥1 mg/dL in serum creatinine if baseline serum creatinine was above the upper limit of the normal range. The observed proportions of subjects with nephrotoxicity by visit and worst post-baseline value will be reported by treatment group.

4.5.3. Vital Signs

Descriptive statistics of the highest and lowest values at each visit and the highest and lowest value at any post-baseline visit (including unscheduled post-baseline measurements) will be summarized by study drug group for each vital sign parameter (heart rate, blood pressure, respiratory rate, and temperature).

The change from baseline to the highest and lowest values at each post-baseline visit and the highest and lowest value at any post-baseline visit (including unscheduled post-baseline measurements) will be provided for each vital sign parameter by treatment group. Change from baseline to the highest and lowest values at each post-baseline visit will be calculated for each subject and parameter as the highest or lowest value at the specified visit minus the baseline highest or lowest value. If multiple values are obtained during the Screening period, the last non-missing values collected prior to the first dose of study drug will be used for the baseline.

A summary of potentially clinically significant (PCS) values, identified as values meeting both the criterion value and the change from baseline criterion listed in **Table 4-3**, will be provided for the worst post-baseline value (which includes unscheduled post-baseline measurements). The incidence of PCS values will be summarized by treatment group for the worst post-baseline value and will be listed and flagged in by-subject listings.

For all analyses of temperature, temperatures obtained by non-oral methods of rectal or tympanic will be converted to oral temperatures by subtracting 0.3 °C from the temperature in °C. Temperatures obtained by temporal methods will be converted to oral temperatures by adding 0.3°C to the temperature in °C.

A by-subject listing of vital signs reported at each visit will be provided.

Table 4-3: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criterion Value	Change from Baseline
Systolic Blood Pressure (mm Hg)	High (CH)	≥180 mmHg	Increase of ≥20 mmHg
	Low (CL)	≤90 mmHg	Decrease of ≥20 mmHg
Diastolic Blood Pressure (mm Hg)	High (CH)	≥105 mmHg	Increase of ≥15 mmHg
	Low (CL)	≤50 mmHg	Decrease of ≥15 mmHg
Heart Rate (bpm)	High (CH)	≥120 bpm	Increase of ≥15 bpm

Vital Sign Parameter	Flag	Criterion Value	Change from Baseline
	Low (CL)	≤50 bpm	Decrease of ≥15 bpm
Temperature (°C)	High (CH)	>38°C	Increase of ≥1°C
	Low (CL)	≤36 °C	Decrease of ≥1°C
Respiratory Rate (breaths/minute)	High (CH)	≥30 breaths/minute	Increase of ≥10 breaths/minute
	Low (CL)	≤8 breaths/minute	Decrease of ≥4 breaths/minute

4.5.4. Electrocardiogram

Descriptive statistics of ECG parameters will be presented by treatment group and will include change from baseline. If multiple values are obtained during the Screening period, the last non-missing values collected prior to the first dose of treatment will be used for the baseline. QTcF is calculated using the formula: QTcF = QT (msec)/(RR in seconds)$^{1/3}$ where RR (sec) can be calculated from 60 divided by Heart rate (bpm). The number and percentage of subjects with the change from baseline QTcF >=30 msec and >=60 msec will be presented.

A by-subject listing of ECG parameters reported at each visit will be provided.

4.5.5. Physical and Retinal Examinations

Physical exam findings from Screening, Day 14 (±1), Day 30 (±2), End of Treatment (≤2 days of last dose), the Follow-up visit and unscheduled visits will be presented in a by-subject listing. Abnormal findings from retinal examinations and whether or not the subject had evidence of candida endophthalmitis or chorioretinitis will be provided in a by-subject listing. Signs and symptoms of tremor, ataxia and peripheral neuropathy determined from neurological examinations at Screening, End of Treatment (≤2 days of last dose) and unscheduled visits will be presented in a by-subject listing.

4.5.6. Neurological Questionnaires

Assessments of Chemotherapy-Induced Peripheral Neuropathy questionnaire (QLQ-CIPN20 version 3.0) and Scale for the Assessment and Rating of Ataxia (SARA, version date 13 Jun 2006) were conducted on patients enrolled prior to Protocol Amendment 3. Results from these two neurological questionnaires will be presented in by-subject listings.

4.6. PK Sampling

Blood samples will be collected from all subjects receiving study drug, although only PK samples from subjects receiving Rezafungin for Injection will be analyzed. Bioanalytical analysis will be performed by an independent, central bioanalytical laboratory using a validated assay.

Only samples taken within the timepoint windows will be included in summary statistics and evaluations of safety and efficacy by PK tertiles described below.

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Timepoint windows are defined as follows:

- Day 1, 10 Minutes before end of infusion (EOI): between 15 minutes prior to EOI and 5 minutes after EOI.
- Day 1, Between EOI and 12 Hours after EOI: between 5 minutes prior to EOI to 15 hours after EOI.
- DAY 2, 3, 4, or 5 Random Draw: any time
- DAY 8 PRE-DOSE: within 30 minutes prior to Day 8 infusion start
- DAY 14: any time.
- DAY 15 PRE-DOSE: any time on Day 15 prior to Day 15 infusion start
- DAY 22 PRE-DOSE: any time on Day 22 prior to Day 22 infusion start

Summary statistics (number of subjects, arithmetic mean, SD, coefficient of variation (CV%), median, minimum, maximum, tertiles, and geometric mean of plasma concentration) will be provided for the PK Population by timepoint mentioned above.

Timing of pharmacokinetic samples will be presented in a by-subject listing.

The FDA and EMA primary endpoints of all-cause mortality and global response, respectively, will be summarized by upper, mid, and lower tertiles of plasma concentration on Day 1 (10 minutes before the end of infusion) and on Day 8 (pre-dose) in the PK Population.

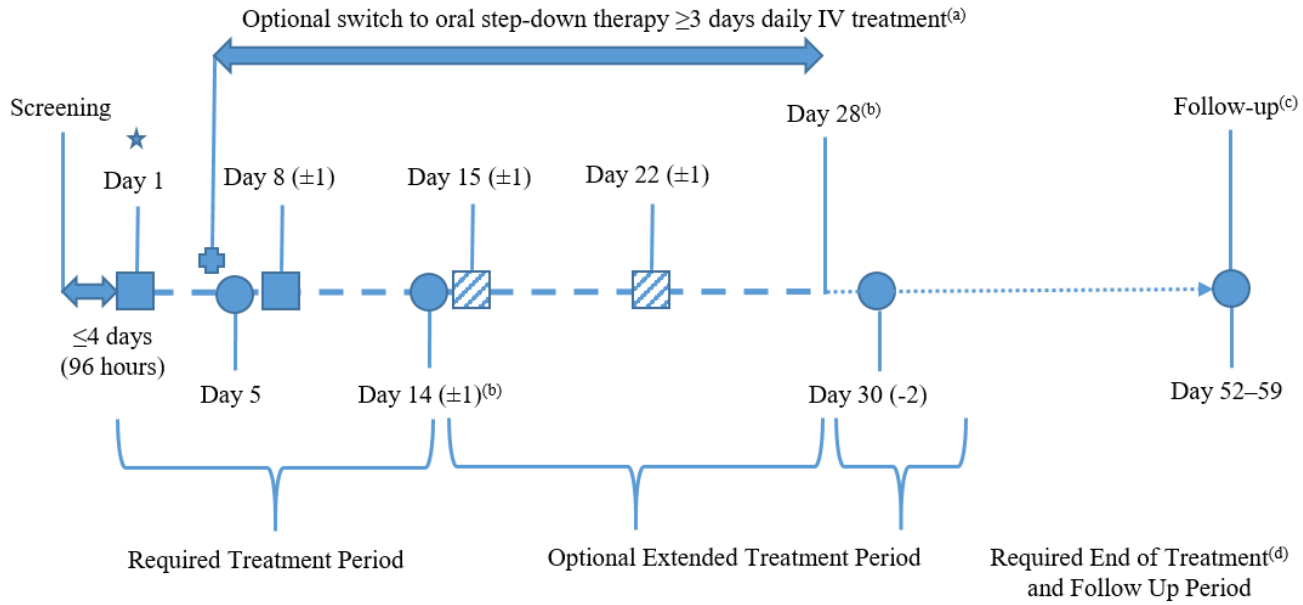
The number and percentage of any TEAE in the rezafungin group and any TEAEs occurring in >40% (by SOC and PT) will be summarized by upper, mid, and lower tertiles of plasma concentration on Day 1 (10 minutes before the end of infusion) and on Day 8 (pre-dose) in the PK Population

The following rules will be applied prior to summarizing if plasma concentration values that are below the limit of quantification (BLQ), or missing (e.g., no result [NR]):

- BLQ or NR values will be set to missing for summary purposes. Values that are BLQ will be displayed as “BLQ” in listings.
- If there are fewer than 3 values in the data series, only the minimum, maximum and n will be presented. The other summary statistics will be denoted as not calculated (NC).

5. APPENDICES

5.1. Appendix 1: Study Design Diagram



(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.

Time may vary w/in specified protocol limits

Randomization

Required Rezafungin for Injection or placebo IV

Optional switch to oral allowed

Optional Rezafungin for Injection or placebo IV

Daily caspofungin or placebo IV, or fluconazole or placebo oral

Efficacy assessments

Time off study drug

5.2. Appendix 2: Schedule of Assessments and Procedures for the Required Treatment, End of Treatment, and Follow-up Periods

	Screening	**Required Treatment Period (Days)**								**Day 30 (-2)**	**EOT**	**Follow-up** [c]
Assessment or Procedure	≤4 days (96 hours) before randomization	**1** [a]	**2**	**3**	**4**	**5–7**	**8 (±1)** [b]	**9–13**	**14 (±1)** [b]	Efficacy, Safety	≤2 days after last dose (IV or oral)	Days 52–59
Informed consent [d]	X											
Medical history [e]	X											
Physical examination, including weight and height [f]	X	X [g]	X [g]	X [g]	X [g]	X [h]	X [g]	X [g]	X	X	X	X
Neurological examination [h]	X	X [h]	X [h]	X [h]	X [h]	X [h]	X [h]	X [h]	X [h]	X [h]	X	X [h]
Vital signs [i]	X	X	X	X	X	X	X	X	X	X	X	X
Assess Central Venous Catheters [j]	X	X	X	X	X	X	X	X	X	X	X	
Blood for hematology and chemistry tests (see Appendix 3 of Protocol)	X	X	X		X		X		X	X	X	X
Blood for PT/INR (see Appendix 3 of Protocol)	X											

Assessment or Procedure	**Screening** ≤4 days (96 hours) before randomization	**Required Treatment Period (Days)**								**Day 30 (-2)** Efficacy, Safety	**EOT** ≤2 days after last dose (IV or oral)	**Follow-up** [c] Days 52–59
		1 [a]	**2**	**3**	**4**	**5–7**	**8 (±1)** [b]	**9–13**	**14 (±1)** [b]			
Calculate Child-Pugh score [k] (see Appendix 4 of Protocol)	X											
Calculate modified APACHE II with Glasgow coma score [l]	X											
12-lead ECG [m]	X	X										
Radiologic test results [n]	X	→								→	X	X
Urine for urinalyses, microscopy [o] (see Appendix 3 of Protocol)	X										X	
Serum pregnancy test [p]	X											X
Retinal examination for *Candida* eye infection [q]	X [r]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]
Blood or normally sterile tissue/fluid for culture [r, s]	X [r]	X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	X [s]
Blood for Rapid IVD [t]	X [t]											

Assessment or Procedure	**Screening** ≤4 days (96 hours) before randomization	**Required Treatment Period (Days)**								**Day 30 (-2)** Efficacy, Safety	**EOT** ≤2 days after last dose (IV or oral)	**Follow-up** [c] Days 52–59
		1 [a]	**2**	**3**	**4**	**5–7**	**8 (±1)** [b]	**9–13**	**14 (±1)** [b]			
Study randomization [u]		X										
Administer study drug and/or placebo (See Appendix 4)		X	X	X	X	X	X	X	X			
Record prior and/or concomitant medications [v]	X	→									X	X
Record adverse events [w]	X	→									X	X
Assess presence or absence of systemic signs of candidemia/ invasive candidiasis	X [x]					X [z]			X	X		X
Assess for clinical response [y]						X [z]			X	X	X	X
Assess for radiologic response[aa]						X			X	X	X	X
Assess ACM										X		X
Blood for PK testing [bb]	X [cc]	X [bb]	X [dd]	X [dd]	X [dd]	X [dd]	X [bb]		X [ee]			

Abbreviations: ACM = all-cause mortality; APACHE II = Acute Physiology and Chronic Health Evaluation II; ECG = electrocardiogram; eCRF = electronic case report form; EOT = End of Treatment; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; ICF = Informed Consent Form; ICH = International Council for Harmonisation; ICU = intensive care unit; IDSA = Infectious Diseases Society of America; IV = intravenous(ly); IVD = in vitro diagnostic; PCR = polymerase chain reaction; PI = Principal Investigator; PK = pharmacokinetic; spp. = species; PT/INR= Prothrombin Time/International Normalized Ratio.

[a] Study Day 1 is defined as the first day of study drug administration; subsequent study days are counted as the number of consecutive calendar days thereafter.

[b] Windows apply to subjects who are receiving oral step-down therapy on an outpatient basis or who are inpatient and are scheduled to be discharged by the next calendar day.

[c] Follow-up is to occur on Days 52–59. Subjects who stop study drug prior to Day 22 AND are considered clinical failures (i.e., require a change in antifungal therapy to treat candidemia and/or invasive candidiasis) may have their Follow-up visit earlier but must still be ≥30 days following the last once weekly infusion of Rezafungin for Injection/placebo (i.e., Day 1, Day 8, Day 15, or Day 22).

[d] Written informed consent must be obtained prior to initiating any study related assessments or procedures. Consent from a legally acceptable representative (i.e., acceptable to ICH and local law, as applicable) may be obtained if the subject is unable to consent for themselves.

[e] Medical history for the last 5 years and *Candida* risk factors for the last 3 months (e.g., central line, active malignancy, broad-spectrum antibiotic therapy, diabetes mellitus, immunosuppression, major surgery, total parenteral nutrition, transplant recipient, trauma, dialysis, burns, pancreatitis) and intensive care unit (ICU) admission and discharge (if applicable).

[f] Height at Screening only; weight at Screening, Day 14, and Follow-up (Days 52–59); all other assessments at specified visits.

[g] A focused physical exam (including a neurological exam) should be performed as clinically indicated by adverse event screening and course of the underlying disease.

[h] As part of the physical exam, a thorough neurologic exam is to be performed at Screening and at the EOT visit. At all other time points, a focused physical exam (including a neurological exam) is to be performed as clinically indicated, driven by the subject's signs and symptoms.

[i] Temperature and the method used [oral, rectal, temporal, tympanic, or core], heart rate, blood pressure, and respiratory rate. Axillary temperatures are allowed but not preferred.

[j] Presence of central line during Screening or placed during the study should be documented with dates of insertion and removal. Short-term central venous catheters (e.g., peripherally-inserted central catheters, internal jugular, or subclavian central venous catheters) and long-term central venous catheters (e.g., tunneled catheters) are recommended to be removed within 48 hours after diagnosis with candidemia, consistent with IDSA and ESCMID guidelines.

[k] Child-Pugh score is only required for subjects with a history of chronic cirrhosis.

[l] APACHE II score is a stratification factor for randomization and must be calculated prior to enrollment using vital signs and laboratory results from Screening. If multiple vital signs and laboratory values are obtained during the Screening period, it is preferred to use those collected most closely to the time of randomization. See Appendix 5 of Protocol for APACHE II and Appendix 6 of Protocol for Glasgow coma score.

[m] 12-lead ECG must be conducted prior to randomization and at any time on Day 1 following administration of study drug (i.e., post-end IV infusion).

[n] Radiologic test type with findings and interpretation should only be recorded if the test provides evidence of invasive candidiasis or evidence of progression, stabilization, improvement, or resolution of invasive candidiasis compared with previous radiographs.

[o] While potentially indicative of disease, a positive urine culture for *Candida* spp. may not be used as the qualifying culture for entry into the study, though the presence of a positive urine culture is not a reason to exclude a patient from participation in the study. Subjects who are anuric do not require a urinalysis.

[p] Serum pregnancy test required only for women of childbearing potential; do not perform for women ≥2 years postmenopausal or surgically sterile.

[q] A retinal examination for evidence of a *Candida* eye infection, including endophthalmitis or chorioretinitis, should be performed in all subjects with candidemia during Screening when possible, although the exam may occur as late as Day 7. Retinal examination is standard of care for subjects with candidemia and should be performed by an ophthalmologist, when available. The retinal examination should be repeated in subjects who were negative at baseline if the subject develops visual signs or symptoms of a *Candida* eye infection during the study. Additionally, any neutropenic subjects who recover their neutrophil counts during the study should have an additional retinal examination. Subjects who were negative at baseline and diagnosed with a *Candida* eye infection after initiating study drug must discontinue study drug but may continue in the study at the Investigator's discretion (see Section 7.4.2 of Protocol).

[r] A culture must be obtained as part of the standard of care for inclusion in the study. Established mycological diagnosis of candidemia or invasive candidiasis from a sample taken ≤4 days (96 hours) before randomization defined as: ≥1 blood culture positive for yeast or *Candida*, a positive test for *Candida* from sponsor-approved rapid IVD, or 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. If the positive blood culture used to qualify the subject for the study is drawn >12 hours prior to randomization, an additional set of blood cultures must be obtained ≤12 hours before randomization. Identification and susceptibility testing at the local laboratory for *Candida* for blood or normally sterile tissue/fluid for culture is required at Screening and for any positive culture requiring a change of antifungal therapy (i.e., local identification and susceptibility testing is not required for *Candida* isolates cultured from specimens on other study days provided there is no required change of antifungal therapy).

[s] Specimens for culture for demonstration of efficacy, or when clinically indicated. Blood cultures should be repeated daily (preferred) or every other day until the first negative blood culture result for *Candida* spp. with no subsequent positive culture (in cases when one or more samples are drawn and cultured after the first negative culture is available). All fungal isolates cultured from blood and normally sterile tissue/fluid from Screening through Follow-up must be sent to the Central Laboratory. Record the spp for any new bacteria isolated from blood and the spp and susceptibilities for any new bacteria isolated from any other normally sterile site.

[t] Sponsor-approved rapid IVDs are allowed to fulfill Inclusion Criteria #3 for entry into the study. However, a culture from blood or another normally sterile site obtained during the Screening period must be positive for *Candida* spp. for the subject to be eligible for the mITT population. Currently approved rapid IVDs include the T2Candida panel and the Septifast PCR test.

[u] Confirm all inclusion and exclusion criteria are met prior to randomization.

[v] Record all prior and/or concomitant medications from Screening through Follow-up. All systemic antifungal therapy administered within 4 weeks and all non-antifungal therapy administered within 1 week prior to randomization will be documented and recorded in the eCRF. Subjects who received systemic treatment with an antifungal agent at approved doses for treatment of candidemia for >48 hours before randomization will be excluded from the study.

[w] Adverse events are collected from the time the ICF is signed at Screening through Follow-up.

[x] The Screening period for assessing systemic signs of candidemia/ invasive candidiasis for inclusion in the study may include the 12 hours prior to the collection of the qualifying positive blood culture, when systemic signs of infection were the reason for specimen collection (blood culture or fluid from a sterile site culture or qualifying rapid IVD [e.g., T2Candida Panel]), through study randomization.

[y] Clinical response is assessed by the PI. Criteria for cure, indeterminate, and failure responses are found in **Table** 2-4: Investigator's Assessment of Clinical Response Definitions

[z] .

[aa] Assessment to be performed on Day 5 (i.e., not required for Day 6 and Day 7).

[bb] Subjects diagnosed with invasive candidiasis with evidence of deep tissue disease by radiology or other imaging should have follow-up imaging to demonstrate progression, stabilization, improvement, or resolution of disease. Improvement or resolution of disease by imaging would indicate radiological cure, while stabilization or progression of disease by imaging would indicate radiological failure. Missing imaging following baseline evidence of invasive candidiasis will result in an indeterminate response. Criteria for cure, indeterminate, and failure responses are found in Table 2-4.

[cc] Blood samples for PK analysis will be collected from the OPPOSITE arm of the infusion or through an arterial line during the infusion; after the infusion is complete, opposite arm or arterial line draws are preferred but not mandatory. Blood samples will be collected as follows: On Day 1, 10 minutes before the end of infusion, and one sample taken anytime between end of infusion and 12 hours after the end of infusion; Day 2, 3, 4, or 5, one sample taken at any time on one day only; Day 8, pre-dose; Day 14 (for subjects not receiving a Day 15 dose), one sample taken at any time; Day 15, pre-dose (if applicable); Day 22, pre-dose (if applicable). Note: Pre-dose samples should be collected ≤30 minutes prior to the start of the infusion. For subjects receiving hemodialysis, an attempt should be made to obtain PK samples directly following hemodialysis if still within the required time window.

[dd] **Only for subjects enrolled prior to Amendment 5:** Blood samples will be obtained at any time during Screening (one blood sample for protein binding and one blood sample for albumin core analyses). To limit invasive procedures these samples would ideally be collected at the same time into two vacutainers, though each sample could be collected separately.

[ee] One blood sample for PK will be collected at any time on one of the following Days 2, 3, 4, or 5 (i.e., if blood sample for PK not collected on Day 2 or must be collected on Day 3 (or Day 4 or Day 5).

[ff] Day 14 draw is only for subjects completing treatment on Day 14 and should be drawn at the same time as Day 14 hematology and chemistry blood draws (i.e., random PK draw).

5.3. Appendix 3: Schedule of Assessments and Procedures for the Optional Treatment Period

	Optional Treatment Period (Days)				EOT	Follow-up
Assessment or Procedure	**15 (±1)**	**16–21**	**22 (±1)**	**23–28**	≤2 days after last dose (IV or oral)	Days 52–29
Physical examination	X	X [a]	X	X [a]	See Appendix 5.2	See Appendix 5.2.
Neurological examination [b]	X [b]	X [b]	X [b]	X [b]		
Vital signs [c]	X	X	X	X		
Blood or normally sterile tissue/fluid for culture, if clinically indicated [d]	X	X	X	X		
Radiologic test results [e]	→	→	→	→		
Administer study drug and/or placebo (See Appendix 4)	X	X	X	X		
Record concomitant medications [f]	→	→	→	→		
Record adverse events [g]	→	→	→	→		
Blood for PK testing [h]	X		X			
Assess Central Venous Catheters [i]	→	→	→	→		

Abbreviations: EOT = End of Treatment; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; ICF = Informed Consent Form; IDSA = Infectious Diseases Society of America; PK = pharmacokinetic.

[a] A focused physical exam (including a neurological exam) should be performed as clinically indicated by adverse event screening and course of the underlying disease.

[b] As part of the physical exam, a thorough neurologic exam is to be performed at Screening and at the EOT visit. At all other timepoints, a focused physical exam (including a neurological exam) is to be performed as clinically indicated, driven by the subject's signs and symptoms (see Appendix 1 of Protocol).

[c] Temperature and the method used [oral, rectal, temporal, tympanic, or core], heart rate, blood pressure, and respiratory rate. Axillary temperatures are allowed, but not preferred.

[d] Cultures from blood or other normally sterile locations only if clinically indicated. Identification and susceptibility testing at the local laboratory for *Candida* for blood or normally sterile tissue/fluid for culture for any positive culture requiring a change of antifungal therapy (i.e., local identification and susceptibility testing is not required for *Candida* isolates cultured from specimens on other study days provided there is no required change of antifungal therapy). All fungal isolates must be sent to the Central Laboratory.

[e] Radiologic test type with findings and interpretation should only be recorded if the test provides evidence of invasive candidiasis or evidence of progression, stabilization, improvement, or resolution of invasive candidiasis compared with previous radiographs.

[f] Record all concomitant medications from Screening through Follow-up (Days 52–59). Systemic antifungal therapy is especially important to document.

[g] Adverse events are collected from the time the ICF is signed at Screening through Follow-up (Days 52–59).

[h] Blood will be collected pre-dose (≤30 minutes prior to the start of the infusion).

[i] Presence of central line during Screening or placed during the study should be documented with dates of insertion and removal. Short-term central venous catheters (e.g., peripherally-inserted central catheters, internal jugular, or subclavian central venous catheters) and long-term central venous catheters (e.g., tunneled catheters) are recommended to be removed within 48 hours after diagnosis with candidemia, consistent with IDSA and ESCMID guidelines.

5.4. Appendix 4: Dosing Schedule by Day

Study Day Regimen [a]	Randomized Treatment	
	Rezafungin for Injection	**Caspofungin [b] with Oral Step-Down Option**
1	Rezafungin for Injection 400 mg IV	caspofungin 70 mg IV (loading dose)
2–3	placebo for caspofungin IV	caspofungin 50 mg IV
≥3	**Optional switch to oral step-down therapy allowed [c]**	
4–7		
IV only	placebo for caspofungin IV	caspofungin 50 mg IV
oral step-down	placebo for oral step-down therapy	oral step-down therapy (fluconazole)
8 (±1)		
IV only	Rezafungin for Injection 200 mg IV	caspofungin 50 mg IV
oral step-down	Rezafungin for Injection 200 mg IV **-and-** placebo for oral step-down therapy	placebo for Rezafungin for Injection IV **-and-** oral step-down therapy (fluconazole)
9–14		
IV only	placebo for caspofungin IV	caspofungin 50 mg IV
oral step-down	placebo for oral step-down therapy	oral step-down therapy (fluconazole)
15–28	**Optional treatment period begins. An End of Treatment visit is required within 2 calendar days after the last dose of study drug.**	
15 (±1)		
IV only	Rezafungin for Injection 200 mg IV	caspofungin 50 mg IV
oral step-down	Rezafungin for Injection 200 mg IV **-and-** placebo for oral step-down therapy	placebo for Rezafungin for Injection IV **-and-** oral step-down therapy (fluconazole)
16–21		
IV only	placebo for caspofungin IV	caspofungin 50 mg IV
oral step-down	placebo for oral step-down therapy	oral step-down therapy (fluconazole)
22 (±1)		
IV only	Rezafungin for Injection 200 mg IV	caspofungin 50 mg IV
oral step-down	Rezafungin for Injection 200 mg IV **-and-** placebo for oral step-down therapy	placebo for Rezafungin for Injection IV **-and-** oral step-down therapy (fluconazole)
23–28		
IV only	placebo for caspofungin IV	caspofungin 50 mg IV
oral step-down	placebo for oral step-down therapy	oral step-down therapy (fluconazole)

Abbreviation: CRRT = continuous renal replacement therapy; IV = intravenous(ly).

[a] IV only regimen means the subject has not been switched to oral step-down therapy by the Investigator. Oral step-down regimen means the subject has been switched to oral step-down therapy by the Investigator.

[b] Refer to dosing section for alternative regimens of caspofungin in subjects meeting hepatic impairment criteria or weight category criteria, and/or are receiving certain concomitant medications.

[c] Oral step-down therapy is as follows: Subjects weighing over 130 kg will not be eligible for oral step-down therapy. Subjects with a creatinine clearance >50 mL/min will receive 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. Subjects with creatinine clearance ≤50 mL/min will receive oral fluconazole at a dose of 3 mg/kg administered once daily rounded to the nearest 200 mg increment with a maximum daily dose of 400 mg. Subjects receiving hemodialysis receive the same dose as subjects with a creatinine clearance >50 mL/min; however, they are only dosed following hemodialysis. Subjects receiving CRRT should be treated as a subject with normal renal function at 6 mg/kg rounded to the nearest 200 mg each day (Cousin 2003). Subjects receiving peritoneal dialysis should be treated with 1.5 mg/kg rounded to the nearest 200 mg each day (Cousin 2003).

Investigators are advised to pay close attention to signs of overdosing and underdosing with underweight (<50 kg) and overweight (>85 kg) subjects, respectively. Additionally, signs of potential fluconazole toxicity, including hepatic toxicity and QT prolongation, should be closely monitored for any subject on oral step-down therapy.

5.5. Appendix 5: Directionality of Worst Laboratory Parameters

Table 5-1: Directionality of Worst Laboratory Parameters

Laboratory Test	Parameter	Worst Value
Hematology	Hemoglobin	Lowest value
	Hematocrit	Lowest value
	White blood cell count	Both highest value and lowest value
	Neutrophils	Both highest value and lowest value
	Lymphocytes	Both highest value and lowest value
	Monocytes	Both highest value and lowest value
	Eosinophils	Highest value
	Basophils	Highest value
	Red blood cell count	Lowest value
	Platelets	Both highest value and lowest value
Chemistry	Blood urea nitrogen (BUN)	Highest value
	Bilirubin (total and direct)	Highest value
	Alkaline phosphatase (ALP)	Highest value
	Aspartate aminotransferase (AST/SGOT)	Highest value
	Alanine aminotransferase (ALT/SGPT)	Highest value
	Albumin	Lowest value
	Sodium	Both highest value and lowest value
	Potassium	Both highest value and lowest value
	Chloride	Both highest value and lowest value
	Glucose	Both highest value and lowest value
	Creatinine	Highest value
	Total protein	Both highest value and lowest value
	Calcium	Both highest value and lowest value
	Bicarbonate	Both highest value and lowest value
	Magnesium	Both highest value and lowest value

5.6. Appendix 6: Clinical Laboratory Toxicity Grading Scales

Laboratory toxicity grades will be derived based on the available numeric criteria only without taking the clinical components into consideration.

Table 5-2: Hematology Toxicity Grading Scale

Hematology							
Parameter	**Direction**	**Grade 0 / Normal**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemoglobin	Decrease	≥LLN	<LLN-10.0 g/dL	<10.0-8.0 g/dL	<8.0 g/dL	Life Threatening	Death
Leukocytes	Increase*	<11,000/mm^3	11,000-13,000 /mm^3	>13,000-15,000 /mm^3	>15,000-30,000 /mm^3	>30,000 /mm^3	-
	Decrease	≥LLN	<LLN-3000/mm^3	<3000-2000/mm^3	<2000-1000/mm^3	<1000/mm^3	-
Absolute Neutrophil Count	Decrease	≥LLN	<LLN to 1500/mm^3	<1500 to 1000/mm^3	<1000 to 500/mm^3	<500/mm^3	-
Platelets	Decrease	≥LLN	<LLN to 75,000/mm^3	<75,000 to 50,000/mm^3	<50,000 to 25,000/mm^3	<25,000/mm^3	-
*DMID							

Table 5-3: Chemistry Toxicity Grading Scale

Chemistry							
Parameter	**Direction**	**Grade 0 / Normal**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blood urea nitrogen (BUN)*	Elevation	<1.25 ×ULN	1.25-2.5 ×ULN	>2.5-5 ×ULN	>5-10 ×ULN	>10 ×ULN	-
Bilirubin (total and direct)	Elevation	≤ULN	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0-10.0 xULN	>10.0 x ULN	-
Albumin	Hypoalbuminemia	≥LLN	<LLN-3 g/dL	<3-2 g/dL	<2 g/dL	Life-threatening consequences ; urgent intervention indicated	Death
Sodium	Hyponatremia	≥LLN	<LLN-130 mmol/L	-	<130-120 mmol/L	<120 mmol/L	Death
	Hypernatremia	≤ULN	>ULN-150 mmol/L	>150-155 mmol/L	>155-160 mmol/L	>160 mmol/L	Death
Potassium	Hypokalemia	≥LLN	<LLN – 3.0 mmol/L	<LLN-3.0 mmol/L; symptomatic; intervention indicated	<3.0-2.5 mmol/L	<2.5 mmol/L	Death
	Hyperkalemia	≤ULN	>ULN – 5.5 mmol/L	>5.50-6.0 mmol/L	>6.0-7.0 mmol/L	>7.0-mmol/L	Death
Glucose (non-fasting)	Hypoglycemia	≥LLN	<LLN-55 mg/dL	<55-40 mg/dL	<40-30 mg/dL	<30 mg/dL; Life threatening consequences; seizures	Death
	Hyperglycemia**	<116 mg/dL	116 -160 mg/dL	>160-250 mg/dL	>250-500 mg/dL	>500 mg/dL	Death
Chloride	Not Available						
Creatinine	Elevation	≤ULN	>ULN -1.5 ULN	>1.5-3.0 x baseline: >1.5-3.0 x ULN	>3.0 baseline; >3.0 – 6.0 x ULN	>6.0x ULN	-

Total protein	Not Available						
Calcium (corrected for albumin)***	Hypocalcemia	≥LLN	<LLN-8.0 mg/dL	<8.0-7.0 mg/dL	<7.0-6.0 mg/dL	<6.0 mg/dL	Death
	Hypercalcemia	≤ULN	>ULN-11.5 mg/dL	>11.5-12.5 mg/dL	>12.5-13.5 mg/dL	>13.5 mg/dL	Death
Bicarbonate**	Low	≥LLN	16 mEq-<LLN	11.0-<16 mEq/L	8.0-<11 mEq/L	<8.0 mEq/L	

*DMID
**DAIDS
*** Corrected calcium (mg/dL) = Calcium (mg/dL) – 0.8 [albumin(g/dL) -4] or Corrected calcium (mmol/L) = Calcium (mmol/L) +0.02 [40- albumin(g/L)]

Table 5-4: Enzymes Toxicity Grading Scale

Enzymes							
Parameter	**Direction**	**Grade 0 / Normal**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Alkaline phosphatase (ALP)	Elevation	≤ULN	>ULN – 2.5 x ULN	>2.5 – 5.0 ULN	>5.0 – 20.0 ULN	>20.0 ULN	-
Aspartate aminotransferase (AST/SGOT)	Elevation	≤ULN	>ULN – 3.0 x ULN	>3.0 -5.0 ULN	>5.0 – 20.0 ULN	>20.0 ULN	-
Alanine aminotransferase (ALT/SGPT)	Elevation	≤ULN	>ULN – 3.0 x ULN	>3.0 -5.0 ULN	>5.0 – 20.0 ULN	>20.0 ULN	-

5.7. Appendix 7: Laboratory Normals

Lab test	Lab test code	SOURCE	SEX	LLN	ULN	UNIT [1]
Albumin	ALB	NLM	M	34	54	g/L
Albumin	ALB	NLM	F	34	54	g/L
Alkaline Phosphatase	ALP	NLM	M	44	147	U/L
Alkaline Phosphatase	ALP	NLM	F	44	147	U/L
Alanine Aminotransferase	ALT	NLM	M	10	40	U/L
Alanine Aminotransferase	ALT	NLM	F	7	35	U/L
Aspartate Aminotransferase	AST	NLM	M	10	34	U/L
Aspartate Aminotransferase	AST	NLM	F	10	34	U/L
Basophils/Leukocytes	BASOLE	NLM	M	0.5	1	%
Basophils/Leukocytes	BASOLE	NLM	F	0.5	1	%
Bicarbonate	BICARB	NLM	M	23	29	mmol/L
Bicarbonate	BICARB	NLM	F	23	29	mmol/L
Direct Bilirubin	BILDIR	NLM	M	0	5.13	umol/L
Direct Bilirubin	BILDIR	NLM	F	0	5.13	umol/L
Bilirubin	BILI	NLM	M	5.13	32.49	umol/L
Bilirubin	BILI	NLM	F	5.13	32.49	umol/L
Calcium	CA	NLM	M	2.125	2.55	mmol/L
Calcium	CA	NLM	F	2.125	2.55	mmol/L
Chloride	CL	NLM	M	96	106	mmol/L
Chloride	CL	NLM	F	96	106	mmol/L
Creatinine	CREAT	NLM	M	61.88	114.92	umol/L
Creatinine	CREAT	NLM	F	53.04	97.24	umol/L
Eosinophils/Leukocytes	EOSLE	NLM	M	1	4	%
Eosinophils/Leukocytes	EOSLE	NLM	F	1	4	%
Glucose (Random)	GLUC	NLM	M		6.9375	mmol/L
Glucose (Random)	GLUC	NLM	F		6.9375	mmol/L
Hematocrit	HCT	NLM	M	0.407	0.503	fraction of 1
Hematocrit	HCT	NLM	F	0.361	0.443	fraction of 1
Hemoglobin	HGB	NLM	M	138	172	g/L
Hemoglobin	HGB	NLM	F	121	151	g/L
Potassium	K	NLM	M	3.7	5.2	mmol/L
Potassium	K	NLM	F	3.7	5.2	mmol/L
Lymphocytes/Leukocytes	LYMLE	NLM	M	20	40	%
Lymphocytes/Leukocytes	LYMLE	NLM	F	20	40	%
Magnesium	MG	NLM	M	0.85	1.10	mmol/L
Magnesium	MG	NLM	F	0.85	1.10	mmol/L
Monocytes/Leukocytes	MONOLE	NLM	M	2	8	%
Monocytes/Leukocytes	MONOLE	NLM	F	2	8	%
Neutrophils/Leukocytes	NEUTLE	NLM	M	40	60	%
Neutrophils/Leukocytes	NEUTLE	NLM	F	40	60	%
Platelet count	PLAT	NLM	M	150	450	X10(9)/L
Platelet count	PLAT	NLM	F	150	450	X10(9)/L
Protein	PROT	NLM	M	60	83	g/L
Protein	PROT	NLM	F	60	83	g/L
Erythrocytes	RBC	NLM	M	4.7	6.1	X10(12)/L

Erythrocytes	RBC	NLM	F	4.2	5.4	X10(12)/L
Sodium	SODIUM	NLM	M	135	145	mmol/L
Sodium	SODIUM	NLM	F	135	145	mmol/L
Urea Nitrogen	UREAN	NLM	M	2.142	7.14	mmol/L
Urea Nitrogen	UREAN	NLM	F	2.142	7.14	mmol/L
Leukocytes	WBC	NLM	M	4.5	10	X10(9)/L
Leukocytes	WBC	NLM	F	4.5	10	X10(9)/L

[1] SI units

5.8. Appendix 8: Adverse Event and Prior/Concomitant Medication Date Imputations

Adverse Event Start/Stop Date and Death Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs or Death Date	D	M and Y same as M and Y of first dose of test article	Date of first dose of test article
		M and/or Y not same as date of first dose of test article	First day of month
	D and M	Y same as Y of first dose of test article	Date of first dose of test article
		Y prior to Y of first dose of test article but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of test article
Stop date for AEs	D	M and Y same as M and Y of last dose of test article	Date of last dose of test article
		M and/or Y not same as date of last dose of test article	Use last day of month
	D and M	Y same as Y of last dose of test article	Date of last dose of test article
		Y not same as Y of last dose of test article	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month. In all cases, if it cannot be determined if the adverse event occurred prior to or after the first dose of test article, the adverse event should be defined as treatment emergent.

Prior and Concomitant Medication Start Date Imputation

Parameter	Type of Medication	Imputation
Start date for con meds	Non-Antifungal	If it cannot be determined whether or not the start date of a medication (non-antifungal) is prior to the first dose of treatment, it will be assumed that the medication was received prior to the first dose of treatment
	Antifungal	Missing start dates for antifungals will be queried for a value. If it cannot be determined whether or not the start date of an antifungal is prior to the first dose of test article, it will be assumed that the medication was received prior to the first dose of treatment unless the indication notes that the medication was received after the first dose of treatment.
Stop date for con meds	Non-Antifungal	If it cannot be determined whether or not the stop date of a medication (non-antifungal) is after the first dose of treatment, it will be assumed that the medication was received after the first dose of treatment
	Antifungal	Missing stop dates for antifungals will be queried for a value. If it cannot be determined whether or not the stop date of an antifungal is after the first dose of treatment, it will be assumed that the medication was received after the first dose of treatment unless the indication notes that the medication was received prior to the first dose of treatment. If it cannot be determined whether the antifungal was received prior to any scheduled assessments, the antifungal will be assumed to have been received through the FU Visit.

5.9. Appendix 9: Document Version History

DOCUMENT HISTORY	
Document	**Date**
Original SAP (based on Protocol Amendment V3)	15 March 2019
SAP V2.0 (based on Protocol Amendment V4)	04 March 2020
SAP V3.0 (based on Protocol Amendment V5)	24 February 2021
SAP V4.0 (based on Protocol Amendment V5)	02 November 2021

Brief Summary of Changes in V2.0 from Original SAP:

- mITT2 population was newly defined and planned for EMA primary analysis (global cure) and for the secondary and additional efficacy analyses.
- Global cure in mITT population was moved to Secondary objective.
- Estimand attributes were added.
- Details for mycological response derivation for various scenarios were added.
- Radiologic response data collection was clarified.
- Final diagnosis was added to the list of subgroups.
- Sample size section was updated to include mITT2 population.
- A rule for adverse event with Death NOS was added.
- Visit window rules were updated.
- Concomitant medication definition was clarified.
- Neurological questionnaires and PK sampling Sections were added.
- A table of lab standard normal ranges was added.

Brief Summary of Changes in V3.0 from V2.0:

- mITT2 population was removed from the analysis population, from the sample size section, and from the planned analyses based on mITT2.
- Population for EMA primary analysis was updated to use mITT.
- Details for time to first negative blood culture analysis for various scenarios were added.

- Subsets of subjects based on timing of culture at randomization were defined.
- Sequence for the superiority tests was clarified for both ACM and global response analyses.
- Analyses related to COVID-19 including subgroup analyses based on pre-, peri-, and post-COVID period were added.
- Details for the health outcome derivation rules were added.
- Normalization rule for WBC differentials in % was updated.
- QTcF summary was added.

Brief Summary of Changes in V4.0 from V3.0:

- Geographic region group was updated to include new sites.
- Estimated creatinine clearance formula was updated to use the adjusted ideal body weight
- Clarification was made on the duration of catheter placement, the baseline fungal pathogen summary, and SAE leading to death definition.
- Summary of hospitalization at the time of enrollment was added to the analysis of health outcome.
- AE overall summary and AEs by SOC and PT for higher risk subgroups, related AEs by PT, and related AEs leading to treatment interruption or discontinuation were added.
- Time to negative blood culture analysis for candidemia only subjects was added.

6. CHANGES TO PLANNED ANALYSES

There are no changes between the protocol-defined statistical analyses and those presented in this SAP.

7. REFERENCES

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