# STATISTICAL ANALYSIS PLAN

## A Phase 2, Multicenter, Randomized, Double-blind Study of the Safety, Tolerability, and Efficacy of Intravenous CD101 vs Intravenous Caspofungin Followed by Oral Fluconazole Step-down in the Treatment of Subjects with Candidemia and/or Invasive Candidiasis

| | |
|---|---|
| **Protocol Number:** | CD101.IV.2.03 |
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| **Name of Test Drug:** | Intravenous CD101 |
| **Indication:** | Candidemia and Invasive Candidiasis |
| **Phase:** | Phase 2 |
| **Methodology:** | Multicenter, prospective, randomized, double-blind |
| **Sponsor:** | Cidara Therapeutics, Inc.<br>6310 Nancy Ridge Drive, Suite 101<br>San Diego, CA 92121<br>Tel: (858) 752-6170<br>Fax: (858) 408-3509 |
| **Sponsor Representative:** | Taylor Sandison, MD MPH<br>Chief Medical Officer |
| **Analysis Plan Date:** | 17 May 2019 |
| **Analysis Plan Version:** | FINAL Version 4.0 |

# APPROVAL SIGNATURE PAGE

**Protocol Title:** A Phase 2, Multicenter, Randomized, Double-blind Study of the Safety, Tolerability, and Efficacy of Intravenous CD101 vs Intravenous Caspofungin Followed by Oral Fluconazole Step-down in the Treatment of Subjects with Candidemia and/or Invasive Candidiasis

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Date: 04/Jun/2019

**Sponsor Approval:**

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

**Sponsor Signatories:**

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Chief Medical Officer

Signature: [signature]
Date: 17 MAY 2019

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Date: 29 May 2019

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| APTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| bpm | Beats per minute |
| BMI | Body mass index |
| BUN | Blood urea nitrogen |
| C | Celsius |
| CH | Potentially Clinically Significant High |
| CI | Confidence Interval |
| CL | Potentially Clinically Significant Low |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficient of Variability |
| dL | deciliter |
| DMID | Division of Microbiology and Infectious Diseases |
| DAIDS | Division of AIDS |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EOT | End-of-Treatment |
| FU | Follow-up |
| g | Gram |
| gm | Gram |
| ICH | International Conference on Harmonisation |
| IC | Invasive Candidiasis |
| ICU | Intensive Care Unit |
| IEC | Independent Ethics Committee |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| ITT | Intent-to-treat |
| IV | Intravenous |
| IVD | In vitro diagnostic |
| IWRS | Interactive Web Response System |
| kg | kilogram |
| L | Liter |

| Abbreviation | Definition |
|---|---|
| LLN | Lower limit of normal |
| Max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mEq | Milliequivalence |
| mg | Milligram |
| MIC | Minimum inhibitory concentration |
| Min | Minimum |
| mITT | Microbiological Intent-to-treat |
| mL | Milliliter |
| $m^2$ | Square meter |
| $mm^3$ | Cubic millimeter |
| mmHg | Millimeter of mercury |
| msec | Millisecond |
| NLM | National Library of Medicine |
| N | Negative |
| % | Percent |
| P | Positive |
| PCS | Potentially Clinically Significant |
| pH | Hydrogen ion concentration |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PT | Preferred Term or Prothrombin time |
| PTT | Partial thromboplastin time |
| QTcF | QT interval with Fridericia correction |
| RBC | Red blood cell (count) |
| SAE | Serious treatment-emergent adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SI | Systeme Internationale |
| SOC | System organ class |
| TEAE | Treatment-emergent adverse event |
| ULN | Upper limit of normal |
| US | United States |
| WBC | White blood cell (count) |
| 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 2, Multicenter, Randomized, Double-blind Study of the Safety, Tolerability, and Efficacy of Intravenous CD101 vs Intravenous Caspofungin Followed by Oral Fluconazole Step-down in the Treatment of Subjects with Candidemia and/or Invasive Candidiasis." 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 will not be included in this SAP.

CD101 is a new semi-synthetic echinocandin antifungal agent that is being developed specifically to treat subjects with systemic infections caused by *Candida*.

### 1.1.2. Study Objectives

The primary objectives of this study are to:

- Evaluate the safety and tolerability of intravenous CD101 (CD101 IV) in the Safety population.
- Evaluate overall success (mycological eradication and resolution of systemic signs attributable to candidemia and/or invasive candidiasis [IC]) of CD101 IV in subjects with candidemia and/or IC at Day 14 (±1 day) in the Microbiological Intent-to-treat (mITT) population.

The secondary objectives of this study are to:

- Evaluate overall success (mycological eradication and resolution of systemic signs attributable to candidemia and/or IC) of CD101 IV at Day 5, Day 28 (±2 days; only for subjects with IC), and Follow-up (FU, Days 45-52 or Days 52-59 for subjects with IC) in the mITT population.
- Evaluate mycological success (eradication) of CD101 IV at Day 5, Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC) and FU (Days 45-52 or Days 52-59 for subjects with IC) in the mITT population.
- Evaluate clinical cure as assessed by the Investigator for CD101 IV at Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), and FU (Days 45-52 or Days 52-59 for subjects with IC) in the mITT population.
- Evaluate the PK of CD101 IV.

## 1.2. Study Design

### 1.2.1. Synopsis of Study Design

This is a Phase 2, multicenter, prospective, randomized, double-blind study of CD101 IV or intravenous caspofungin followed by oral fluconazole step-down therapy for treatment of subjects with candidemia and/or IC. Subjects will be randomized at about 60 sites in North America (the United States [US] and Canada) and countries in Europe.

In Part A, subjects will be randomized in a 1:1:1 ratio to receive CD101 IV treatment group 1, CD101 IV treatment group 2, or IV caspofungin using an interactive web response system (IWRS). Upon meeting specified criteria, oral step-down therapy is allowed in all 3 treatment groups: oral placebo in the CD101 IV groups and oral fluconazole in the IV caspofungin group. After approximately 90 subjects have been enrolled in the mITT population in Part A, enrollment into Part A of the study will close and Part B will begin. It is expected that approximately 114 subjects need to be randomized to achieve 90 subjects in the mITT population for Part A.

In Part B, subjects enrolled under Amendment 5 will be randomized in a 2:1 ratio until there are ≥30 subjects in the CD101 IV treatment group 1 and ≥15 subjects in the comparator group (≥45 additional subjects and no more than 120 subjects). Following the results of the unblinded analysis of Part A, the Part B subjects enrolled under Amendment 6 will be randomized in a 2:1 ratio to receive the CD101 IV treatment group 2 or IV Caspofungin. Total enrollment for Part B will depend on the enrollment rate for the period between the end of Part A and the start of the Phase 3 study, which is the trigger for Part B to stop enrollment. Oral step-down therapy is allowed in both treatment groups in Part B; oral placebo in the CD101 IV group and oral fluconazole in the caspofungin group. The total IV plus oral treatment duration will be ≥14 days and up to a maximum of 21 days total for subjects with candidemia and up to a maximum of 28 days total for subjects with IC.

Subjects randomized to the CD101 IV treatment group 1 will receive 1 dose of CD101 IV (400 mg) over 60 (±10) minutes on Day 1 and Day 8 and IV placebo on other study days in order to maintain the blind; subjects who require >14 days of IV therapy will receive an optional third dose of CD101 IV (400 mg) on Day 15. Subjects with IC are allowed an optional CD101 IV dose (400 mg) on Day 22 if additional therapy is required. Subjects in group 1 will receive IV placebo on other study days in order to maintain the blind. Subjects randomized to the CD101 IV treatment group 2 will receive 1 dose of CD101 IV (400 mg) over 60 (±10) minutes on Day 1, 200 mg on Day 8 and IV placebo on other study days in order to maintain the blind; subjects who require >14 days of IV therapy will receive an optional third dose of CD101 IV (200 mg) on Day 15. Subjects with IC are allowed an optional CD101 IV dose (200 mg) on Day 22 if additional therapy is required. Subjects in group 2 will receive IV placebo on other study days in order to maintain the blind. Subjects may receive oral step-down therapy after ≥3 days of IV therapy, if criteria are met. Step-down therapy in both CD101 IV treatment groups will be oral placebo, in order to maintain the blind. Subjects who have already switched to oral step-down therapy will receive both oral placebo and CD101 IV on Day 8 and optional oral placebo and CD101 IV on Day 15 for subjects who require >14 days of therapy. Dosage adjustments are not allowed. Intravenous study drug is administered 24 (±2) hours after study drug was administered on the previous day.

Subjects randomized to the caspofungin group will receive IV caspofungin (70 mg loading dose on Day 1 and then 50 mg/day) for ≥3 days up to a maximum of 21 days for subjects with candidemia only or up to a maximum of 28 days for subjects with IC. After ≥3 days of IV therapy, subjects in the IV caspofungin group can be switched to oral step-down therapy if criteria are met. Step-down therapy in the caspofungin treatment group will be oral fluconazole (a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter). In order to maintain the blind, subjects who have already switched to oral step-down therapy will receive both oral fluconazole and IV placebo on Day 8, Day 15 for subjects who require >14 days of therapy. Intravenous study drug is administered 24 (±2) hours after study drug was administered on the previous day.

Subjects in the caspofungin group with moderate hepatic impairment (Child-Pugh score of 7-9) will receive a loading dose of caspofungin of 70 mg on Day 1 and 35 mg/day thereafter. Subjects in the caspofungin group weighing >80 kg or on concomitant rifampin, nevirapine, efavirenz, phenytoin, dexamethasone, or carbamazepine may receive 70 mg caspofungin daily. Dose adjustment due to drug-drug interactions or subject weight may be considered at the Investigator's discretion. Dosage adjustments in the CD101 IV treatment groups are not allowed.

Subjects in the caspofungin group with renal impairment who are switched to oral step-down therapy may receive reduced doses of fluconazole. For subjects with creatinine clearance ≤50 mL/min, oral step-down therapy should be fluconazole (a loading dose of 400 mg [2 capsules] on the first day followed by 200 mg [1 capsule]/day thereafter) in the caspofungin treatment group and oral placebo (2 capsules on the first day followed by 1 capsule/day thereafter) in the CD101 treatment groups.

For subjects receiving hemodialysis, oral step-down therapy should be fluconazole (a full loading dose of 800 [4 capsules] followed by 400 mg [2 capsules] only after each episode of hemodialysis) in the caspofungin treatment group and oral placebo (4 capsules on the first day followed by 2 capsules after each hemodialysis) in the CD101 treatment groups.

### 1.2.2. Randomization and Blinding

After informed consent has been obtained, subjects will be screened for study eligibility before randomization. Subjects in Part A will be assigned a subject number and randomized (1:1:1) to receive CD101 IV treatment group 1, CD101 IV treatment group 2, or caspofungin on Day 1 just prior to dosing. Subjects in Part B enrolled under Amendment 5 will be assigned a subject number and randomized (2:1) to receive CD1010 IV treatment group 1 or caspofungin on Day 1 just prior to dosing. Subjects in Part B enrolled under Amendment 6 will be assigned a subject number and randomized (2:1) to receive CD1010 IV treatment group 2 or caspofungin. Randomization will be stratified based on the method used at Screening to establish the diagnosis (blood culture/rapid in vitro diagnostic [IVD] and positive Gram stain/culture from a specimen obtained from a normally sterile site). If a subject has both a positive blood culture/rapid IVD and Gram stain/culture from a specimen obtained from a normally sterile site, the subject will be randomized within the positive Gram stain/culture from a specimen obtained from a normally sterile site stratum. The study site's pharmacist (or pharmacist designee) will obtain the study drug assignment from the IWRS. A subject is considered randomized when a randomization transaction has been recorded in the IWRS and the subject is assigned a randomization number.

All subjects and study personnel, including the Sponsor, Principal Investigator (PI), and site personnel involved in study conduct will remain blinded to by subject study medication assignment for both Part A and Part B until the study is completed and the database is locked, with the exception of the Pharmacy Monitor to monitor drug preparation and drug accountability during the study and cases in which unblinding is required due to a safety or tolerability issue. Additionally, in Part A only, some personnel including the PK analyst and an unblinded statistician, will be unblinded but will not be involved in the study conduct or the final analysis. An unblinded statistician will perform the analysis on the interim and final unblinded Part A data. To maintain study blinding, study drug preparation will be performed by an unblinded site pharmacist (or qualified unblinded personnel at the study site not involved with study procedures or evaluations).

Instructions for study drug preparation and dosing are outlined in the Pharmacy Manual provided separately to the site. In the case of a medical emergency requiring the PI to know the identity of the study drug, the PI will follow the procedures outlined in SAP Section 1.2.3.

### 1.2.3. Stopping Rules

The Sponsor reserves the right to terminate an investigational site or this clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- The incidence or severity of adverse events (AEs) in this or other studies of CD101 IV indicate a potential health hazard to subjects
- Serious or persistent noncompliance by the Investigator with the protocol, clinical research agreement, or applicable regulatory guidelines in conducting the study
- Institutional Review Board/ Independent Ethics Committee (IRB/IEC) decision to terminate or suspend approval for the investigation or the Investigator
- Investigator request to withdraw from participation
- Subject enrollment is unsatisfactory

For subjects who prematurely discontinue study drug (ie, before the anticipated full course of study drug therapy required for effective treatment of candidemia and/or IC), End-of-Treatment (EOT) assessments should be performed on the day of discontinuation. Reasons for withdrawal from study drug may include, but are not limited to:

- Screening cultures negative for *Candida* spp.
- Safety
- Invasive Candidiasis involving a site involving the central nervous system or eye
- Insufficient therapeutic effect
- Investigator discretion

The decision to continue or discontinue a subject on the study drug in the event that the subject requires systemic concomitant antifungal therapy will be discussed between the PI and Medical Monitor.

### 1.2.4. Unblinding

This study is a double-blind design. Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific subject, may the PI unblind a subject's treatment assignment.

Prior to any unblinding, the PI is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel. As soon as possible and without revealing the subject's study treatment 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 and the PI was unable to contact the Sponsor prior to unblinding. The PI will record in source documentation the date and reason for revealing the blinded treatment assignment for that subject.

The data from Part A will be unblinded for an interim analysis of select efficacy and safety outcomes but individual treatment assignments will not be made available to the Sponsor. After the database is locked for Part A, but prior to completion of Part B, Part A will be unblinded and

full summary results reported when available. Individual subject treatment assignments will not be made available the Sponsor at the time the summary results for Part A are reported.

### 1.2.5. Study Procedures

After informed consent is obtained, all potential study participants undergo screening evaluations, which include a medical history, clinical assessments, and laboratory assessments. Mycological diagnosis of candidemia at Screening will be established by ≥1 blood culture positive for yeast or *Candida* spp., a Sponsor-approved rapid IVD test positive for *Candida* spp., or a positive Gram stain for yeast or a positive culture for *Candida* spp. from a specimen obtained from a normally sterile site from a sample taken within 96 hours before randomization. If the positive blood culture used to qualify the subject for the study is drawn >12 hours from randomization, then an additional set of blood cultures must be obtained ≤12 hours before randomization. Assessments of mycological eradication and clinical response will be performed at Day 5, Day 14 (±1 day), Day 28 (±2 days) for subjects with IC and the FU visit (Days 45-52 or Days 52-59 for IC subjects). Blood cultures should be performed daily or every other day until 2 blood cultures drawn ≥12 hours are negative without an intervening positive culture. The schedule of assessments and procedures, as outlined in the study protocol, is presented in Table 1-1.

Study participation will require from 45 to 52 days (or 52-59 days for subjects with IC) after the first administration of study drug; study drug administration from Day 1 up to Day 21 (for subjects with candidemia) or up to Day 28 (±2 days; only for subjects with IC); PK assessments on Days 1, 2, 4, 8, and 15; safety, tolerability, and efficacy assessments up to Day 21 (for subjects with candidemia only) or up to Day 28 (±2 days; only for subjects with IC); and a FU visit at Days 45 to 52 (or 52-59 days for subjects with IC).

## Table 1-1: Schedule of Assessments and Procedures

| | | Study Drug Administration, Days | | | | | | | | | | | | | | EOT +2 days after last dose of study drug (IV and oral) | FU Visit Days 45-52 for subjects with candidemia only (or Day 52-59 for IC subjects with or without candidemia) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (window)** | **Screen** | **1**[a] | **2** | **3** | **4** | **5** | **6, 7** | **8**[b] **(±1)** | **9-13** | **14**[b] **(±1)** | **15**[b] **(±1)** | **16-21** | **22**[b,c] **(±1)** | **23-27**[c] | **28**[b,d] **(±2)** | | |
| Informed consent [e] | X | | | | | | | | | | | | | | | | |
| Medical history [f] | X | | | | | | | | | | | | | | | | |
| Physical examination including height and weight [g] | X | | | | | | | | | X | | | | | X | | X |
| Calculate Child-Pugh score [h] | X | | | | | | | | | | | | | | | | |
| Modified APACHE II score with Glasgow coma score [i] | X | | | | | | | | | | | | | | | | |
| Vital signs [j] | X | X | X | X | X | X | X[k] | X | X[k] | X | X[k] | X[k] | X | X[k] | X | X | X |
| 12-lead ECG [l] | X | | | | | | | | | | | | | | | X | |
| Radiologic test results [m] | → | | | | | | | | | | | | | | | | |
| Blood for hematology and chemistry tests [n] | X | | X | | X | | | X | | X | | | | | | X | X |
| Blood for coagulation panel | X | | | | | | | | | | | | | | | | |
| Urine for urinalyses, microscopy | X | | | | | | | | | | | | | | | X | |
| Urine pregnancy test [o] | X | | | | | | | | | | | | | | | | X |

| | | Study Drug Administration, Days | | | | | | | | | | | | | | EOT +2 days after last dose of study drug (IV and oral) | FU Visit Days 45-52 for subjects with candidemia only (or Day 52-59 for IC subjects with or without candidemia) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (window)** | **Screen** | **1**[a] | **2** | **3** | **4** | **5** | **6, 7** | **8**[b] **(±1)** | **9-13** | **14**[b] **(±1)** | **15**[b] **(±1)** | **16-21** | **22**[b,c] **(±1)** | **23-27**[c] | **28**[b,d] **(±2)** | | |
| Retinal examination for *Candida* eye infection [p] | X | → | → | → | → | → | → | | | | | | | | | | |
| Study randomization [q] | | X | | | | | | | | | | | | | | | |
| Administer IV CD101 or IV placebo | | X[r] | X[s] | X[s] | X[t] | X[t] | X[t] | X[u] | X[t] | X[t] | X[v] | X[w] | X[x] | X[y] | X[y] | | |
| Administer IV caspofungin or IV placebo | | X[r] | X[s] | X[s] | X[t] | X[t] | X[t] | X[u] | X[t] | X[t] | X[v] | X[w] | X[x] | X[y] | X[y] | | |
| Administer oral fluconazole or oral placebo step-down therapy if switched [z] | | | | | X[t] | X[t] | X[t] | X[u] | X[t] | X[t] | X[v] | X[w] | X[x] | X[y] | X[y] | | |
| Record prior and/or concomitant medications [aa] | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | X | X |
| Record adverse events [bb] | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | X | X |
| Blood or normally sterile tissue/fluid for culture [cc] | X[dd] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ee] | X[ff] |
| Rapid In Vitro Diagnostic | X | | | | | | | | | | | | | | | | |
| Determine overall response programmatically [gg] | | | | | | X | | | | X | | | | | X | | X |

| | | Study Drug Administration, Days | | | | | | | | | | | | | | EOT +2 days after last dose of study drug (IV and oral) | FU Visit Days 45-52 for subjects with candidemia only (or Day 52-59 for IC subjects with or without candidemia) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (window)** | **Screen** | **1**[a] | **2** | **3** | **4** | **5** | **6, 7** | **8**[b] **(±1)** | **9-13** | **14**[b] **(±1)** | **15**[b] **(±1)** | **16-21** | **22**[b,c] **(±1)** | **23-27**[c] | **28**[b,d] **(±2)** | | |
| Assess presence or absence of systemic signs and symptoms attributable to candidemia and/or IC | X[hh] | | | | | X[ii] | | | | X | | | | | X | | X |
| Assess for clinical response [jj] | | | | | | | | | | X | | | | | X | | X |
| Blood for PK testing (Part A Only) [kk] | | X | X | | X | | | X | | | X | | | | | | |

APACHE = Acute Physiology and Chronic Health Evaluation; ECG = electrocardiogram; EOT = End-of-Therapy; ESCMID = European Society Clinical Microbiology and Infectious Disease; FU = follow-up; IC = Invasive Candiasis; IDSA = Infectious Disease Society of America; IV=Intravenous; IVD = in vitro diagnostic; PK = pharmacokinetic.

a. Study Day 1 is the first day of study drug administration; subsequent study days are consecutive calendar days.
b. The time windows on Study Day 8, 14, 15, 22, and 28 visits apply only to subjects already stepped down to oral therapy and discharged from the study site.
c. Perform if further therapy is clinically indicated; only for subjects with IC (with or without candidemia). Subjects will be considered to have IC if there is a positive culture for *Candida* spp. from a normally sterile site other than blood or if there is a positive sponsor-approved rapid IVD or blood culture for *Candida* spp. combined with radiographic evidence of IC.
d. The Day 28 visit is only for subjects with IC (with or without candidemia). Note that the Day 28 (±2 days) visit could be the same visit as the EOT visit if the subject receives ≥26 days of therapy.
e. Written informed consent must be obtained prior to initiating any study related assessments or procedures.
f. Medical history for the last 5 years and *Candida* risk factors for the last 3 months (eg, 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 admission and discharge (if applicable). Short-term central venous catheters (eg, peripherally-inserted central catheters, internal jugular or subclavian central venous catheters) and long-term central venous catheters (eg, tunneled catheters) are recommended to be removed within 48 hours after diagnosis with candidemia, consistent with IDSA and ESCMID guidelines
g. Physical exams are required at Screening, on Day 14, Day 28 (±2 days; only for subjects with IC), and at the FU visit. Height is recorded at Screening. Weight is recorded at Screening, on Day 14, and at the FU visit. If a physical exam is performed at any other visit, abnormal findings that represent a new or worsening condition as compared to baseline should be recorded as an adverse event.
h. Calculate Child-Pugh score only if the subject has a history of chronic cirrhosis

i. APACHE II score can be calculated after enrollment, but should use the vital signs and laboratory results from the Screening visit.
j. If hospitalized, record the range of vital signs; highest and lowest daily temperature and the method used (oral, rectal, temporal, tympanic, or core), highest and lowest heart rate, highest and lowest respiratory rate, and highest and lowest blood pressure measured. If not hospitalized, record single measurements for daily temperature and the method used (oral, rectal, temporal, tympanic, or core), heart rate, respiratory rate, and blood pressure.
k. For subjects discharged from the hospital and in the community, vital signs (temperature, heart rate, blood pressure, respiratory rate) are only performed on Days 6-28 if the subject is seen for clinical assessment or IV study drug infusion
l. ECG must be conducted before subject randomization.
m. If radiologic test performed, record radiologic test type with Findings and Interpretation only if radiologic test provides evidence of IC, OR evidence of resolution of IC from previous radiographs.
n. In general, the laboratory values to be entered into the electronic case report form will be from the first laboratory samples drawn each day with routine morning laboratory samples.
o. Perform urine pregnancy test only for women of childbearing potential. Do not perform for women who are ≥2 years post-menopausal or surgically sterile.
p. Perform a retinal examination for evidence of a *Candida* eye infection, including endophthalmitis or chorioretinitis, by Day 7 only on subjects with candidemia by blood culture, and repeat in subjects who were negative at baseline if the subject develops visual signs or symptoms of a *Candida* eye infection during the course of the study.
q. Verify that the subject meets all study inclusion and exclusion criteria before randomization.
r. On Day 1, subjects will receive IV CD101 or IV caspofungin
s. On Days 2-3, subjects will receive IV caspofungin or IV placebo.
t. On Days 4-7, and 9-14, subjects will receive either IV caspofungin; IV placebo (if in a CD101 group); oral fluconazole (caspofungin group) if already switched; or oral placebo (CD101 groups) if already switched.
u. On Day 8, subjects will receive either IV CD101 (if in a CD101 group and not switched to oral therapy); IV caspofungin (if in caspofungin group and not switched to oral therapy), IV CD101 plus oral placebo (if in a CD101 group and already switched to oral therapy); or IV placebo plus oral fluconazole (if in caspofungin group and already switched to oral therapy).
v. On Day 15, subjects may receive either IV CD101 (if in a CD101 group and not switched to oral therapy), if needed; IV caspofungin (if in caspofungin group and not switched to oral therapy), if needed; IV CD101 plus oral placebo (if in a CD101 group and already switched to oral therapy), if needed; IV placebo plus oral fluconazole (if in caspofungin group and already switched to oral therapy), if needed; or no treatment.
w. On Days 16-21, subjects may receive either IV caspofungin (if in caspofungin group), if needed; IV placebo (if in a CD101 group), if needed; oral fluconazole (caspofungin group) if already switched and needed; oral placebo (CD101 groups) if already switched and needed; or no treatment.
x. On Day 22, subjects with IC (with or without candidemia) may receive either IV CD101 (if in a CD101 group and not switched to oral therapy), if needed; IV caspofungin (if in caspofungin group and not switched to oral therapy), if needed; IV CD101 plus oral placebo (if in a CD101 group and already switched to oral therapy), if needed; IV placebo plus oral fluconazole (if in caspofungin group and already switched to oral therapy), if needed; or no treatment.
y. On Days 23-28, subjects may receive either IV caspofungin (if in caspofungin group), if needed; IV placebo (if in a CD101 group), if needed; oral fluconazole (caspofungin group) if already switched and needed; oral placebo (CD101 groups) if already switched and needed; or no treatment
z. Oral step-down therapy will be fluconazole (a loading dose of 800 mg [4 capsules ] on the first day followed by 400 mg [2 capsules ]/day thereafter) in the caspofungin group and oral placebo (4 capsules on the first day followed by 2 capsules/day thereafter) in the CD101 groups.
aa. Record all systemic antifungal therapy administered within 4 weeks and all non-antifungal therapy administered within 1 week prior to randomization Record concomitant antimicrobial agents, including all antifungal agents at each study visit.
bb. Adverse events are collected following signing of the informed consent form at Screening through the last study visit (FU)

cc. Perform identification and susceptibility testing at local laboratory for *Candida* for any positive blood culture or positive culture from a specimen obtained from a normally sterile site at Screening and for any positive culture requiring a change of antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained on other study days without a required change in antifungal therapy).

dd. Blood for culture must be obtained as part of the standard of care for inclusion in the study. Established mycological diagnosis of candidemia and/or IC sufficient for inclusion in the study is defined as ≥1 blood culture positive for yeast or *Candida*, a Sponsor-approved rapid IVD test positive for *Candida* spp, or a positive Gram stain for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site ≤96 hours before randomization. Record species and susceptibilities for all bacteria isolated within 1 week prior to randomization from blood or any other normally sterile site. If the positive blood culture used to qualify the subject for the study is drawn >12 hours from randomization, then an additional set of blood cultures must be obtained ≤12 hours before randomization.

ee. Obtain blood and/or normally sterile tissue/fluid for culture if demonstrating mycological eradication or if clinically indicated. Blood cultures should be repeated daily (preferred) or every other day until 2 negative blood cultures are obtained ≥12 hours apart, without an intervening positive culture. All fungal isolates cultured from blood and normally sterile tissue/fluid from Screening through the last study visit must be sent to the Central Laboratory. Record the species and susceptibilities for any new bacteria isolated from blood or any other normally sterile site.

ff. Obtain blood for culture at FU. If feasible, and if there was a previous culture from a site positive for *Candida* spp., obtain culture from normally sterile tissue/fluid from the same site. All fungal isolates cultured from blood and normally sterile tissue/fluid from Screening through the last study visit must be sent to the Central Laboratory. Record the species and susceptibilities for any new bacteria isolated from blood or any other normally sterile site.

gg. Overall success for subjects with candidemia occurs if 2 blood cultures are negative and ≥12 hours apart without intervening positive blood cultures, there was no change of antifungal therapy for the treatment of candidemia, and signs attributable to candidemia at baseline have resolved; blood cultures are drawn daily until the subject qualifies as a success. Success for subjects with IC (with or without candidemia) occurs if negative culture from a normally sterile site is either documented or presumed, there was no change of antifungal therapy for the treatment of IC, and signs attributable to IC at baseline have resolved: documented mycological eradication occurs if most recent culture on or prior to the day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is negative; presumed mycological eradication occurs if follow-up culture is not available (eg, normally sterile baseline site o*f Candida* infection not accessible) in a subject with a successful clinical outcome (ie, did not receive rescue antifungal treatment and has resolution of systemic signs of IC) and resolution or improvement of any baseline radiographic abnormalities due to IC.

hh. The Screening period for assessing systemic signs for inclusion in the study may include the 4 hours prior to the drawing of the qualifying positive blood 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.

ii. On Day 5, assess presence or absence of systemic signs only (ie, not symptoms) and determine which are attributable to candidemia and/or IC

jj. Principal Investigator to assess if the subject is a cure, indeterminate, or failure based on the criteria in Table 1-5; there is a specific electronic case report form page for completion of this assessment.

kk. In Part A only, obtain blood for PK sampling from the OPPOSITE arm of the infusion on Day 1 (within 10 minutes [ie, >0 to 10 minutes] before the end of infusion, between 15 minutes and 1 hour after the end of infusion, and between 2 hours and 12 hours after the end of infusion), Day 2 (random draw with date of sample same as Day 2 date of dose, with safety labs if possible), Day 4 (random draw with date of sample same as Day 4 date of dose, with safety labs if possible), Day 8 (predose only), and Day 15 (predose only). Day 8 and Day 15 PK draws should be performed within 30 minutes before the second and third dose of study drug, regardless of the exact day and time of these infusions. If therapy is stopped on or before Day 14 and there is no Day 15 dose, then the Day 15 PK sample should be drawn with the safety laboratory samples for the Day 14 visit. Ideally, PK samples would be drawn with the safety laboratory samples for that day to prevent multiple needle sticks.

### 1.2.6. Definitions of Outcome Measures

#### 1.2.6.1. Efficacy Outcome Measures

Efficacy outcome measures include overall response, mycological response and Investigator's Assessment of clinical response as well as all-cause mortality through FU, and time to negative blood culture.

Overall Response

The primary efficacy outcome measure is overall response at Day 14 (±1 day), which will be determined from the mycological response and assessment of systemic signs attributable to candidemia and/or IC (Table 1-2). Mycological response and assessment of systemic signs attributable to candidemia and/or IC are also determined at Day 5, Day 28 (±2 days; only for subjects with IC) and FU Visit (Days 45-52 or Days 52-59 for subjects with IC). The signs that may be present at baseline and attributable to candidemia and/or IC include fever, hypothermia, hypotension, tachycardia, and tachypnea. Subjects who require a change of antifungal therapy to treat candidemia and/or IC prior to a given day of the overall response assessment should have the assessment of systemic signs attributable to candidemia and/or IC moved forward to the early EOT evaluation. Assessments of systemic signs performed prior to the early EOT will be unaffected.

**Table 1-2: Overall Response Categories**

| | **Definition** | |
|---|---|---|
| **Overall Response** | **Mycological Response** | **Systemic Signs** |
| Success | Success (eradication/presumed eradication)* | Resolution of attributable systemic signs of candidemia and/or invasive candidiasis that were present at baseline |
| Failure | Success (eradication/presumed eradication)* | Recurrence or lack of resolution of attributable systemic signs of candidemia and/or invasive candidiasis |
| | Failure | Resolution of attributable systemic signs of candidemia and/or invasive candidiasis that were present at baseline |
| | Failure | Recurrence or lack of resolution of attributable systemic signs of candidemia and/or invasive candidiasis |
| | Failure | Assessment of systemic signs was not completed at visit or at baseline for any reason (including death) |
| Indeterminate | Indeterminate | Resolution of attributable systemic signs of candidemia and/or invasive candidiasis that were present at baseline |
| | Success (eradication/presumed eradication)* | Assessment of clinical signs was not completed for any reason at visit or at baseline |

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

The overall success rate is the proportion of subjects with success out of the total number of subjects evaluated.

Mycological Response

Mycological response will be programmatically determined from the electronic case report form (eCRF) and central mycology data at Day 5, Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC) and FU (Days 45-52 or Days 52-59 for subjects with IC), according to the definitions in Table 1-3. Determination of the identification of fungal pathogens will follow the process defined in SAP Section 4.

**Table 1-3: Mycological Response Definitions**

| **Mycological Response** | **Definition** |
|---|---|
| Success (eradication/presumed eradication) * | • If positive blood culture at baseline:<br>o The last blood culture drawn on or prior to the day of assessment and another blood culture drawn at least 12 hours prior are both negative for *Candida* spp and both blood cultures were drawn after initiation of study drug,<br>AND<br>o Any intervening blood cultures drawn between the 2 qualifying negative blood cultures are also negative for *Candida* spp.<br>• If positive culture from a normally sterile site at baseline:<br>o *Documented* mycological eradication: culture on day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is negative OR if no culture on the day of assessment, the most recent culture obtained after the initiation of study drug is negative,<br>OR<br>o *Presumed* mycological eradication: follow-up culture is not available (eg, normally sterile baseline site of *Candida* infection not accessible) or the most recent culture obtained after the initiation of study drug is positive in a subject with a successful clinical outcome (ie, did not receive rescue antifungal treatment and has resolution of systemic signs of invasive candidiasis that were present at baseline) and resolution or improvement of any baseline radiographic abnormalities due to invasive candidiasis,<br>AND<br>• There was no change of antifungal therapy for the treatment of candidemia and/or invasive candidiasis,<br>AND<br>• The subject is not lost to follow up on the day of assessment.<br><br>**Note**: Subjects with positive cultures from both blood and a normally sterile site will need to meet success criteria for both blood and normally sterile site to be considered success. |

| **Mycological Response** | **Definition** |
|---|---|
| Failure | • If positive blood culture at baseline:<br>o The last blood culture drawn on or prior to the day of assessment or any blood culture drawn prior to and within 12 hours of the last blood culture is positive for *Candida* spp and both blood cultures were drawn after the initiation of study drug,<br>OR<br>o The most recent blood culture drawn at least 12 hours prior to the last blood culture is positive for *Candida* spp. and culture was obtained after the initiation of study drug.<br>OR<br>• If positive culture from a normally sterile site at baseline:<br>o Documented mycological persistence: culture on day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is positive,<br>OR<br>o Presumed mycological persistence: follow-up culture is not available (eg, normally sterile baseline site of *Candida* infection not accessible) or the most recent culture obtained after the intiation of study drug is positive in a subject without a successful clinical outcome or with continued (from baseline) radiographic abnormalities due to invasive candidiasis,<br>OR<br>• The subject requires a change of antifungal therapy to treat candidemia,<br>OR<br>• The subject dies of any cause prior to or on the day of assessment. |
| Indeterminate | • If positive blood culture at baseline: A blood specimen was not available to culture or the result was not available.<br>• 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 of signs of invasive candiasis was not available.<br>• 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 1-4 provides examples of timing of the blood cultures and how these are used for determination of the mycological response.

**Table 1-4: Examples of Timing of Blood Cultures**

| | **Blood Cultures** | **Mycological Response [1]** |
|---|---|---|
| Example 1 | Day of Assessment: Day 14 (T=0 hours)<br>Blood cultures: T=0 (N), T= -18 (N) | Success (eradication) |
| Example 2 | Day of Assessment: Day 14 (T=0 hours)<br>Blood cultures: T=0 (N), T= -10 (P) T= -18 (N) | Failure |
| Example 3 | Day of Assessment: Day 14 (T=0 hours)<br>Blood cultures: T= -20 (N), T= -28 (N) T= -34 (P) | Failure |
| Example 4 | Day of Assessment: Day 14 (T=0 hours)<br>Blood cultures: T= -20 (N), T= -68 (N) | Success (eradication) |

T = Time; time is relative to the date and time of assessment of mycological response.
N = Blood culture negative for any *Candida* spp.
P = Blood culture positive for any *Candida* spp.
[1] For Success (eradication), assumes no other criteria for failure are met.

The mycological success rate is the proportion of subjects with success (eradication/presumed eradication) out of the total number of subjects evaluated.

Clinical Response

The Investigator will make a determination of clinical response at Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), and the FU visit (Days 45-52 or Days 52-59 for subjects with IC) according to the definitions in Table 1-5. Efficacy windows are to be applied for each timepoint and are listed in Table 3-2. Subjects whose disease is progressing or who receive rescue antifungal therapy for candidemia prior to Day 14 (±1 day) will be considered a clinical failure at Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), and the FU visits. Subjects who are a clinical cure at Day 14 (±1 day) and whose symptoms recur between Day 14 (±1 day) and Day 28 (±2 days; only for subjects with IC) or FU or who receive rescue antifungal therapy will be considered a failure at the Day 28 (±2 days; only for subjects with IC) or FU visit.

**Table 1-5: Investigator's Assessment of Clinical Response Definitions**

| Clinical Response | Definition |
|---|---|
| Cure | • Resolution of attributable systemic signs and symptoms of candidemia and/or IC that were present at baseline,<br>AND<br>• No new systemic signs or symptoms attributable to candidemia and/or IC,<br>AND<br>• No additional systemic antifungal therapy administered for candidemia and/or IC,<br>AND<br>• The subject is alive. |
| Failure | • Progression or recurrence of attributable systemic signs or symptoms of candidemia and/or IC,<br>OR<br>• Lack of resolution of attributable systemic signs or symptoms of candidemia and/or IC,<br>OR<br>• Requirement for new or prolonged therapy to treat candidemia and/or IC *,<br>OR<br>• An AE requires discontinuation of study drug therapy (IV and IV/oral) on or prior to the day of assessment,<br>OR<br>• The subject died of any cause. |
| Indeterminate | Study data are not available for the evaluation of efficacy for any reason including:<br>• Lost to follow-up,<br>• Withdrawal of consent,<br>• Extenuating circumstances that preclude the classification of clinical outcome of candidemia and/or IC. |

AE = adverse event; IC = invasive candidiasis; IV = intravenous.

* Prolonged antifungal therapy is defined as therapy for the treatment of candidemia extending beyond the allowable 21 days for study drug or for the treatment of IC extending beyond the allowable 28 days of study drug. The determination of prolonged therapy will only apply to the Follow-up visit clinical response assessment.

The cure rate is the proportion of subjects with a cure clinical response out of the total number of subjects evaluated.

Exploratory Mycological Response

Exploratory mycological response will be programmatically determined from the electronic case report form (eCRF) and central mycology data at Day 14 (±1) and will be defined similarly to mycological response with only 1 blood sample used in the derivation. The responses will be derived according to the definitions in Table 1-6.

## Table 1-6: Exploratory Mycological Response Definitions

| Exploratory Mycological Response | Definition |
|---|---|
| Success (eradication/presumed eradication) * | • If positive blood culture at baseline:<br>o The last blood culture drawn on or prior to the day of assessment is negative for *Candida* spp and blood culture was drawn after initiation of study drug,<br>• If positive culture from a normally sterile site at baseline:<br>o *Documented* mycological eradication: culture on day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is negative OR if no culture on the day of assessment, the most recent culture obtained after the initiation of study drug is negative,<br>OR<br>o *Presumed* mycological eradication: follow-up culture is not available (eg, normally sterile baseline site of *Candida* infection not accessible) or the most recent culture obtained after the initiation of study drug is positive in a subject with a successful clinical outcome (ie, did not receive rescue antifungal treatment and has resolution of systemic signs of invasive candidiasis that were present at baseline) and resolution or improvement of any baseline radiographic abnormalities due to invasive candidiasis,<br>AND<br>• There was no change of antifungal therapy for the treatment of candidemia and/or invasive candidiasis,<br>AND<br>• The subject is not lost to follow up on the day of assessment.<br><br>**Note**: Subjects with positive cultures from both blood and a normally sterile site will need to meet success criteria for both blood and normally sterile site to be considered success. |
| Failure | • If positive blood culture at baseline:<br>o The last blood culture drawn on or prior to the day of assessment is positive for *Candida* spp and blood culture was drawn after the initiation of study drug,<br>OR<br>• If positive culture from a normally sterile site at baseline:<br>o Documented mycological persistence: culture on day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is positive,<br>OR<br>o Presumed mycological persistence: follow-up culture is not available (eg, normally sterile baseline site of *Candida* infection not accessible) or the most recent culture obtained after the intiation of study drug is positive in a subject without a successful clinical outcome or with continued (from baseline) radiographic abnormalities due to invasive candidiasis,<br>OR<br>• The subject requires a change of antifungal therapy to treat candidemia,<br>OR<br>• The subject dies of any cause prior to or on the day of assessment. |

| **Exploratory Mycological Response** | **Definition** |
|---|---|
| Indeterminate | • If positive blood culture at baseline: A blood specimen was not available to culture or the result was not available.<br>• 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 of signs of invasive candiasis was not available.<br>• 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.

Exploratory Overall Response

Exploratory overall response will be programmatically determined in same way as defined in Table 1-2 with exploratory mycological response replacing the mycological response column.

Additional efficacy outcome measures include:

- All-cause mortality (ACM) through the FU Visit: defined as death due to any cause from the date and time of randomization through the FU Visit. Subjects who did not die or are lost to follow-up will be censored in the analysis at the last date known to be alive.
- Time to negative blood culture: defined as the time, in hours from the first dose of study drug to the first of 2 negative blood cultures drawn ≥12 hours apart following the first pre-treatment blood culture confirmed positive for any *Candida* species. Determination of the identification of fungal pathogens will follow the process defined in SAP Section 4. Subjects will be censored at the earliest start date and time of receipt of an alternative antifungal (ie, 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 a subject is lost to follow-up prior to having 2 negative blood cultures, the subject will be censored at the date of the last blood culture.

#### 1.2.6.2. Safety Outcome Measures

Safety will be assessed through the evaluation of AEs, 12-lead electrocardiograms (ECGs), radiologic tests, vital signs (temperature, heart rate, blood pressure, and respiratory rate), and clinical laboratory evaluations (hematology and coagulation evaluations, chemistry panel, and urinalyses).

# 2. SUBJECT POPULATION

## 2.1. Population Definitions

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

- Intent-to-Treat (ITT) Population: All subjects randomized to treatment. A subject is considered randomized when a randomization transaction has been recorded in the IWRS, regardless of whether the subject actually receives study drug.
- Safety Population: All subjects randomized to treatment and who received any amount of study drug.
- Microbiological Intent-to-treat Population (mITT): A subset of subjects in the Safety population with documented *Candida* infection based on a Central Laboratory evaluation of an isolate from a blood culture obtained within 96 hours of randomization or from a specimen obtained from a normally sterile site. Determination of the identification of fungal pathogens will follow the process defined in SAP Section 4.
- Microbiological Intent-to-treat 2 Population (mITT2): A subset of subjects in the mITT population had documented *Candida* infection based on Central Laboratory evaluation of:
    - 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.
- Microbiological Intent-to-treat 3 Population (mITT3): A subset of subjects in the mITT population who had documented *Candida* infection based on Central Laboratory evaluation of:
    - 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.
- Pharmacokinetics (PK) Population: All CD101 treated subjects with at least 1 plasma sample obtained for PK analysis.

Demographics (including age, race, and gender), diagnosis (candidemia and/or IC), medical history, baseline assessments, mycological data, systemic signs and symptoms, and administration of study drug will be summarized for the ITT population, unless otherwise specified. The Safety population is the primary population for the analysis of safety endpoints. All efficacy analyses will be conducted in the mITT population, unless otherwise specified. A select set of efficacy analysis will also be perfomed in the mITT2 and mITT3 populations.

## 2.2. Protocol Deviations

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, and classified as major or minor.

The Sponsor or designee will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file), in collaboration with Veristat and the data monitoring group as applicable. This file will be finalized prior to hard database lock.

# 3. GENERAL STATISTICAL METHODS

## 3.1. Sample Size Justification

This is an exploratory study and therefore, is not powered for inferential statistical analyses. A sufficient number of subjects are randomized to the CD101 IV and IV caspofungin treatment groups in Part A to provide an initial, substantive analysis of safety, tolerability, and estimate efficacy.

It is expected that approximately 114 subjects in Part A will need to be randomized given an estimated discontinuation rate of 20%, in order to achieve 90 evaluable subjects in the mITT population. In Part A, assuming a 73% overall success rate, the sample size of 30 subjects in the mITT population in each CD101 IV treatment group and the IV Caspofungin group will yield a 95% confidence interval (CI) for this success rate of 53.8% to 87.5%.

The addition of Part B in Amendment 5 of the protocol increased the study sample size by approximately 50% to 130% (depending on the rate of enrollment over the additional months to the staged start of the Phase 3 study and the rolling close-out of Part B). In Part B, subjects will be randomized until there are at least 30 subjects in the CD101 IV treatment groups at any dose and 30 subjects in the comparator group (≥45 additional subjects and no more than 120 subjects). In Part B, total enrollment will depend on the enrollment rate for the period between the end of Part A and the start of the Phase 3 study. With the addition of Part B subjects and assuming a 73% overall success rate, a total approximate sample size of 60 subjects in the CD101 treatment group (consisting of Group 1 from Amendment 5 and Group 2 from Amendment 6) will yield a 95% CI of 60.0% to 83.7%, and a total approximate sample size of 110 subjects in the CD101 treatment group (consisting of Group 1 from Amendment 5 and Group 2 from Amendment 6) will yield a 95% CI of 63.7% to 81.0%.

## 3.2. General Methods

All tables, figures, and listings will be presented in landscape orientation in Courier New, 8-point font.

All tables, figures, and listings 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).

All data listings and tables displaying by-subject data that contain an evaluation date will display a relative study day (Study Day). Study Day 1 is defined as the first day of study drug administration and subsequent study days are defined by the number of consecutive calendar days thereafter. The day prior to the first dose of study drug is Study Day -1; there is no Study Day 0.

If a clinical 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.

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. 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).

- For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum (min), and maximum (max) values will be presented.
- Time-to-event data will be summarized using Kaplan-Meier methodology using 25$^{th}$, 50$^{th}$ (median), and 75$^{th}$ percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations.
- Point estimates for overall response, mycological success and clinical success with exact 2-sided 95% CIs will be determined using the Clopper-Pearson method.

## 3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software v9.3, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v19.0. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary March 2016.

## 3.4. Baseline Definitions

For all analyses with exception of the analysis involving attributable systemic signs, baseline will be defined as the most recent measurement prior to the first administration of study drug. In the event the screening visit and treatment administration occur on the same date, baseline will be defined as measurements obtained at the screening visit.

All blood and normally sterile site samples taken 96 hours before randomization will be used to determine the presence of *Candida* at baseline. In instances where multiple samples of the same type occur with the same pathogen within 96 hours before randomization, the sample with highest MIC to study drug will be used as baseline pathogen.

For attributable systemic signs, all assessments of signs taken in the period 4 hours prior to the draw of the qualifying blood culture (when systemic signs of infection resulted in obtaining blood cultures), qualifying positive culture from a sterile site, or qualifying rapid IVD, through the first dose of study drug will be used to determine the presence of attributable systemic signs at baseline.

## 3.5. Methods of Pooling Data

Data will be pooled across sites for all analyses. Data for selected analyses (as described in Section 5) will also be pooled across Part A and B.

## 3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

## 3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

## 3.8. Subgroups

The demographic and baseline characteristic subgroups shown in Table 3-1 will be used for select analyses.

**Table 3-1: Subgroup Definitions and Associated Analysis**

| Parameter | Subgroup Description | Efficacy Outcomes [1] | | | Other: Select Demographics/ Baseline/ TEAEs |
|---|---|---|---|---|---|
| | | Overall | Myco-logical | Clinical | |
| Diagnosis | - Candidemia Only<br>- IC (with or without candidemia) | Y | Y | Y | |
| Geographic Region | - North America<br>- Europe | Y | Y | Y | Y/Y/N |
| Hepatic insufficiency at screening | - History of Chronic Liver Disease/Cirrhosis and Child-Pugh >=7<br>- No history or Child-Pugh < 7 | Y | Y | Y | Y/Y/Y |
| Renal function status at screening (based on normalized eCrCl)[2] | - Severe / Early Stage Renal Disease (<30 or receiving dialysis)<br>- Moderate (30 - <60)<br>- Mild (60 - < 90)<br>- Normal/Augmented (90+) | Y | Y | Y | Y/Y/Y |
| Renal disease at screening (based on normalized eCrCl)[2] | - Moderate/Severe/ESRD (<60)<br>- Augmented/Normal/Mild (>=60) | Y | Y | Y | Y/Y/Y |
| Baseline *Candida* species [3] | - albicans<br>- dubliniensis<br>- glabrata<br>etc. | Y | Y | Y | |
| Prior antifungal therapy activity within 4 days of treatment start | - No therapy<br>- 1 - <24 hours<br>- ≥24 hours | Y | Y | | |
| APACHE II score | - <10<br>- 10-19<br>- ≥20 | Y | Y | Y | |
| Catheter status within 48 hours after diagnosis | - Removed<br>- Not Removed | Y | Y | Y | |

[1] Efficacy outcomes at Day 14 (±1) will be presented for all subgroups listed. Efficacy outcomes at additional timepoints will also be presented for some subgroups as described in Section 5.3.

[2] Normalized estimated creatine clearance (eCrCl) is based on the Cockcroft-Gault formula normalized to an average height of 1.73 meters, using the lower of actual body weight and ideal body weight to calculate body surface area. The eCrCl results are in mL/min per $1.73*m^2$.

[3] For the *Candida* species subgroup analyses, only success (eradication or cure) rates for the corresponding efficacy outcomes will be provided. The other subgroup analyses will present all three response categories.

In addition to the above subgroups, overall response at Day 14 (±1) will be presented for the following subsets:

- Subjects in the mITT population excluding those who received more than 1 dose of a systemic concomitant antifungal up to Day 14 for treatment of an infection other than candidemia/IC (with the exception of subjects who received a rescue antifungal for the treatment of candidemia). Any subjects deemed a success will be excluded if receiving more than 1 dose of systemic antifungal for any indication.
- Subjects in the mITT2 population who receive no prior antifungal therapy.
- Subjects in the mITT3 population who receive no prior antifungal therapy.

Lastly, overall response and investigator's clinical response at FU will be presented for the mITT population excluding both of the following two subsets:

- Candidemia subjects deemed successes who received more than 1 dose of a systemic concomitant antifungal up through Day 21 for treatment of an infection other than candidemia/IC (with the exception of subjects who received a rescue antifungal for the treatment of candidemia) or who received more than 1 dose of a non-study antifungal after Day 21 for the treatment of an infection other than candidemia/IC.
- IC subjects deemed successes who received more than 1 dose of a systemic concomitant antifungal up through Day 28 for treatment of an infection other than candidemia/IC (with the exception of subjects who received a rescue antifungal for the treatment of candidemia) or who received more than 1 dose of a non-study antifungal after Day 28 for the treatment of an infection other than candidemia/IC.

## 3.9. Withdrawals, Dropouts, Loss to Follow-up

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

## 3.10. Missing, Unused, and Spurious Data

Every effort will be made to collect all data at specified times.

For the efficacy response outcomes, subjects with missing response data are considered to have an indeterminate response unless the subject was a determined to be a failure at an earlier timepoint. Subjects with an indeterminate response are included in the denominator of the success/cure rate calculation and thus, are treated in the same manner as failures in the analysis.

If the start time for a non-study medication starting on same day of treatment start is missing, the medication will be considered concomitant. If the start time for an adverse event starting on same day of treatment start is missing, the adverse event will be considered treatment-emergent. If start and end dates are missing entirely the event will be considered treatment-emergent.

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR.

## 3.11. Visit Windows

Study procedures should be completed within the windows provided in the Schedule of Assessments and Procedures in Table 1-1. Visit windows for each evaluation are specified in Table 3-2.

**Table 3-2: Visit Windows**

| Evaluation | Protocol-Specified Interval | Efficacy Analysis Window |
|---|---|---|
| Screening | Study Day -2 to Study Day 1 | Study Day -2 to Study Day 1 |
| Baseline | Study Day 1 (last measurement prior to the administration of the first dose of study drug) | Study Day 1 (last measurement prior to the administration of the first dose of study drug) |
| Day 5 | Study Day 5 to Study Day 9 | Study Day 5 to Study Day 9 |
| Day 14 (±1 day) | Study Day 13 to Study Day 15 | Study Day 13 to Study Day 21, unless study drug was terminated prior to Day 13 and had the efficacy assessment on EOT. 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. |
| Day 28 (±2 day) | Study Day 26 to Study Day 30 (for IC subjects) | Study Day 26 to Study Day 30 (for IC subjects) |
| Follow-up | Study Day 45 to Study Day 52 (Study Day 52 to Study Day 59 for IC subjects) | Study Day 38 to Study Day 59 (Study Day 45 to Study Day 66 for IC subjects) |

For summaries of safety, including vital signs, 12-lead ECGs, and clinical laboratory parameters, summaries will be provided by Study Day (as appropriate) while on therapy, at the EOT and FU visits. If more than 1 measurement is available within the EOT visit window (+2 days after last dose of study drug), the measurement taken closest to last dose of study drug will be used. If more than 1 measurement is available within the FU visit (Days 45-52; Days 52-59 for IC subjects), the measurement taken on the nominal visit will be used. If no nominal FU visit is available, the earliest measurement in the window will be used.

## 3.12. Interim Analyses

To demonstrate preliminary efficacy and safety of CD101, an interim analysis will be performed after approximately 50-70 subjects in the mITT population have been enrolled in Part A, completed study drug therapy, and the data are deemed clean. Several steps will be implemented to help avoid bias including: the analysis will be performed by an unblinded statistician who is not involved in the day to day statistical and data management aspects of the study, the tables will provide summary data by treatment group assignment but the group assignment of each individual subject will remain blinded until the completion of the study, and only a few key efficacy and safety tables will be provided.

This unblinded interim analysis will consist of the 5 efficacy and safety tables listed below:

- Table 14.2.1.1 Overall Response at Day 14 (mITT Population)
- Table 14.2.4.1 Investigator's Assessment of Clinical Response at Day 14 and Follow-up (mITT Population)
- Table 14.3.1.1 Summary of Treatment-Emergent Adverse Events (Safety Population)
- Table 14.3.1.3 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)
- Table 14.3.3.3 Post-Baseline Shifts of >=2 Toxicity Grades for Laboratory Parameters (Safety Population)

Guidelines for determining continuation of Part B following the interim analysis will be provided in a note-to-file memo and will be utilized by the unblinded analysis team. The determination of whether or not to continue Part B as described in the protocol will be made by the unblinded analysis team and the recommendation will be forwarded on to Sponsor. If any of the 'stopping criteria' outlined in the memo are met, the medical team and statistician will be unblinded for the 5 tables only, and determine if it is safe to proceed to Part B.

## 3.13. Timing of Part A and Part B Analyses

Once Part A is completed, the database for Part A will be locked and a full unblinded analysis with all summary tables will be performed on Part A alone. Individual subject data will only be made available to the Sponsor if needed to better understand the efficacy and safety of CD101.

The data from Part B will only be unblinded and analyzed after database lock for Part B at completion of the study.

All analyses will be completed for Part A. Selected analyses will be completed only for Part B and for Parts A and B combined.

# 4. PATHOGEN DETERMINATION

Fungal pathogen determination from blood specimens is based on the genus and species identification of isolates. If the genus identification is the same between the local and central mycology laboratory but the species identification is discrepant, the central laboratory identification will be used. If the local laboratory grows an isolate but the central laboratory is not able to grow the isolate, if isolates were lost during transportation or storage, or there are major discrepancies between the local and central laboratory in the identification of species, the central laboratory will request the local laboratory to resend the isolate. If the central laboratory identification is not available for an isolate, the local laboratory identification will be used. For any remaining major discrepancies in species identification between the central and local laboratory, the central laboratory identification will be used as the default identification. This procedure will be followed for identification of fungal pathogens at baseline and any post-baseline time points.

Any *Candida* species isolated from blood cultures or normally sterile sites will be considered pathogens in this study. Fungal isolates other than *Candida* and bacterial isolates from blood cultures will not be considered pathogens for this study.

# 5. STATISTICAL ANALYSIS

## 5.1. Study Population

All analyses describing the study population (Section 5.1.1 through Section 5.1.7) will be conducted separately for Parts A and B unless otherwise noted.

### 5.1.1. 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 reason(s) for exclusion from the mITT population will be summarized and a corresponding listing for the ITT population will be provided showing each subject's inclusion in or exclusion from the Safety and mITT populations and reason(s) for exclusion. The number and percentage of subjects prematurely withdrawing from the study and the primary reason for premature withdrawal will be summarized by treatment group for the ITT population as will the number and percentage of subjects prematurely discontinuing study drug regimen and the primary reason for premature discontinuation. 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 criterion not met and exclusion criterion met.

### 5.1.2. Protocol Deviations

A by-subject listing of all protocol deviations, with a flag for minor and major deviations by treatment group will be produced.

### 5.1.3. Demographics and Baseline Characteristics

Demographic information including sex, females of child-bearing potential, race, ethnicity, age, age category (<65 years versus ≥65 years), diagnosis (candidemia and/or IC), height, weight, body mass index (BMI), estimated creatinine clearance (based on Cockcroft-Gault formula), Child-Pugh score category for those subjects with a history of chronic cirrhosis (<7 and 7-9) and APACHE II score category (<10, 10-19, and ≥20) will be summarized by treatment group and overall for each study population. Age will be calculated and entered into the eCRF by the site and will be based on the date of informed consent (date of informed consent minus the date of birth, in years). BMI ($kg/m^2$), calculated by dividing weight (kg) by height ($m^2$) will be captured in the eCRF.

The Cockcroft-Gault formula for estimated creatinine clearance (eCrCl) is:

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

Demographic summaries by treatment group will also be presented for the ITT population in the geographic region, hepatic insufficiency, renal function status, and renal disease subgroups defined in Section 3.8. By-subject listings for all demographics and baseline characteristics will also be provided.

### 5.1.4. Medical and Surgical History

Medical and surgical history, including procedures recorded at screening will be summarized by treatment group, system organ class (SOC), and preferred term (PT) using version 19.0 of MedDRA in the Safety population. For these summaries, subjects with more than 1 medical/surgical history within the same SOC or PT will be counted only once for that SOC or PT.

### 5.1.5. *Candida* Risk Factors

Analyses of *Candida* risk factors will be completed for Part A and for combined Parts A and B.

The number and percentage of subjects with each of the following risk factors at Screening will be summarized by treatment group in the mITT population: central vascular catheter (CVC), active malignancy, use of broad-spectrum antibiotic therapy, diabetes mellitus, immunosuppression, major surgery, total parenteral nutrition, transplant recipient (solid organ, bone marrow), trauma, dialysis, burns, pancreatitis, and admission to the Intensive Care Unit (ICU). For subjects admitted to the ICU, descriptive statistics for the length of time in days will be summarized. For subjects who had a catheter, a summary of the number and percentage of subjects by type of catheter will also be provided. Descriptive statistics for the longest duration of catheter placement by type of catheter for each subject at screening will also be provided. 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.

### 5.1.6. Systemic Signs of Candidemia and/or IC at Baseline

The number and percentage of subjects with systemic signs at baseline determined to be attributed to candidemia and/or IC by the PI will be summarized by treatment group for subjects in the mITT population. Signs include fever, hypothermia, hypotension, tachycardia, and tachypnea. A by-subject listing of systemic signs and symptoms assessed at baseline, Day 5 (signs only), Day 14 (±1), Day 28 (±2 for IC subjects) and the FU 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.

### 5.1.7. Baseline Fungal Pathogens

The genus and species of fungal pathogens identified from baseline blood cultures and normally sterile sites will be summarized by treatment group for subjects in the mITT population.

For each baseline *Candida* species, 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 CD101, caspofungin, anidulafungin, micafungin, and fluconazole. In addition, for each baseline *Candida* species, the $MIC_{50}$, $MIC_{90}$, and $MIC_{Range}$ for CD101, caspofungin, and fluconazole will be summarized, 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.

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 results for any baseline *Candida* species that is resistant to fluconazole.

## 5.2. Extent of Exposure and Concomitant Procedures

Analyses of study drug exposure will be conducted for Part A, Part B, and Parts A and B combined. Analyses of prior and concomitant medications and procedures will be conducted separately for Parts A and B.

### 5.2.1. Study Drug Exposure

Descriptive statistics for the duration of study drug therapy (IV and oral) will be summarized by treatment group for the Safety and mITT populations. Treatment duration is defined as the date of the last dose of study drug - first dose of study drug +1 day. The number and percentage of subjects with 1–7, 8-14, 15-21 and >21 days of exposure (IV and oral) as defined above will be presented. 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 with 1-3, 4-7, 8-14 and 15-21 days of IV therapy will be presented. Additionally, the study drug exposure summaries by treatment group will be presented for the Safety population in the geographic region, hepatic insufficiency, renal function status, and renal disease subgroups defined in Section 3.8.

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.

Analyses of study drug exposure in mITT population will only be conducted in Parts A and B combined.

### 5.2.2. 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) (March 2016) classification level 3 and PT. Medications are considered prior if they are received prior to the first dose of study drug (start date is prior to the first dose of study drug or in the case of antifungals if the start date and time is prior to the date and time of 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/time is on or after the first dose of study drug, stop date/time is after the first dose of study drug), or if the stop date is unknown or continuing.

The number and percentage of subjects who receive the following categories of prior and concomitant medications will be summarized by treatment group in the mITT population for Parts A and B combined:

- Systemic antifungal medications received prior to the first dose of study drug and given for indication of either candidemia or IC.
- Systemic antifungal medications (excluding study drug) received on/after the first dose of study drug through the FU visit and given for indication of either candidemia or IC.

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.

### 5.2.3. Concomitant Procedures

Concomitant procedures will be summarized by treatment group, SOC, and PT using version 19.0 of MedDRA in the mITT population. If the same procedure (based on PT) is

reported for the same subject more than once, the medical/surgical history 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/time is on or after the first dose of study drug, stop date/time 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.

## 5.3. Analysis of Efficacy

All efficacy analyses will be conducted in the mITT population for Part A, Part B, and Parts A and B combined, unless otherwise specified. Subjects will be analyzed in the treatment group to which they were randomized. By subject listings of the overall response, Investigator's assessment of response and systemic signs and symptoms assessments will be provided.

### 5.3.1. Primary Efficacy Outcome - Overall Success at Day 14 (±1 day)

The number and percentage of subjects programmatically determined to be an overall success (mycological eradication and resolution of clinical signs of candidemia and/or IC), failure, or with an indeterminate overall response at Day 14 (±1) will be summarized by treatment group for subjects in the mITT population. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method.

The overall response summary at Day 14 (±1 day) will also be summarized separately for the following subgroup analyses defined in Section 3.8:

- Diagnosis of candidemia only and IC (with or without candidemia)
- Geographic Region
- Hepatic Insufficiency at Screening
- Renal Function Status at Screening
- Renal Disease at Screening
- Prior antifungal therapy activity
- APACHE II score
- Catheter status at Baseline

For these subgroup analyses, exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group within the subgroups will be determined using the Clopper-Pearson method. If the number of subjects in the subgroup overall is <10, 95% CI will not be provided for the percentage of subjects who achieve success. The subgroup analyses by prior antifungal therapy, APACHE II score, and catheter status will only be summarized for Parts A and B combined.

The reasons for failure or indeterminate overall response at Day 14 (±1) will be summarized by treatment group for all subjects in the mITT population with an overall response of failure or indeterminate at Day 14 (±1).

A summary will be provided for overall response at Day 14 (±1) excluding those subjects in the mITT population who received more than 1 dose of a concomitant antifungal (with the exception of subjects who received a rescue antifungal for the treatment of candidemia) up

through Day 14 (±1) in addition to study drug. This subset to be excluded is described in Section 3.8. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method.

A summary of overall response at Day 14 (±1) will be provided for Parts A and B combined in the mITT2 and mITT3 populations and for subjects in the mITT2 and mITT3 populations without prior antifungal therapy. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method. If the number of subjects in a category (with prior antifungal therapy or without prior antifungal therapy) is <10, 95% CI will not be provided for the percentage of subjects who achieve success in that category.

### 5.3.2. Secondary Efficacy Outcomes

#### 5.3.2.1. Overall Response at Day 5, Day 28 (±2) and Follow-up

The number and percentage of subjects with an overall success, failure, and indeterminate response at Day 5 and FU will be summarized by treatment group for subjects in the mITT population. The overall response summary will also be performed by diagnosis. The overall response at Day 5 and FU will be performed for subjects with candidemia only in the mITT population and at Day 5, Day 28 and FU for subjects with IC (with or without candidemia) in the mITT population. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method. If the number of subjects with IC overall is <10, 95% CI will not be provided for the percentage of subjects who achieve success.

An additional analysis of overall response at FU will be conducted excluding subjects who received more than 1 dose of a concomitant antifungal (with the exception of subjects who received a rescue antifungal for the treatment of candidemia and/or IC) up through Day 21 (for subjects with candidemia only) or Day 28 (for subjects with IC, with or without candidemia) or who receive more than 1 dose of a non-study antifungal after Day 21 or Day 28 for the treatment of an infection other than candidemia and/or IC. This subset to be excluded is described in Section 3.8. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method.

The overall response summary at Day 5 and Follow-up will also be summarized separately for the following subgroup analyses defined in Section 3.8:

- Diagnosis of candidemia only and IC (with or without candidemia)
- Geographic Region
- Hepatic Insufficiency at Screening
- Renal Function Status at Screening
- Renal Disease at Screening

Additionally, the overall response summary at Day 28 (±2) will be summarized only for diagnosis of IC (with or without candidemia). For each subgroup analyses, exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group within the subgroups will be determined using the Clopper-Pearson method. If the number of subjects in the subgroup overall is <10, 95% CI will not be provided for the percentage of subjects who achieve success.

#### 5.3.2.2. Mycological Response at Day 5, Day 14 (±1), Day 28 (±2) and Follow-up

The number and percentage of subjects programmatically determined as having a mycological success (eradication), failure, or with an indeterminate mycological response at Day 5, Day 14 (±1), and FU will be summarized, by treatment group for subjects in the mITT population. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method. If the number of subjects with IC overall is <10, 95% CI will not be provided for the percentage of subjects who achieve success.

The mycological response summary at Day 5, Day 14 (±1), and Follow-up will also be summarized separately for the following subgroup analyses defined in Section 3.8:

- Diagnosis of candidemia only and IC (with or without candidemia)
- Geographic Region
- Hepatic Insufficiency at Screening
- Renal Function Status at Screening
- Renal Disease at Screening
- Prior antifungal therapy activity
- APACHE II score
- Catheter status at Baseline

Additionally, the mycological response summary at Day 28 (±2) will be summarized only for diagnosis of IC (with or without candidemia). For each subgroup analyses, exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group within the subgroups will be determined using the Clopper-Pearson method. If the number of subjects in the subgroup overall is <10, 95% CI will not be provided for the percentage of subjects who achieve success. The subgroup analyses by prior antifungal therapy, APACHE II score, and catheter status will only be summarized for Parts A and B combined.

#### 5.3.2.3. Investigator's Assessment of Clinical Response at Day 14 (±1), Day 28 (±2), and the Follow-up Visit

The number and percentage of subjects determined by the PI to be a clinical cure, failure, or with an indeterminate clinical response at Day 14 (±1) and at the FU visit will be summarized by treatment group for subjects. The Investigator's assessment of clinical response will also be provided by diagnosis. The Investigator's assessment of clinical response at Day 14 and FU will be performed for subjects with candidemia only in the mITT population and at Day 14, Day 28, and FU for subjects with IC (with or without candidemia) in the mITT population. Exact 2-sided 95% CIs for the percentage of subjects who achieve cure in each treatment group will be determined using the Clopper-Pearson method. If the number of subjects with IC overall is <10, 95% CI will not be provided for the percentage of subjects who achieve success.

The reasons for failure or indeterminate clinical response at Day 14 (±1) and FU visit will be summarized by treatment group for all subjects in the mITT population.

An additional analysis of clinical response at FU will be conducted excluding subjects who received more than 1 dose of a concomitant antifungal (with the exception of subjects who received a rescue antifungal for the treatment of candidemia and/or IC) up through Day 21 (for subjects with candidemia only) or Day 28 (for subjects with IC, with or without candidemia) or

who receive more than 1 dose of a non-study antifungal after Day 21 or Day 28 for the treatment of an infection other than candidemia and/or IC. This subset to be excluded is described in Section 3.8. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method.

The clinical response summaries will also be stratified separately for the following subgroup analyses defined in Section 3.8:

- Diagnosis of candidemia only and IC (with or without candidemia)
- Geographic Region
- Hepatic Insufficiency at Screening
- Renal Function Status at Screening
- Renal Disease at Screening
- APACHE II score
- Catheter status at Baseline

For these subgroup analyses, exact 2-sided 95% CIs for the percentage of subjects who are determined to be a cure in each treatment group within the subgroups will be determined using the Clopper-Pearson method. If the number of subjects in the subgroup overall is <10, 95% CI will not be provided for the percentage of subjects who achieve success. The subgroup analyses by APACHE II score and catheter status will only be summarized for Parts A and B combined.

A summary of subjects determined by the PI to be a clinical cure, failure, or with an indeterminate clinical response at Day 14 (±1) and at the FU visit will be provided for Parts A and B combined in the mITT2 and mITT3 populations and for subjects in the mITT2 and mITT3 populations without prior antifungal therapy. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method.

#### 5.3.3. Additional Efficacy Outcomes

##### 5.3.3.1. All-cause Mortality through Day 30 and Follow-up

The number and percentage of subjects who died up through the FU visit (all-cause mortality) will be summarized by treatment group in the ITT and mITT populations. The 25$^{th}$, 50$^{th}$ (median), and 75$^{th}$ percentiles will be provided by treatment group using Kaplan-Meier methods. Subjects who do not die or who are lost to follow-up will be censored at the last date known to be alive. The number and percentage of subjects censored will be provided. The Kaplan-Meier estimate of 30-day all-cause mortality will also be provided along with the 95% CI calculated using Greenwoods formula. The Kaplan-Meier curve will be presented by treatment group. A listing of the primary cause of death will also be provided.

##### 5.3.3.2. Time to Negative Blood Culture

The time to negative blood culture (hours) will be analyzed using Kaplan-Meier methodology by treatment group, and for the CD101 treatment groups combined, in the mITT population. Summaries will include the 25$^{th}$, 50$^{th}$ (median), and 75$^{th}$ percentiles. The number and percentage of subjects censored and the reason for censoring (receipt of more than 1 dose of non-study antifungal for the treatment of candidemia and/or IC [with the exception of a rescue antifungal],

lost to follow up prior to having 2 negative blood cultures) will also be provided. A graph of the Kaplan-Meier curves will be provided.

#### 5.3.3.3. Overall Success at Day 14 (±1) by Baseline *Candida* species

The number and percentage of subjects programmatically determined to be an overall success (mycological eradication and resolution of clinical signs of candidemia) at Day 14 (±1) will be summarized by baseline *Candida* spp. and treatment group for subjects in the mITT population.

Overall success by baseline *Candida* species and MIC cutoff for CD101, caspofungin and fluconazole at Day 14 (±1) will be summarized by treatment group for subjects in the mITT population.

#### 5.3.3.4. Mycological Success at Day 14 (±1) by Baseline *Candida* species

The number and percentage of subjects determined to be a mycological success (eradication/presumed eradication) at Day 14 (±1) will be summarized by baseline *Candida* species and treatment group for subjects in the mITT population.

Mycological success by baseline *Candida* species and MIC cutoff for CD101, caspofungin and fluconazole at Day 14 (±1) will be summarized by treatment group for subjects in the mITT population.

#### 5.3.3.5. Investigator's Assessment of Clinical Cure by Baseline *Candida* species

The number and percentage of subjects determined to be a clinical cure at Day 14 (±1) will be summarized by baseline *Candida* species and treatment group for subjects in the mITT population. The Investigator's assessment of clinical cure by baseline *Candida* species and MIC cutoff for CD101, caspofungin and fluconazole at Day 14 (±1) will be summarized by treatment group for subjects in the mITT population.

#### 5.3.3.6. Exploratory Overall Response at Day 14 (±1) and Exploratory Mycological Response at Day 14 (±1)

The number and percentage of subjects having overall success, failure, and indeterminate response at Day 14 (±1) will be summarized by treatment group for subjects in the mITT population. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method.

The number and percentage of subjects programmatically determined as having a mycological success (eradication), failure, or with an indeterminate mycological response at Day 14 (±1) will be summarized by treatment group for subjects in the mITT population. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method.

#### 5.3.3.7. Exploratory Overall Success at Day 14 (±1) by Baseline *Candida* species

The number and percentage of subjects with an exploratory overall success at Day 14 will be summarized by baseline *Candida* species and treatment group for subjects in the mITT population for Parts A and B combined. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method.

#### 5.3.3.8. Exploratory Mycological Success at Day 14 (±1) by Baseline *Candida* species

The number and percentage of subjects programmatically determined as having an exploratory mycological response at Day 14 (±1) of success (eradication) will be summarized by baseline *Candida* species and treatment group for subjects in the mITT population for Parts A and B combined. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group will be determined using the Clopper-Pearson method.

### 5.3.4. CD101 Plasma Concentration

Summary statistics (number of subjects, mean, SD, coefficient of variability % (CV%), median, min, max, geometric mean) of CD101 plasma concentration will be provided by time point and dose group for CD101 treated subjects in the PK population. Each CD101 dose group will be summarized separately for all timepoints and combined for all timepoints except Day 15. Only samples collected on Day1, Day 2, Day 4, Day 8 and Day 15 and within 10% of the nominal time (where applicable) will be included. Analyses of CD101 plasma concentration will only be conducted for Part A.

## 5.4. 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 treatment will be analyzed in the treatment group based on the drug received. All safety analyses will be completed for Part A, Part B, and for combined Parts A and B.

### 5.4.1. Adverse Events

Verbatim descriptions of AEs will be coded using MedDRA Version 19.0. Summary tables will be provided for all treatment-emergent adverse events (TEAE). A TEAE is defined as an AE that occurs during or after the administration of the first dose of study drug and up through the FU visit. 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. If AE start and end dates are missing entirely the event will be considered treatment-emergent.

An overall summary of TEAEs will include the number and percentage of subjects in each treatment group who experienced at least 1 TEAE in the following categories: any TEAE, any study drug-related TEAE, any severe TEAE, any serious TEAE (SAE), any study drug-related SAE, any SAE leading to death, and any TEAE leading to discontinuation of study drug. Subjects with multiple events will be counted only once within each category. Severity and relationship will be counted using the maximum severity 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 severity (mild, moderate, or severe); and by SOC, PT, and relationship (unrelated or related) to study drug. The incidence of all TEAEs and all non-serious TEAEs that occur in at least 5% of subjects in the combined CD101 treatment groups will be summarized separately by PT and treatment group, sorted by decreasing frequency in the combined CD101 treatment groups. 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 severity 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 leading to discontinuation of study drug will be summarized by SOC and PT.

The TEAE and maximum severity TEAE summaries by treatment group will also be presented for the Safety population in the hepatic insufficiency, renal function status, and renal disease subgroups defined in Section 3.8.

In addition to a listing of all reported AEs, by-subject listings of all SAEs (including any SAEs with an outcome of death) and all TEAEs leading to discontinuation of IV/oral study drug will be provided.

### 5.4.2. 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):

$$s = x\frac{U_S}{U_X}$$

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.

Descriptive statistics (based on Systeme Internationale [SI] units) for chemistry, hematology and coagulation (baseline and unscheduled post-baseline only), and urinalysis (only pH and specific gravity) 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 SAP Section 6.1. 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.

The normalized laboratory values will be classified by toxicity grade according to the toxicity grading scales in SAP Section 6.2, which are based on the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Scale, November 2007, the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004, and the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0), Publish Date: 28 May 2009.

Shift tables will be presented to show the number of subjects with each toxicity grade 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 (eg, 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.

The number and percentage of subjects in each treatment group with an elevated transaminase level (>3 ×ULN, >5 ×ULN, and >10 ×ULN), an elevated total and direct bilirubin level (>1.5 ×ULN and >2 ×ULN) will be presented by study visit. A listing of subjects who meet the laboratory criteria for Hy's law will also be provided for Parts A and B combined. Two alternative definitions of criteria for Hy's law will be considered, defined as 1) (ALT or AST) >3 ×ULN, ALP ≤2.0 ×ULN, and total bilirubin >1.5 ×ULN; and 2) (ALT or AST) >3 ×ULN, ALP ≤2.0 ×ULN, and total bilirubin >2 ×ULN. Using a conservative approach for detecting any potential Hy's law cases, subjects meeting either criteria based on any combination of post-baseline laboratory results, irrespective of their temporal association, 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.

Detailed patient listings of all laboratory data collected during the study will be provided. Laboratory values outside normal limits will be identified in the patient data listings. A column will display any applicable toxicity grading of the laboratory value.

### 5.4.3. Vital Signs

Several analyses of vital signs data will be presented. 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 treatment 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 value. For this summary, data for subjects who are no longer hospitalized at a particular visit will be included in both summaries of highest and lowest value for that visit, since highest and lowest values are only captured in the eCRF for visits during which a subject is hospitalized.

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 5-1, will be provided for the worst post-baseline value (which includes unscheduled post-baseline measurements). Both the highest and lowest daily vital signs values will be entered into the eCRF for hospitalized subjects. The highest daily value will be used to assess PCS High (CH) values; the lowest daily value will be used to assess PCS Low (CL). 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 5-1: Criteria for Potentially Clinically Significant Vital Signs**

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

### 5.4.4. Electrocardiogram

Descriptive statistics for heart rate, PR interval, RR interval, QRS interval, QT interval, and QT interval with Fridericia correction (QTcF) at Baseline and the EOT visit and the change from baseline at the EOT visit will be summarized by treatment group for subjects in the Safety population. Change from baseline will be calculated for each subject as the value at the EOT visit minus the baseline value. QTcF will be derived programmatically using the QT and RR intervals captured in the eCRF according to the following formula (Fridericia):

$$QT_cF = \frac{QT}{\sqrt[3]{RR}}$$

The number and percentage of subjects with any post-baseline increase in QTcF and any post-baseline increase of >30 msec or >60 msec in QTcF will be summarized by treatment group. The number and percentage of subjects with a post-baseline QTcF of >450 msec or >500 msec will also be summarized by treatment group. The number and percentage of subjects with a post-baseline increase in QTcF of >30 msec resulting in a post-baseline QTcF of >450 msec or >500 msec will also be summarized by treatment group. The distribution of QTcF values (≤450 msec, >450 - ≤480 msec, >480 - ≤500 msec, and >500 msec) at EOT and the distribution of change from baseline in QTcF values at EOT (0 or less (no increase), 1-29 msec, 30-60 msec, and >60 msec) will be summarized by treatment group for subjects in the Safety population.

A by subject listing of all measurements obtained from ECG assessments will be provided.

### 5.4.5. Physical and Retinal Examinations

Physical exam findings from Screening, Day 14 (±1), Day 28 (±2), and the FU visit will be presented in a by-subject listing. Abnormal findings from retinal examinations and whether or not the subject had evidence of *Candida* endophthalmitis will be provided in a by-subject listing.

### 5.4.6. Radiological Evaluations

Results of radiological testing will be provided in by-subject listings.

# 6. APPENDICES

## 6.1. Appendix 1: Directionality of Worst Laboratory Parameters

**Table 6-1: 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 |
| Coagulation | Prothrombin time | Highest value |
| | International normalized ratio (INR) | Highest value |
| | Partial thromboplastin time (PTT) | Highest value |
| | Activated PTT | Highest value |

## 6.2. Appendix 2: Clinical Laboratory Toxicity Grading Scales

### Table 6-2: Hematology and Coagulation Toxicity Grading Scale

| **Hematology and Coagulation** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Direction** | **Grade 0 / Normal** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Source** |
| Hemoglobin | Decrease | >10.5 gm/dL | 9.5 – 10.5 gm/dL | 8.0 – 9.4 gm/dL | 6.5 – 7.9 gm/dL | <6.5 gm/dL | DMID |
| WBCs | Increase | 1,000-10,999 /$mm^3$ | 11,000-13,000 /$mm^3$ | 13,000-15,000 /$mm^3$ | 15,000-30,000 /$mm^3$ | >30,000 or <1,000 /$mm^3$ | DMID |
| Absolute Neutrophil Count | Decrease | >1500 /$mm^3$ | 1000-1500 /$mm^3$ | 750-999 /$mm^3$ | 500-749 /$mm^3$ | <500 /$mm^3$ | DMID |
| Platelets | Decrease | >99,999 /$mm^3$ | 75,000-99,999 /$mm^3$ | 50,000-74,999 /$mm^3$ | 20,000-49,999 /$mm^3$ | <20,000 /$mm^3$ | DMID |
| Prothrombin Time (PT) | Increase | <1.01 ×ULN | 1.01-1.25 ×ULN | 1.26-1.5 ×ULN | 1.51-3.0 ×ULN | >3 ×ULN | DMID |
| Activated Partial Thromboplastin (APPT) | Increase | <1.01 ×ULN | 1.01-1.66 ×ULN | 1.67-2.33 ×ULN | 2.34-3 ×ULN | >3 ×ULN | DMID |

## Table 6-3: Chemistry Toxicity Grading Scale

| Chemistry | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Direction** | **Grade 0 / Normal** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Source** |
| Blood urea nitrogen (BUN) | Elevation | <1.25 ×ULN | 1.25-2.5 ×ULN | 2.6-5 ×ULN | 5.1-10 ×ULN | >10 ×ULN | DMID |
| Bilirubin (total and direct) | Hyperbilirubinemia (when accompanied by any increase in other liver function test) | <1.1 ×ULN | 1.1-<1.25 ×ULN | 1.25-<1.5 ×ULN | 1.5-1.75 ×ULN | >1.75 ×ULN | DMID |
| | Hyperbilirubinemia (when other liver functions are in the normal range) | <1.1 ×ULN | 1.1-<1.5 ×ULN | 1.5-<2.0 ×ULN | 2.0-3.0 ×ULN | >3.0 ×ULN | DMID |
| Albumin | Hypoalbuminemia | | 3.0 g/dL-<LLN | 2.0-<3 g/dL | <2.0 g/dL | N/A | CTCAE |
| Sodium | Hyponatremia | >135-<146 mEq/L | 130-135 mEq/L | 123-129 mEq/L | 116-122 mEq/L | <116 mEq/L | DMID |
| | Hypernatremia | >135-<146 mEq/L | 146-150 mEq/L | 151-157 mEq/L | 158-165 mEq/L | >165 mEq/L | DMID |
| Potassium | Hypokalemia | >3.4-<5.6 mEq/L | 3.0-3.4 mEq/L | 2.5-2.9 mEq/L | 2.0-2.4 mEq/L | <2.0 mEq/L | DMID |
| | Hyperkalemia | >3.4-<5.6 mEq/L | 5.6-6.0 mEq/L | 6.1-6.5 mEq/L | 6.6-7.0 mEq/L | >7.0 mEq/L | DMID |
| Glucose | Hypoglycemia | >64-<116 mg/dL | 55-64 mg/dL | 40-54 mg/dL | 30-39 mg/dL | <30 mg/dL | DMID |
| | Hyperglycemia (nonfasting and no prior diabetes) | >64-<116 mg/dL | 116-160 mg/dL | 161-250 mg/dL | 251-500 mg/dL | >500 mg/dL | DMID |
| Creatinine | Elevation | <1.1 ×ULN | 1.1-1.5 ×ULN | 1.6-3.0 ×ULN | 3.1-6 ×ULN | >6 ×ULN | DMID |
| Total protein | | | | | | | |
| Calcium | Hypocalcemia | >8.4-<10.6 mg/dL | 8.4-7.8 mg/dL | 7.7-7.0 mg/dL | 6.9-6.1 mg/dL | <6.1 mg/dL | DMID |
| | Hypercalcemia | >8.4-<10.6 mg/dL | 10.6-11.5 mg/dL | 11.6-12.5 mg/dL | 12.6-13.5 mg/dL | >13.5 mg/dL | DMID |
| Bicarbonate | Low | | 16 mEq-<LLN | 11.0-15.9 mEq/L | 8.0-10.9 mEq/L | <8.0 mEq/L | DAIDS |

**Table 6-4: Enzymes Toxicity Grading Scale**

| Enzymes | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Direction** | **Grade 0 / Normal** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Source** |
| Alkaline phosphatase (ALP) | Elevation | <1.1 ×ULN | 1.1-<2.0 ×ULN | 2.0-<3.0 ×ULN | 3.0-8.0 ×ULN | >8 ×ULN | DMID |
| Aspartate aminotransferase (AST/SGOT) | Elevation | <1.1 ×ULN | 1.1-<2.0 ×ULN | 2.0- <3.0 ×ULN | 3.0- 8.0 ×ULN | >8 ×ULN | DMID |
| Alanine aminotransferase (ALT/SGPT) | Elevation | <1.1 ×ULN | 1.1-<2.0 ×ULN | 2.0-<3.0 ×ULN | 3.0-8.0 ×ULN | >8 ×ULN | DMID |

## 6.3. Appendix 3: Laboratory Normals

**Table 6-5: Hematology Laboratory Normals**

| Hematology | | | |
|---|---|---|---|
| | **LLN** | **ULN** | **Source** |
| Hemoglobin | | | |
| Male | 13.8 gm/dL | 17.2 gm/dL | NLM |
| Female | 12.1 gm/dL | 15.1 gm/dL | NLM |
| Hematocrit | | | |
| Male | 40.7% | 50.3% | NLM |
| Female | 36.1% | 44.3% | NLM |
| White blood cell count | 4,500 cells/mcL | 10,000 cells/mcL | NLM |
| Differential leukocyte count | | | |
| Neturophils | 40% | 60% | NLM |
| Lymphocytes | 20% | 40% | NLM |
| Monocytes | 2% | 8% | NLM |
| Eosinophils | 1% | 4% | NLM |
| Basophils | 0.50% | 1% | NLM |
| Red blood cell count | | | |
| Male | 4.7 $\times 10^6$ cells/mcL | 6.1 $\times 10^6$ cells/mcL | NLM |
| Female | 4.2 $\times 10^6$ cells/mcL | 5.4 $\times 10^6$ cells/mcL | NLM |
| Platelet count | 150,000/dL | 450,000/dL | NLM |

## Table 6-6: Coagulation Laboratory Normals

| **Coagulation** | | | |
|---|---|---|---|
| | **LLN** | **ULN** | **Source** |
| Prothrombin time (International Normalized Ratio) | | | |
| No warfarin | 11 seconds (0.8) | 13.5 seconds (1.1) | NLM |
| With warfarin | (2.0) | (3.0) | NLM |
| Partial thromboplastin time (PTT) or activated partial thromboplastin time (APTT) | | | |
| No warfarin | 25 seconds | 35 seconds | NLM |

## Table 6-7: Serum Chemistry Laboratory Normals

| **Serum Chemistry** | | | |
|---|---|---|---|
| | **LLN** | **ULN** | **Source** |
| Blood urea nitrogen | 6 mg/dL | 20 mg/dL | NLM |
| Bilirubin | | | |
| Direct | 0 mg/dL | 0.3 mg/dL | NLM |
| Total | 0.3 mg/dL | 1.9 mg/dL | NLM |
| Alkaline phosphatase (ALP) | 44 IU/L | 147 IU/L | NLM |
| Aspartate aminotransferase (AST/SGOT) | 10 U/L | 34 U/L | NLM |
| Alanine aminotransferase (ALT/SGPT) | | | |
| Male | 10 U/L | 40 U/L | NLM |
| Female | 7 U/L | 35 U/L | NLM |
| Albumin | 3.4 g/dL | 5.4 g/dL | NLM |
| Sodium | 135 mEq/L | 145 mEq/L | NLM |
| Potassium | 3.7 mEq/L | 5.2 mEq/L | NLM |
| Chloride | 96 mEq/L | 106 mEq/L | NLM |
| Calcium | 8.5 mg/dL | 10.2 mg/dL | NLM |
| Glucose | | | |
| Fasting | 70 mg/dL | 100 mg/dL | NLM |
| Random | | 125 mg/dL | NLM |
| Creatinine | | | |
| Male | 0.7 mg/dL | 1.3 mg/dL | NLM |
| Female | 0.6 mg/dL | 1.1 mg/dL | NLM |
| Total Protein | 6.0 gm/dL | 8.3 gm/dL | NLM |
| Bicarbonate | 23 mEq/L | 29 mEq/L | NLM |
| Procalcitonin | N/A | N/A | NLM |

# 7. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this SAP.

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# 9. REVISION HISTORY

The normalization method applied to clinical laboratory values described in Section 5.4.2 will now use the scale normalization formula instead of location-scale normalization formula described in previous versions of this document.