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
Study Drug	Intravenous CD101
Original Protocol	18FEB2016
Amendment 1	14MAY2016
Amendment 1-IT (Italy only)	02SEP2016
Amendment 2	14SEP2016
Amendment 3	23FEB2017
Amendment 4	05APR2017
Amendment 5	04AUG2017
Amendment 6	20APR2018
Sponsor	Cidara Therapeutics Inc. 6310 Nancy Ridge Dr., Suite 101, San Diego CA 92121 Telephone: 001-858.752.6170 Facsimile: 001-858.408.3509
Sponsor Medical Monitor	Name: Taylor Sandison, MD MPH Company: Cidara Therapeutics Inc. Address: 6310 Nancy Ridge Dr., Suite 101, San Diego CA 92121 Telephone: 001-858.249.7429 Mobile: 001-858.249.9459 Facsimile: 001-858.408.3509
Sponsor Clinical Project Manager	Name: Karen Mena Company: Cidara Therapeutics Inc. Address: 6310 Nancy Ridge Drive, Suite 101, San Diego, CA 92121 Telephone: 001-858.249.7430 Facsimile: 001-858.408.3509
European Union Drug Regulating Authorities Clinical Trials (EudraCT) #	2015-005599-51

PROTOCOL APPROVAL PAGE

Protocol: CD101.IV.2.03

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

Original Protocol: 18FEB2016
Amendment 1: 14MAY2016
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Amendment 2: 14SEP2016
Amendment 3: 23FEB2017
Amendment 4: 05APR2017
Amendment 5: 04AUG2017
Amendment 6: 20APR2018

Signature

24 APRIL 2018
Date

Taylor Sandison, MD MPH
Chief Medical Officer
Cidara Therapeutics, Inc.

1.0 PROTOCOL SYNOPSIS

Sponsor: Cidara Therapeutics Inc., San Diego CA

Product Name: Intravenous CD101

Active Ingredients: CD101 acetate

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

Planned Study Centers: Approximately 60

Phase of Development: 2

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 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) 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 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) 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 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) in the mITT population
- Evaluate the pharmacokinetics (PK) of CD101 IV

Study Design: This is a Phase 2, multicenter, prospective, randomized, double-blind, study of CD101 IV or IV caspofungin followed by oral fluconazole step-down therapy for treatment of subjects with candidemia and/or IC. 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 (Figure 1, Figure 2, Figure 3, Table 1). Oral step-down therapy is allowed in all 3 treatment groups in Part A; oral placebo in the CD101 IV groups and oral fluconazole in the 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. In Part B, subjects will be randomized in a 2:1 ratio to receive CD101 IV treatment or IV caspofungin (Figure 1, Figure 2, Figure 3, Table 1) until ≥45 additional subjects and no more than 120 subjects have been enrolled. (Note: Subjects enrolled under Amendment 5 and assigned to CD101 IV receive Group 1 treatment and subjects enrolled under Amendment 6 and assigned to CD101 IV receive Group 2 treatment. Subjects enrolled to Amendment 5 continue study participation according to the same amendment regardless of subsequent approval of Amendment 6.) Total enrollment will depend on the enrollment rate for the 6- to 8-month period between the end of Part A and the staged start of the Phase 3 study, which is the trigger for the rolling close-out of Part B. 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.

Subjects with candidemia only may be treated with study drug for a maximum of 21 days. Subjects with IC (with or without candidemia) may be treated with study drug for a maximum of 28 days. For this study, subjects will be presumed 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 in vitro diagnostic (IVD) or blood culture for *Candida spp.* combined with radiographic evidence of IC.

Subjects in the CD101 IV treatment Group 1 will receive CD101 IV 400 mg on Day 1 and Day 8, with an optional dose of 400 mg on Day 15 (for all subjects) and an optional dose of 400 mg on Day 22 (only for

subjects with IC), if needed. Subjects in the CD101 IV treatment Group 2 will receive CD101 IV 400 mg on Day 1 and 200 mg on Day 8, with an optional dose of 200 mg on Day 15 (for all subjects) and an optional dose of 200 mg on Day 22 (only for subjects with IC), if needed. Subjects in the caspofungin group will receive IV caspofungin (a single 70 mg loading dose on Day 1 followed by 50 mg once daily) for ≥3 days up to a maximum of 21 days for subjects with candidemia only and up to a maximum of 28 days for subjects with IC (with or without candidemia). The optional doses of CD101 IV on Day 15 and Day 22 may be administered according to the subject's clinical response and the medical judgment of the Principal Investigator (PI).

After ≥3 days of IV therapy, subjects in the caspofungin group can be switched to oral step-down therapy of fluconazole (a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if criteria are met. In order to maintain the blind, subjects in the CD101 IV groups who have switched to oral step-down therapy will receive oral placebo (4 capsules on the first day followed by 2 capsules /day thereafter) and subjects in the caspofungin treatment group will receive IV placebo on Day 8, and on Days 15 and 22 if study drug is administered through these timepoints. The total IV plus oral treatment duration will be ≥14 days and up to a maximum of 28 days.

The dose and duration of any prior antifungal treatment taken within 4 weeks from randomization will be recorded at Screening. A retinal examination for evidence of a *Candida* eye infection, including endophthalmitis or chorioretinitis, will be performed during Screening or by Day 7 only on subjects with candidemia by blood culture, and should be repeated in subjects who were negative at baseline if the subject develops visual signs or symptoms of a *Candida* eye infection during the course of the study. Subjects who were negative at baseline and diagnosed with a *Candida* eye infection after initiating study drug should have an urgent ophthalmologic consultation (if not already done), should stop study drug, and be initiated on appropriate therapy for *Candida* eye infection per the local guidelines. If possible, all subjects diagnosed with endophthalmitis or choriorentinitis should remain in the study and all subsequent antifungal drugs, interventions, and outcomes for endophthalmitis or chorioretinitis should be recorded.

The Schedule of Assessments and Procedures is presented in Table 2. Study Day 1 is defined as the first day of study drug administration. Subsequent study days are defined by the number of consecutive calendar days thereafter. All subjects will be monitored for adverse events (AEs) and serious adverse events (SAEs) following signing of the Informed Consent Form at screening and throughout the study until the FU visit (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) for each treatment group. Vital signs (temperature, heart rate, blood pressure, respiratory rate) will be recorded daily while receiving IV study drug and at Day 4, Day 5, Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), End-of-Treatment (EOT) (+2 days allowed after last dose of study drug) and FU (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia). Hematology and chemistry laboratory tests will be performed at Screening; Days 2 and 4; Day 8, Day 14 (±1 day), EOT (+2 days allowed after last dose of study drug), and at the FU visits. Coagulation laboratory tests (prothrombin time/international normalized ratio [PT/INR] and either partial thromboplastin time [PTT] or activated partial thromboplastin time [aPTT]) will be performed at Screening. Electrocardiograms (ECGs) will be performed at Screening (before subject randomization) and EOT (+2 days allowed after the last dose of study drug).

Mycological diagnosis of candidemia or IC sufficient for inclusion in the study will be established by a positive microbiological test for yeast or *Candida* within 96 hours from time of collection of the sample until randomization. Acceptable positive microbiological tests for yeast or *Candida* include ≥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. 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. Blood cultures should be performed daily (preferred) or every other day until 2 blood cultures drawn ≥12 hours apart are negative without an intervening positive culture. Generally, blood cultures should involve 2 separate draws with ≥1 draw from a peripheral vein without an IV catheter. Two bottles should be filled from each draw site, totaling 4 bottles for each set of blood cultures. If possible, use 3 aerobic and 1 anaerobic bottle (if available at the site) for each blood culture set.

In Part A only, blood samples will be collected for PK analysis from the OPPOSITE arm of the infusion on Day 1 (within 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 safety labs if possible), Day 4 (random draw, with safety labs if possible), Day 8 (predose only), and Day 15 (predose only). 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. For the purpose of maintaining the blind, blood samples will be collected from all subjects, when possible, in all 3 treatment groups in Part A, but only PK samples from the CD101 IV groups will be analyzed (using a validated assay) by an independent, central bioanalytical laboratory. In part B, PK samples will not be collected.

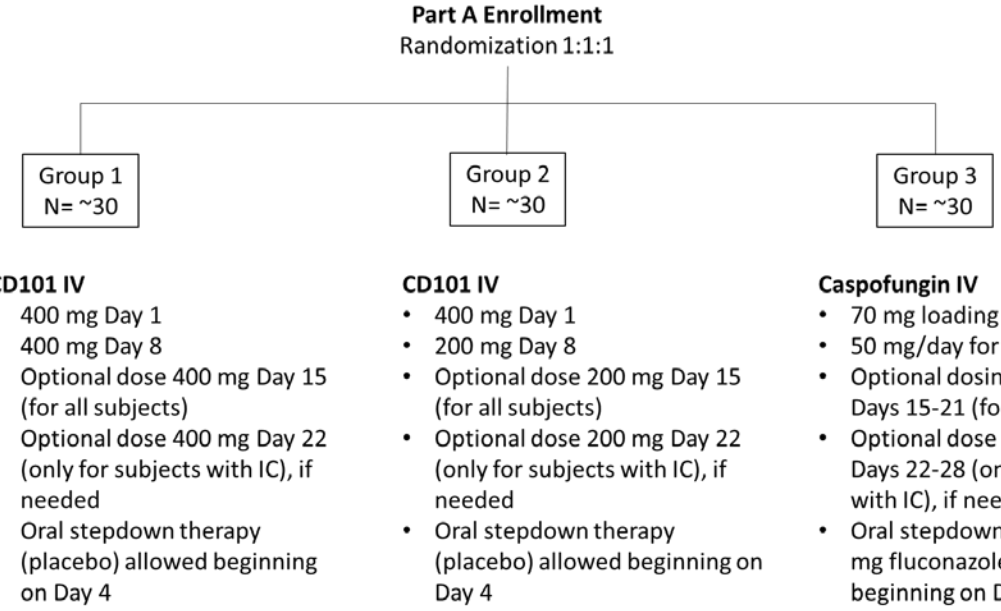
Overall success and mycological eradication will be assessed at Day 5, Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), and FU (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia). Clinical response will be assessed at Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), and FU (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia).

Number of Subjects

In Part A, subjects will be randomized (1:1:1) until there are approximately 30 subjects in the CD101 IV treatment Group 1, 30 subjects in the CD101 IV treatment Group 2, and 30 subjects in the comparator group in the mITT population. It is expected that approximately 114 subjects will need to be randomized to achieve 90 subjects in the mITT population (assuming 80% of randomized subjects will be included in mITT population).

In Part B, subjects will be randomized (2:1) until there are ≥30 subjects in the CD101 IV treatment groups and ≥15 subjects in the comparator group (≥45 additional subjects and no more than 120 subjects). Total enrollment will depend on the enrollment rate for the 6- to 8-month period between the end of Part A and the staged start of the Phase 3 study, which is the trigger for the rolling close-out of Part B.

Figure 1: Study Randomization and Treatment Regimens



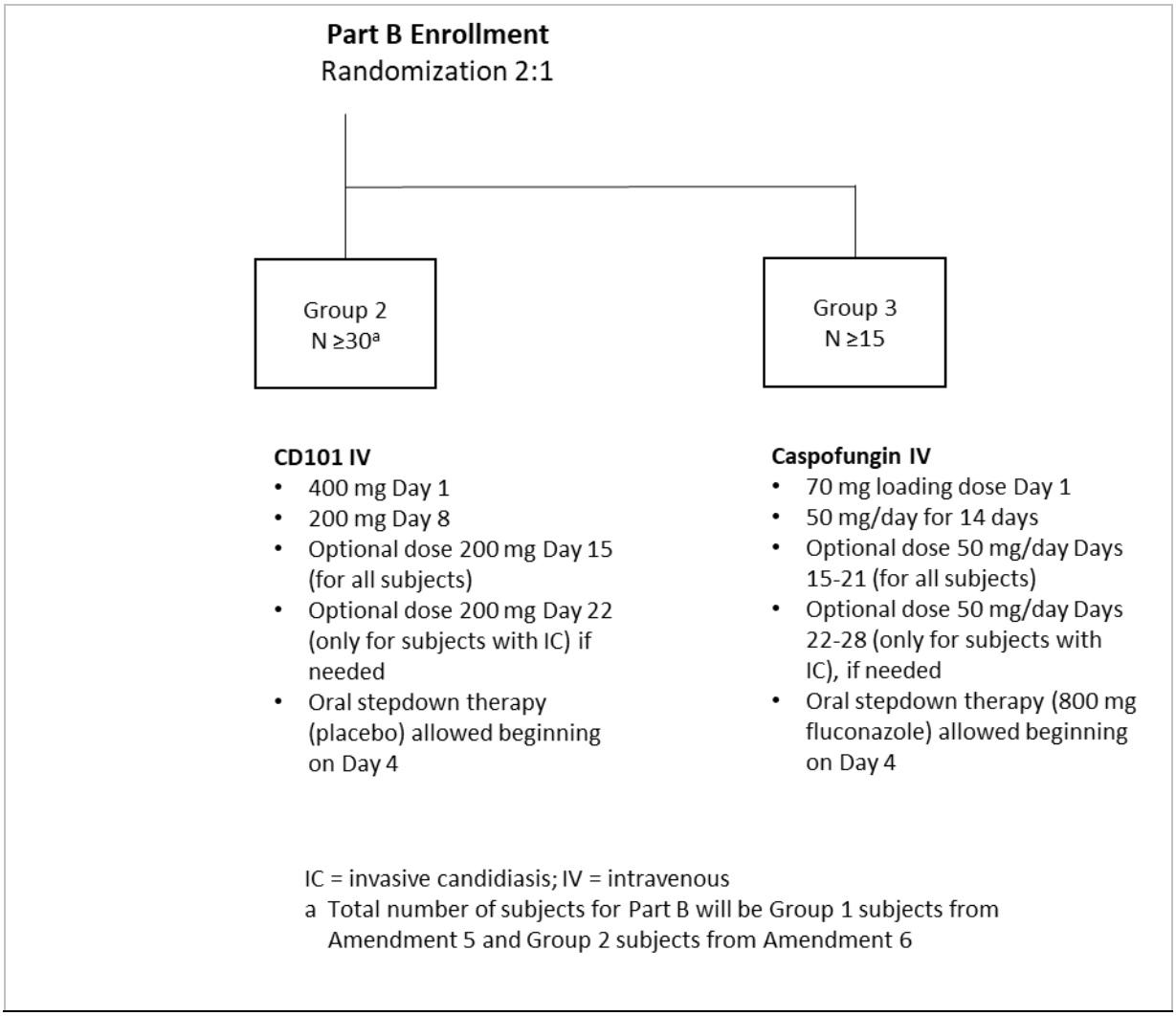
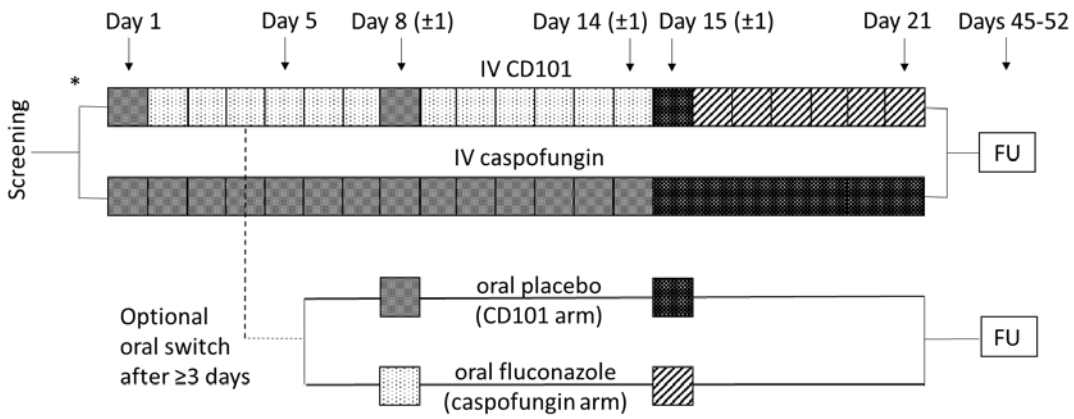

Part B Enrollment
Randomization 2:1
Group 2
N ≥30[a]
Group 3
N ≥15
CD101 IV
• 400 mg Day 1
• 200 mg Day 8
• Optional dose 200 mg Day 15 (for all subjects)
• Optional dose 200 mg Day 22 (only for subjects with IC) if needed
• Oral stepdown therapy (placebo) allowed beginning on Day 4
Caspofungin IV
• 70 mg loading dose Day 1
• 50 mg/day for 14 days
• Optional dose 50 mg/day Days 15-21 (for all subjects)
• Optional dose 50 mg/day Days 22-28 (only for subjects with IC), if needed
• Oral stepdown therapy (800 mg fluconazole) allowed beginning on Day 4
IC = invasive candidiasis; IV = intravenous
a Total number of subjects for Part B will be Group 1 subjects from Amendment 5 and Group 2 subjects from Amendment 6

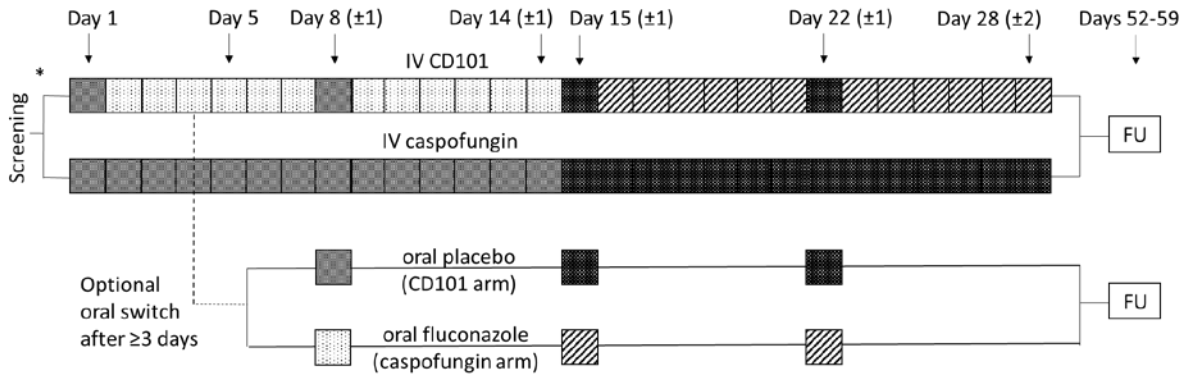
Figure 2: Study Design Diagram for Subjects with Candidemia Only



* Applies to CD101 Group 1 (Part A only) and Group 2 (Parts A and B)

Total IV plus oral therapy ≥14 days and ≤21 days
Total IV therapy ≥3 days and ≤21 days
Optional CD101 IV therapy allowed on Day 15 if require >14 days of therapy
Optional caspofungin IV therapy allowed on Days 15-21
Switch to oral step-down therapy allowed after ≥3 days IV therapy and up to Day 21
Day 8 IV therapy (required) PLUS oral therapy if on oral step-down therapy
Day 15 IV therapy (optional) PLUS oral therapy if on oral step-down therapy
Efficacy assessments on Days 5, 14, and FU (Days 45-52)
FU = follow-up visit; IV = intravenous

Figure 3: Study Design Diagram for Subjects with Invasive Candidiasis (with or without Candidemia)



* Applies to CD101 Group 1 (Part A only) and Group 2 (Parts A and B)

Total IV plus oral therapy ≥14 days and ≤28 days
Total IV therapy ≥3 days and ≤28 days
Optional CD101 IV therapy allowed on Day 15 and Day 22 if require additional therapy
Optional caspofungin IV therapy allowed on Days 15-28
Switch to oral step-down therapy allowed after ≥3 days IV therapy and up to Day 28
Day 8 IV therapy (required) PLUS oral therapy if on oral step-down therapy
Day 15 and Day 22 IV therapy (optional) PLUS oral therapy if on oral step-down therapy
Efficacy assessments on Days 5, 14, 28, and FU (Days 52-59)
FU = follow-up visit; IV = intravenous

Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria to be enrolled:

1. Males or females ≥18 years.
2. Established mycological diagnosis of candidemia and/or IC from a sample taken ≤96 hours before randomization defined as:
   a. ≥1 blood culture positive for yeast or *Candida*
      OR
   b. Positive test for *Candida* from a Sponsor-approved rapid IVD
      OR
   c. Positive Gram stain for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site
3. Willing to initiate or continue medical treatment to cure infections, including receipt of antibiotics and surgical procedures, if required. Subjects receiving only medications and measures for comfort and not cure should not be enrolled.
4. Female subjects of child-bearing potential <2 years postmenopausal must agree to and comply with using 1 barrier method (eg, female condom with spermicide) plus 1 other highly effective method of birth control (eg, oral contraceptive, implant, injectable, indwelling intrauterine device, vasectomized partner), or sexual abstinence while participating in this study. Male subjects must be vasectomized, abstain from sexual intercourse, or agree to use barrier contraception (condom with spermicide), and also agree not to donate sperm from first dose of CD101 (Day 1) until 90 days following last administration of study drug.
5. Willing and able to provide written informed consent. If the subject is unable to consent for himself/herself, a legally acceptable representative must provide informed consent on their behalf.
6. Presence of 1 or more systemic signs attributable to candidemia and/or IC (eg, fever, hypothermia, hypotension, tachycardia, tachypnea)

Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria to be enrolled:

1. Any of the following forms of IC:
   a. Septic arthritis in a prosthetic joint (septic arthritis in a native joint is allowed)
   b. Osteomyelitis
   c. Endocarditis or myocarditis
   d. Meningitis, endophthalmitis, or any central nervous system infection
2. Neutropenia (absolute neutrophil count ≤500/μL) at Screening or anticipated neutropenia during the study
3. Alanine aminotransferase or aspartate aminotransferase levels >10-fold the upper limit of normal
4. Severe hepatic impairment in subjects with a history of chronic cirrhosis (Child-Pugh score >9)
5. Received systemic treatment with an antifungal agent at approved doses for treatment of candidemia or IC for >48 hours (for example, >2 doses of a once daily antifungal agent or >4 doses of a twice daily antifungal agent) in the last 96 hours before randomization
   a. Exception: Receipt of antifungal therapy to which any *Candida* spp. isolated at Screening in qualifying cultures is not susceptible
6. Pregnant females
7. Lactating females who are nursing
8. Known hypersensitivity to CD101 IV, caspofungin, any echinocandin, or to any of their excipients
9. Previous participation in this or any previous CD101 study.
10. Recent use of an investigational medicinal product within 28 days of the first dose of study drug or presence of an investigational device at the time of Screening
11. The PI considers that the subject should not participate in the study
12. Presence of an indwelling vascular catheter or device that cannot be removed and is likely to be the source of candidemia

Test Product, Dose, and Mode of Administration

Rezafungin for injection is a sterile product of lyophilized powder in a single-use vial for reconstitution with sterile water for injection prior to dilution into normal saline infusion bags.

Subjects randomized to the CD101 IV treatment Group 1 will receive 1 dose of CD101 IV (400 mg) on Day 1 and Day 8 (Table 1). Subjects in Group 1 who require >14 days of IV therapy will receive an optional third dose of CD101 IV (400 mg) on Day 15. Subjects in Group 1 with IC (with or without candidemia) who require >21 days of IV therapy will receive an optional fourth dose of CD101 IV (400 mg) on Day 22. 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 on Day 1 and 200 mg on Day 8 (Table 1). Subjects in Group 2 who require >14 days of IV therapy will receive an optional third dose of CD101 IV (200 mg) on Day 15. Subjects in Group 2 with IC (with or without candidemia) who require >21 days of IV therapy will receive an optional fourth dose of CD101 IV (200 mg) on Day 22. Subjects in Group 2 will receive IV placebo on other study days in order to maintain the blind.

Intravenous infusion of CD101 IV is nominally over 60 (±10) minutes, but the time may be increased as needed up to 180 (±10) minutes to manage symptoms of infusion reaction consistent with management of echinocandin class infusion reactions, whereby decreasing the rate of infusion often alleviates symptoms. (Note: infusion must be completed within the 4-hour stability limit, which starts at the time of reconstitution of rezafungin for injection lyophilized powder in the single-use vial.) Intravenous study drug is administered 24 (±2) hours after study drug was administered on the previous day. Dosage adjustments of CD101 IV are not allowed.

Subjects may receive oral step-down therapy after ≥3 days of IV therapy. Step-down therapy in both CD101 IV treatment groups will be oral placebo, in order to maintain the blind. Subjects with creatinine clearance >50 mL/min will receive oral placebo (4 capsules on the first day followed by 2 capsules/day thereafter) in the CD101 treatment group. Subjects with creatinine clearance ≤50 mL/min will receive oral placebo (2 capsules on the first day followed by 1 capsule /day thereafter) in the CD101 treatment group. Subjects receiving hemodialysis will receive oral placebo (4 capsules on the first day followed by 2 capsules after each hemodialysis) in the CD101 treatment group. Subjects who have already switched to oral step-down therapy will receive both oral placebo and IV CD101 on Day 8, and if required on Day 15 and Day 22 for subjects who are administered study drug through these timepoints.

Comparator

Subjects randomized to the caspofungin group will receive IV caspofungin (a single 70 mg loading dose on Day 1 followed by 50 mg once daily) for ≥3 days and up to a maximum of 21 days for subjects with candidemia only and up to a maximum of 28 days for subjects with IC (with or without candidemia) (Table 1). Intravenous infusion of caspofungin is nominally over 60 (±10) minutes, but the time may be increased as needed up to 180 (±10) minutes to manage symptoms of infusion reaction. Intravenous study drug is administered 24 (±2) hours after study drug was administered on the previous day.

Use of concomitant cyclosporine should be limited to subjects for whom potential benefit outweighs potential risk of drug-drug interactions with caspofungin.

Subjects in the caspofungin group with moderate hepatic impairment (Child-Pugh score of 7-9 with a history of chronic cirrhosis) 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 may be considered at the Investigator's discretion.

Subjects in Part A and Part B may receive oral step-down therapy after ≥3 days of IV therapy. Step-down therapy in the caspofungin treatment group will be oral fluconazole. Subjects with creatinine clearance >50 mL/min will receive oral fluconazole (a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter). Subjects in the caspofungin group with renal impairment who are switched to oral stepdown therapy may receive reduced doses of fluconazole. For subjects with creatinine clearance ≤50 mL/min, the loading dose of fluconazole should be 400 mg [2 capsules] and the daily dose of fluconazole should be 200 [1 capsule] mg/day. For subjects receiving hemodialysis, the loading dose of fluconazole should be 800 mg [4 capsules] followed by 400 mg [2 capsules] of fluconazole after each hemodialysis. 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, and if required on Day 15 and Day 22 for subjects who are administered study drug through these timepoints.

Oral Step Down Therapy

An oral step-down therapy is allowed in all treatment groups, provided the following criteria are met:

- Able to take oral medication
- ≥3 days of IV study drug
- The *Candida* species isolated is susceptible to fluconazole.
- The subject's clinical status is considered stable based on Investigator assessment
- If a blood culture is positive at Screening, 2 post-baseline blood cultures drawn ≥12 hours apart are negative for *Candida* spp. without an intervening positive culture, and the first of the 2 cultures was drawn ≥48 hours prior to oral study drug initiation
- No evidence of moderate or severe hepatic insufficiency (alanine aminotransferase or aspartate aminotransferase >3× the upper limit of normal)
- No history of hypersensitivity or any other contraindications to the use of fluconazole and, in the Investigator's opinion, the subject can tolerate oral fluconazole therapy (refer to current fluconazole Prescribing Information)

Oral step-down therapy will be fluconazole in the caspofungin group and oral placebo in the CD101 treatment groups.

The total IV plus oral treatment duration will be ≥14 days and up to 28 days.

Table 1: Study Treatments

Study Day	CD101 IV Group 1 Group 2	Caspofungin Group
1	IV CD101 (400 mg)	IV caspofungin (a single 70 mg loading dose)
2-3 [a]	IV placebo	IV caspofungin (50 mg/day)
4-7	IV placebo if not stepped down **OR** oral step-down therapy (placebo) if already stepped down	IV caspofungin (50 mg/day) if not stepped down **OR** oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down
8 [b]	IV CD101 (400 mg Group 1; 200 mg Group 2) if not stepped down **OR** IV CD101 (400 mg Group 1; 200 mg Group 2) PLUS oral step-down therapy (placebo) if already stepped down	IV caspofungin (50 mg/day) if not stepped down **OR** IV placebo PLUS oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down
9-14 [c]	IV placebo if not stepped down **OR** oral step-down therapy (placebo) if already stepped down	IV caspofungin (50 mg/day) if not stepped down **OR** oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down

15 [b] (if needed)	IV CD101 (400 mg Group 1; 200 mg Group 2) if not stepped down **OR** IV CD101 (optional) [d] (400 mg Group 1; 200 mg Group 2) PLUS oral step-down therapy (placebo) if already stepped down **OR** No treatment	IV caspofungin (50 mg/day) if not stepped down **OR** IV placebo (optional) [d] PLUS oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down **OR** No treatment
16-21 [e] (if needed)	IV placebo if not stepped down **OR** oral step-down therapy (placebo) if already stepped down **OR** No treatment	IV caspofungin (50 mg/day) if not stepped down **OR** oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down **OR** No treatment
22 [b] (if needed, only for subjects with IC)	IV CD101 (400 mg Group 1; 200 mg Group 2) if not stepped down **OR** IV CD101 (optional) [f] (400 mg Group 1; 200 mg Group 2) PLUS oral step-down therapy (placebo) if already stepped down **OR** No treatment	IV caspofungin (50 mg/day) if not stepped down **OR** IV placebo (optional) [f] PLUS oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down **OR** No treatment
23-28 [g, h] (if needed, only for subjects with IC)	IV placebo if not stepped down **OR** oral step-down therapy (placebo) if already stepped down **OR** No treatment	IV caspofungin (50 mg/day) if not stepped down **OR** oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down **OR** No treatment

IC = invasive candidiasis; IV= intravenous

a. Subjects must receive IV therapy for ≥3 days before switching to oral step-down therapy
b. The Day 8, Day 14, Day 15, and Day 22 visits have a window of ±1 day if subject already stepped down to oral therapy and discharged from the study site
c. Total IV plus oral treatment duration must be ≥14 days
d. Subjects who require >14 days of therapy may receive an optional third dose of IV study drug on Day 15, if needed.
e. Total IV plus oral treatment duration must be ≤21 days for subjects with candidemia only.
f. Subjects with IC (with or without candidemia) who require >21 days of therapy may receive an optional fourth dose of IV study drug on Day 22, if needed
g. The Day 28 visit has a window of ±2 days if subject already stepped down to oral therapy and discharged from the study site
h. Total IV plus oral treatment duration must be ≤28 days for subjects with IC (with or without candidemia)

Duration of Treatment

Study participation will require from 45 to 52 days for subjects with candidemia only (or from 52-59 days for subjects with IC, with or without candidemia) after the first dose 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); 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 (Days 45 to 52 for subjects with candidemia only or Days 52-59 days for subjects with IC, with or without candidemia).

Criteria for Evaluation

Efficacy

Efficacy assessments will be recorded on Day 5, Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), and FU (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia)

The primary efficacy endpoint is overall success at Day 14 (±1 day), as defined below:

- Mycological eradication defined as:
  - If positive blood culture at baseline: 2 negative blood cultures drawn ≥12 hours apart without intervening positive blood cultures

    OR
  - If positive culture from a normally sterile site (other than blood):
    - *Documented* mycological eradication: most recent culture on or prior to Day 14 (±1 day) from all normally sterile sites of baseline *Candida* infection (if accessible) is negative

      OR
    - *Presumed* mycological eradication: follow-up culture is not available (eg, normally sterile baseline site of *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 that were present at baseline) and resolution or improvement of any baseline radiographic abnormalities due to IC

AND

- Resolution of attributable systemic signs of candidemia and/or IC that were present at baseline

AND

- No change of antifungal therapy for the treatment of candidemia and/or IC

AND

- The subject is not lost to follow up on the day of assessment

Secondary efficacy outcome measures include:

- Mycological eradication
- Clinical cure as assessed by the Investigator

Additional efficacy outcome measures include:

- All-cause 30-day mortality
- Time to first of 2 negative blood cultures drawn ≥12 hours apart, without an intervening positive culture

Safety

Safety will be assessed from the signing of the Informed Consent Form at Screening to the FU visit through the evaluation of AEs, vital signs (temperature, heart rate, blood pressure, and respiratory rate), ECGs, and clinical laboratory data (clinical chemistry panels, hematology evaluations, and urinalyses).

Pharmacokinetics (Part A only)

Blood samples will be obtained from subjects to evaluate the PK of CD101 IV. Blood samples will be collected for all 3 treatment groups for the purpose of maintaining the blind, but only PK samples from the CD101 IV groups will be analyzed by a central bioanalytical laboratory. When >1 assessment occurs at any time point, the PK blood sample will be given priority and taken at the correct protocol-specified time. Plasma samples will be analyzed for the concentration of CD101 by a validated liquid chromatography-tandem mass spectrometry method.

Blood for PK analyses will be drawn from the OPPOSITE arm of the infusion at the following times:

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.

Statistical Methods

The study is not powered for inferential statistical analysis. A sufficient number of subjects are randomized to the CD101 IV and caspofungin groups in Part A to provide an initial, substantive analysis of safety and tolerability, and estimate efficacy. In Part A, assuming a 73% overall success rate, the sample size of 30 subjects in each CD101 IV group will yield a 95% confidence interval (CI) of 53.8% to 87.5%. 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%.

Analysis populations are:

- The Intent-to-treat (ITT) population: all randomized subjects
- The Safety population: all subjects who received any amount of study drug
- The Microbiological Intent-to-treat population (mITT): all subjects who had documented *Candida* infection based on Central Laboratory evaluation of a blood culture obtained within 96 hours of randomization, or from a specimen obtained from a normally sterile site, and received ≥1 dose of study drug

To demonstrate preliminary efficacy and safety of CD101 and to confirm the correct CD101 dose regimen is utilized in Part B, an unblinded interim analysis will be performed after approximately 40 to 60 subjects in the mITT population have been enrolled and completed study drug therapy. This unblinded interim analysis of a few key efficacy and safety outcomes will be performed by an independent unblinded statistician. Interim efficacy and safety summary tables will be produced, but the identity of the group assignment for each individual subject will remain blinded until the completion of the study and the database for both Parts A and B are locked. Once Part A is completed, the database will be locked and a full unblinded analysis with all summary tables will be performed on Part A alone. As with the initial interim analysis and to help avoid bias, the full Part A analysis will be performed by an independent unblinded statistician, keeping the identity of the group assignment for each individual subject blinded until the completion of the study and the database for both Parts A and B are locked. (Note: An addendum to the Unblinding Plan for Part A allowed for unblinded safety review of adverse events of interest identified during blinded safety review; the addendum allowed for no more than 5% of subjects to be unblinded.)

A Statistical Analysis Plan (SAP) will be prepared and finalized before the interim analysis. Any changes to the SAP from the time of the interim analysis to the final database lock of Part B will be documented in an addendum to the SAP. Any deviations from the final SAP/addendum will be described and justified in the study report. All statistical analyses will be performed using SAS®. All analyses will be completed for Part A. Selected analyses will be completed only for Part B and for Part A and B combined.

The primary efficacy outcome is overall response and is determined programmatically from the mycological response and assessment of systemic signs of infection attributable to candidemia and/or IC at Day 14 (±1 day).

The number and percentage of subjects with a success, failure, or indeterminate will be presented by treatment group. Two-sided 95% CIs for the point estimates of success in the mITT population will be determined. Analyses will be completed for Part A, Part B, and combined Part A and B.

Safety will be evaluated by presenting summaries of AEs, clinical laboratory evaluations (hematology evaluation, chemistry panel, urinalysis), vital signs, and ECGs. Safety variables will be tabulated and presented for all subjects by study drug. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an AE that occurs during or after study drug administration and up through the FU visit. The incidence of TEAEs will be presented by system organ class and preferred term, by relationship to study drug, by severity, and by whether or not they resulted in alteration of administration of or discontinuation of study drug (IV and IV/oral). In addition, the incidence of serious TEAEs and TEAEs leading to discontinuation of study drug (IV and IV/oral) will be presented by system organ class and preferred term. Descriptive statistics for clinical laboratory test results, vital signs, and ECG parameters, including changes from baseline, will be presented by time point. Incidences of potentially clinically significant clinical laboratory results, vital signs, and ECG parameters, as defined in the SAP, will also be summarized by time point. Analyses will be completed for Part A and for combined Part A and B.

In Part A only, PK parameter assessment will be reported separately for the PK Analysis population and may include: maximum plasma concentration (C_{max}), time to C_{max}, and area under the curve, if applicable.

Table 2: Schedule of Assessments and Procedures

Study Day (window)	Screen	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 Days 52-59 for IC subjects with or without candidemia)
		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																

Table 2: Schedule of Assessments and Procedures

Study Day (window)	Screen	Study Drug Administration, Days 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)	EOT +2 days after last dose of study drug (IV and oral)	FU Visit Days 45-52 for subjects with candidemia only (or Days 52-59 for IC subjects with or without candidemia)
Urine for urinalyses, microscopy	X															X	
Urine pregnancy test [o]	X																X
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

Table 2: Schedule of Assessments and Procedures

Study Day (window)	Screen	Study Drug Administration, Days 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)	EOT +2 days after last dose of study drug (IV and oral)	FU Visit Days 45-52 for subjects with candidemia only (or Days 52-59 for IC subjects with or without candidemia)
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
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 candidiasis; IDSA = Infectious Diseases 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. Continue study drug therapy and assessments if further therapy is clinically indicated; only for subjects with IC (with or without candidemia). Subjects will be presumed 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 postmenopausal 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 11; 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.

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3.0 LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
APACHE	Acute Physiology and Chronic Health Evaluation
aPTT	activated partial thromboplastin time
AUC	area under the concentration time curve
AUC_{0-168}	area under the concentration time curve from time 0 to 168 hours
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
AUC_{0-t}	area under the curve from time 0 to the final sample
BMI	body mass index
C_{144}	plasma concentration at 144 hours post start of infusion
CD101 for Injection	product name for the lyophilized form
CD101 Injection	product name for the liquid dosage form
CD101 IV	Intravenous CD101: CD101 Injection or CD101 for Injection
CDC	Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
C_{max}	maximum plasma concentration
eCRF	electronic case report form
ECG	electrocardiogram
EOT	End-of-Treatment
ESCMID	European Society Clinical Microbiology and Infectious Diseases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
$fAUC_{0-168}$	free-drug area under the concentration time curve from time 0 to 168 hours
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IC	invasive candidiasis
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IND	Investigational New Drug

IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous
IVD	in vitro diagnostic
IWRS	Interactive Web Response System
K_2EDTA	potassium ethylenediaminetetraacetic acid
LC-MS/MS	liquid chromatography- tandem mass spectrometry
MAD	multiple-ascending dose
MALDI	matrix-assisted laser desorption ionization
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimal inhibitory concentration
MIC_{90}	minimal inhibitory concentration required to inhibit the growth of 90% of the isolates tested
mITT	Microbiological Intent-to-Treat
NDA	New Drug Application
NOAEL	no-observed-adverse-effect level
OTC	over the counter
PD	pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT/INR	prothrombin time/international normalized ratio
PTT	partial thromboplastin time
R	resistant
S	sensitive
SAD	single-ascending dose
SAE	serious adverse event
SAER	serious adverse event report
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	standard operating procedure
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to C_{max}

UA	urinalysis
US	United States
Vss	volume of distribution at steady state
Vz	volume of distribution
WFI	water for injection

4.0 BACKGROUND AND RATIONALE

4.1 CANDIDEMIA AND INVASIVE CANDIDIASIS

Intravenous CD101 (CD101 IV), a new echinocandin antifungal agent, is being developed specifically to treat patients with systemic infections caused by *Candida*. These serious and life-threatening infections represent a significant public health issue, particularly in highly vulnerable patient populations such as the elderly, postsurgical, critically ill, and other hospitalized patients with serious medical conditions (Magill et al., 2014; Andes et al., 2012; Wisplinghoff et al., 2004). In addition, because of increasing resistance to existing antifungal drugs, there is an urgent need to develop new and more effective antifungal agents to treat these serious infections (Alexander et al., 2013; Arendrup et al., 2013; Ostrosky-Zeichner 2013; Pfaller, 2012). The Centers for Disease Control and Prevention (CDC) recently warned that fluconazole-resistant *Candida* have the potential to pose a serious threat to public health (CDC, 2013; CDC, 2016). However, since 2007, no new antifungal agents have been approved for treatment of candidemia (The White House, 2014; Executive Office of the President, 2014; CDC, 2013).

Candidemia and other forms of invasive candidiasis (IC) (eg, disseminated candidiasis, peritonitis, intra-abdominal abscess, hepatic candidiasis, endocarditis, and meningitis) are considered to be among the most critical invasive fungal infections in the United States (US) in terms of incidence and impact (Brown et al., 2012; Pfaller and Diekema, 2010; Arendrup et al. 2013; Azie et al., 2012; Menzin et al., 2009; Vincent et al., 2009). In a recent analysis of a large US patient database, *Candida* infections accounted for 40% of all invasive fungal infections and were associated with the highest excess length of stay, excess cost, and attributable mortality (Menzin et al., 2009). In fact, the mortality rate in patients with candidemia has been reported to be >40%, which is higher than that for some populations with invasive aspergillosis (Andes, et al. 2012; Wisplinghoff et al., 2004; Mikulska et al., 2012; Falagas et al., 2006; Labelle et al., 2008; Pfaller and Diekema, 2010; Slavin et al., 2010; Mylonakis et al., 2015; Pfaller and Diekema, 2007).

The US National Center for Health Statistics reported that the incidence of *Candida* infection is 8/100,000 population per year, but estimates range up to 26/100,000 in certain regions of the US, and the incidence continues to increase (Brown et al., 2012; Pfaller and Diekema, 2010; Menzin et al., 2009; Vincent et al., 2009; Cleveland et al., 2012; Zilberberg et al., 2008a; Zilberberg et al., 2008b). In 2004, *Candida* was the fourth leading cause of healthcare-associated bloodstream infections overall (Wisplinghoff et al., 2004). In 2008, the National Healthcare Safety Network reported that *Candida* was the third most common cause of central line–associated bloodstream infections in US intensive care units (Hidron et al., 2008). However, the most recent survey reported that *Candida* was now the most common cause of hospital-acquired bloodstream infections in the US (Magill et al., 2014). Even more disturbing is that some of the highest rates of *Candida* infection have been observed among elderly hospitalized patients (Zaoutis et al., 2005; Zilberberg et al., 2008b).

More than 50% of all *Candida* infections are caused by non-albicans *Candida* species, including *Candida glabrata*, which is the most common non-albicans *Candida* species in North America and Europe. The incidence of infections caused by *C. glabrata* in the US has increased by >4 fold over the past 20 years (Cleveland et al., 2012). In the US-based SENTRY Antifungal Surveillance Program, the frequency of *C. glabrata* as a cause of bloodstream infections recently increased from 18% in 2008/2009 to 25% in 2010/2011 (Pfaller et al., 2014). Azole-resistant *C. glabrata* has recently been identified as a serious threat to public health (The White House, 2014; Executive Office of the President, 2014; CDC, 2013). In the US-based SENTRY Antifungal Surveillance Program, the rate of azole-resistant *C. glabrata* has recently increased from 9% in the 1992-2001 time period to 14% in the 2001-2007 time period (Pfaller et al., 2014; 2013; 2012; 2010a, 2010b, 2009), but it has been reported to be as high as 30% in some centers (Alexander et al., 2013).

The increasing incidence of non-albicans *Candida* and the greater efficacy of echinocandins compared to azoles in *Candida* infections provided support for the recommendation in Infectious Diseases Society of America (IDSA) and European Society Clinical Microbiology and Infectious Diseases (ESCMID) guidelines that an echinocandin be used for initial treatment of candidemia (Pappas et al., 2016; Ullmann et al., 2012; Cornely et al., 2012). These guidelines allow for a subsequent "step-down" to an azole for treatment, if the *Candida* species has been identified and has been demonstrated to be susceptible to the azole. However, not all US hospitals are currently able to perform antifungal susceptibility testing, making it difficult for many hospitals to follow this recommendation. In the context of increasing rates of azole-resistant *C. glabrata*, the current treatment regimen would be ≥2 weeks of a daily echinocandin.

Moreover, because of its haploid genome, *C. glabrata* has the potential to more rapidly develop resistance to antifungal agents than other *Candida* spp. in multiple drug classes, including echinocandins (Ostrosky-Zeichner, 2013; Pfaller et al., 2012, 2008). Echinocandins inhibit the 1,3-β-D-glucan synthase (encoded by *FKS1*, *FKS2*, and *FKS3* genes), which synthesizes a major component of the fungal cell wall. Mutations in "hot spot" regions of *FKS1* and/or *FKS2* are associated with elevated echinocandin minimal inhibitory concentration (MIC) values, reduced glucan synthase enzyme sensitivity, and unfavorable outcomes in animal models (Beyda et al., 2014; Alexander et al., 2013). *FKS* mutations have been identified in 8% to 32% of patients with *C. glabrata* candidemia, particularly in patients with prior echinocandin exposure. *FKS* mutations have been associated with higher clinical failure rates compared to non-*FKS* mutants (60% vs 23%) (Beyda et al., 2014; Shields et al., 2013). In fact, in a recently reported case series, the clinical failure rate among patients with echinocandin-resistant *C. glabrata* was reported to be 91% (Shields et al., 2013).

The emergence of multidrug resistance in *C. glabrata* can be considered a major public health issue because neither the azoles nor the currently available echinocandins would be appropriate for treatment, and high dose amphotericin is the only alternative and is associated with renal toxicity, particularly in older, critically-ill patients with sepsis (Alexander and Wingard, 2005; Chapeland-Leclerc et al., 2010; Krogh-Madsen et al., 2006; Pappas et al., 2016).

4.2 CD101

CD101 is a semi-synthetic echinocandin that inhibits the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall of yeast forms of *Candida* species and regions of active cell growth of *Aspergillus* hyphae. The synthesis of 1,3-β-D-glucan is dependent upon the activity of 1,3-β-D-glucan synthase, an enzyme complex in which the catalytic subunit is encoded by *FKS1*, *FKS2*, and *FKS3* genes. Inhibition of this enzyme results in rapid, concentration-dependent, fungicidal activity for *Candida* spp.

CD101 is a broad-spectrum antifungal agent with excellent activity against wild-type and azole- and echinocandin-resistant strains of *Candida* spp. (Castanheira et al., 2014). CD101 demonstrated potent activity against representative strains of numerous fungal species, including *Candida* spp., *Aspergillus* spp., *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Microsporum gypseum*, similar to that of anidulafungin. Poor activity was observed for single strains of *Cryptococcus neoformans* and *Rhizopus oryzae*, characteristic of echinocandins. When tested against multiple clinical isolates of wild-type and echinocandin-resistant and/or –azole resistant *Candida* spp., CD101 activity was similar to that of anidulafungin versus all strains tested with MIC required to inhibit the growth of 90% of the isolates tested (MIC_{90}) values ≤1 µg/mL for all species except *Candida parapsilosis*, which was 2 µg/mL. The potency of CD101 against strains with documented *fks* mutations was 2- to 8-fold greater than that of caspofungin and similar to that of anidulafungin.

4.3 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

CD101 was found to be stable in liver microsomes from all species tested. A cross-species stability study also determined that CD101 is stable in intestinal microsomes and no metabolic products were identified during incubations of CD101 with mouse, rat, monkey, or human liver microsomes, indicating a lack of biotransformation. In vivo, metabolite profiling of rat plasma and excreta samples is consistent with in vitro results confirming the lack of biotransformation.

The pharmacokinetic (PK) profile of CD101 was investigated in mice, rats, dogs, cynomolgus monkeys, and chimpanzees following IV delivery, the intended clinical route of administration, and also after intraperitoneal administration to mice, intramuscular to rats, subcutaneous to rats and cynomolgus monkeys, and orally to dogs, monkeys, and chimpanzees. CD101 consistently exhibited very low clearance, modest volume of distribution (V_z) or volume of distribution at steady state (Vss), and long half-life ($t_{1/2}$). Across all species tested, CD101 exhibited a favorable PK profile, mainly attributable to lower clearance (resulting in a longer $t_{1/2}$). Additionally, there was low to no drug accumulation or gender differences found with CD101 across all species tested after multiple doses and routes of administration.

Tissue distribution of CD101 was evaluated in rats and mean area under the concentration time curve (AUC) from time 0 to the final sample (AUC_{0-t}) was lowest in brain tissue and highest in kidney tissue. Calculation of tissue/plasma AUC ratios indicated exposure relative to plasma was comparable between major organs (4- to 5-fold higher in kidney, lung, liver, and spleen) with the exception of much lower ratios in tissue from heart and brain (≤1). More importantly, CD101 appears to concentrate within fungal lesions even after the majority of drug has been cleared from an infected organ, as shown in a separate study by David Perlin and colleagues from Rutgers (Zhao, 2017). In the study, the authors utilized matrix-assisted laser desorption ionization (MALDI) imaging mass spectrometry technology to image kidney and liver cross-sections of mice with IC. MALDI imaging allowed for multiplexed analysis of different molecules simultaneously in the same tissue section, providing semi-quantitative information of fungal lesions and drug localization. From cross-sections of liver and kidney, across different timepoints from 1 to 48 hours, Perlin and colleagues noted that CD101 tissue levels begin to decline after reaching the maximum plasma concentration (C_{max}) at 6 hours postdose, but increase and concentrate within fungal lesions at later timepoints (24 and 48 hours).

CD101 has been evaluated in a full battery of Investigational New Drug (IND)-enabling toxicology studies up to 4 weeks in duration in rats and cynomolgus monkeys, and in bacterial and mammalian cell in vitro genetic toxicology studies. The pivotal nonclinical safety studies were conducted according to Good Laboratory Practices (GLP) guidances. CD101was evaluated in single dose and exploratory IV studies, in 2-week IV pilot toxicity studies, and in 4-week IV GLP toxicity studies. In addition, 3 Screening and investigative studies were conducted: one study compared the toxicity of CD101 to the marketed echinocandin, anidulafungin, with focus on assessing hepatotoxicity; a second study investigated different modes of IV tail vein administration in rats; and the third study measured plasma levels of histamine in rats.

The main toxicology finding was a rat-specific histamine-release response that occurred primarily after the first dose. This histamine response was not seen in cynomolgus monkeys at C_{max} levels that exceeded those where these effects were seen in rats. Echinocandins as a class are known to cause histamine release during infusions in rats, but not during infusions in monkeys when assessed during toxicity testing (Eraxis [anidulafungin] New Drug Application [NDA], Cancidas [caspofungin acetate] NDA). Rats appear to be much more sensitive to histamine-release responses of echinocandins versus primates, including humans where histamine-mediated infusion reactions appear to be uncommon (Eraxis [anidulafungin] Prescribing Information, 2013; Mycamine [micafungin sodium] Prescribing Information, 2013; Cancidas [caspofungin acetate] Prescribing Information, 2014).

Hematological signs suggestive of red blood cell regeneration occurred in rats primarily at the high dose, were not considered adverse, and were not seen in monkeys.

Local vascular injury was observed in rats, but adverse effects were confined to high dose males during the 4-week toxicity study; the no-observed-adverse-effect level (NOAEL) concentration for local injury is 6 mg/mL.

The safety margins appear to be large in rats and monkeys administered CD101 for up to 4 weeks. The NOAEL for human relevant toxicities is 45 mg/kg in rats and 30 mg/kg in monkeys. These doses generate AUC plasma exposures 20-fold (rat) and 28-fold (monkey) over the efficacious plasma exposure determined in the neutropenic mouse systemic candidiasis model.

No adverse CD101-related target organ toxicity was observed in either rats or monkeys over the 4-week dosing period.

A CD101-related microscopic finding was seen in macrophages located in the lung of rats at ≥15 mg/kg that was characterized as a minimal alveolar histiocytosis. This change was not considered adverse since it was minimal, not associated with tissue injury, and reversible. This change was not observed in monkeys.

Of importance is the lack of microscopic evidence for target organ toxicity previously identified in animals with marketed echinocandins dosed over a 4- or 5-week period (Eraxis [anidulafungin] NDA, Cancidas [caspofungin acetate] NDA, Mycamine [micafungin sodium] NDA). Target organs have included hepatotoxicity (anidulafungin, caspofungin and micafungin), renal toxicity (anidulafungin and micafungin), and skeletal muscle changes (anidulafungin). In addition, no CD101-related histopathological changes were seen in the spleen and bone marrow, whereas regenerative changes in these organs have been reported for anidulafungin and micafungin

CD101 was negative for mutagenicity (bacteria) and clastogenicity (mammalian cells) during in vitro genetic toxicology studies and negative for clastogenicity in the in vivo bone marrow micronucleus assay in rats at doses up to 45 mg/kg IV.

The results from the female fertility study in rats indicate no effects on reproductive performance and intrauterine survival up to the highest dose tested (45 mg/kg). Embryo-fetal development studies in female rats (up to 45 mg/kg) and rabbits (up to 35 mg/kg) have been conducted and demonstrated no effects on fetal growth, survival, or fetal morphology.

In a fertility study in male rats, no rezafungin-related effects were seen on reproductive performance up to the highest dose tested (45 mg/kg), dose-related lower mean sperm motility, concentration, and/or increased incidence of abnormal sperm morphology, along with microscopic findings of testicular seminiferous tubular epithelial degeneration associated with an effect on spermiation were noted at ≥ 30 mg/kg. Based on these data, the NOAEL for male reproductive toxicity was 15 mg/kg, which is approximately 2-5 fold over steady state following IV 200 mg weekly preceded by an IV loading dose of 400 mg. Based on the lack of any effects on intrauterine survival in females at any dosage level, the NOAEL for early embryonic toxicity was 45 mg/kg, the highest dose evaluated.

In a 3-month study in monkeys, during the sixth week of dosing, unexpected intention tremors were observed. Throughout the 3-month dosing period, dose-related incidence of sporadic slight to moderate tremors/intention tremors were seen at ≥ 30 mg/kg (30 mg/kg is 11-fold versus the Group 2 dose regimen). Tremors were typically seen during dosing days at or around the time of infusion and intention tremors were observed periodically on both dosing and nondosing days. The incidence of tremors and intention tremors reversed for most animals, but intention tremors were seen in one male at the high dose (60 mg/kg) near the end of the recovery period. Due to the observed neurobehavioral effects, a detailed neuropathology assessment was performed which identified axonal/nerve fiber degeneration of peripheral nerves and sensory ganglia, along with prominent Schwann cell hyperplasia/hypertrophy primarily within the sensory ganglia, at ≥ 30 mg/kg. Schwann cell changes reversed, but axonal/nerve fiber degeneration was still present at the end of the 4-week recovery period. No other test article-related microscopic changes were observed, including no test article-related effects in neurons of the sensory ganglia and in structures within the spinal cord or brain, including cerebellum. Although slight increases in serum calcium were observed at ≥ 30 mg/kg, an extensive evaluation of calcium homeostasis (i.e., ionized calcium, calcitonin, parathyroid hormone) failed to associate the minor increase in serum calcium to the observed neuropathological changes. Given the prominent Schwann hyperplasia/hypertrophy, it is not clear whether the axonal/nerve fiber degenerative changes are primary or secondary to an effect on the Schwann cells. The NOAEL level for neuropathology in monkeys is 10 mg/kg, which is approximately 4-fold over the estimated steady state plasma level in humans at 200 mg.

Results from a phototoxicity study in rats indicate evidence of phototoxicity at elevated CD101 exposures. Relative to the repeat-dose human plasma C_{max} level at 400 mg, the NOAEL for phototoxicity was 1.7-fold higher and the lowest-observed-adverse-effect level, where minimal changes were seen, was 3.6-fold higher. Review of the human safety data for CD101 and the medical literature for echinocandins indicate no evidence of phototoxicity. Results of a Phase 1 phototoxicity study in healthy human volunteers to elucidate the true risk of phototoxicity in subjects are pending.

Additional nonclinical data is available in the Investigator Brochure.

4.4 CLINICAL EXPERIENCE

CD101 Injection was safe and well tolerated as a single dose up to 400 mg and multiple doses up to 400 mg. The overall safety, tolerability, and PK profile of CD101 support continued development as a once-weekly therapy for invasive fungal infections.

A Phase 1, single-center, randomized, double-blind, single-ascending dose (SAD) study of CD101 administered by IV injection to healthy adult subjects (CD101.IV.1.01) has completed. The primary objective was to determine the safety, tolerability, and PK profile of CD101. In this study, subjects in 4 cohorts of 8 subjects (6 active, 2 placebo) each were randomized to receive single IV doses of CD101 Injection or placebo (normal saline) infused over 60 (±10) minutes. Dose levels of CD101 assessed follow an ascending single-dose regimen (50, 100, 200, or 400 mg).

A total of 32 subjects were randomized with 31 subjects completing all study assessments. One subject prematurely withdrew for personal reasons unrelated to safety or tolerability. Subjects were primarily White (97%), Hispanic (94%), and males and females were approximately equally represented (53% and 47%, respectively). There were no serious adverse events (SAEs), severe adverse events (AEs), or dose-response relationships for overall AEs. The majority of AEs were mild, and all AEs completely resolved by the end of the study. There were no drug-related AEs resulting from clinically significant hematology or clinical chemistry laboratory abnormalities at any dose. In addition, there were no safety issues related to electrocardiograms (ECGs), vital signs, or physical exam findings.

A Phase 1, single-center, randomized, double-blind, multiple-ascending dose (MAD) study of CD101 administered by IV injection to healthy adult subjects (CD101.IV.1.02) has completed. The primary objective was to determine the safety, tolerability, and PK profile of CD101 when administered IV as multiple doses to healthy adult subjects. In this study, subjects in 3 cohorts of 8 subjects (6 active, 2 placebo) each were randomized to receive multiple IV doses of CD101 Injection or placebo (normal saline) infused over 60 (±10) minutes. Dose levels of CD101 assessed follow an ascending multiple-dose regimen (100 mg ×2 doses, 200 mg ×2 doses, or 400 mg ×3 doses).

A total of 24 subjects were randomized and all subjects completed the study. Subjects were primarily White (88%), Hispanic or Latino (88%), and had a mean body mass index (BMI) of 27.208 kg/m^2 and a mean age of 42.8 years. Males and females were equally represented (50% each). There were no SAEs or severe AEs. The majority of AEs were mild, and all related AEs completely resolved by the end of the study. Four subjects in the CD101 group experienced mild, transient infusion reactions, characterized by flushing, sensation of warmth, nausea, and chest tightness. These infusion reactions were associated primarily with the 400 mg dose cohort and were most common with the third dose. These reactions occurred within minutes of infusion initiation and disappeared within minutes without interruption or discontinuation of the study drug infusion. There were no drug-related AEs resulting from clinically significant hematology or clinical chemistry laboratory abnormalities at any dose. In addition, there were no safety issues related to ECGs, vital signs, or physical exam findings.

The safety and efficacy of rezafungin for injection is being evaluated in this Phase 2, multicenter, prospective, randomized, double-blind, comparator study (IV caspofungin with option for oral fluconazole step-down therapy) for the treatment of subjects with candidemia and/or invasive candidiasis. Subjects were randomly assigned to receive 1 of 2 rezafungin for injection once weekly regimens or a daily IV caspofungin regimen with the option for oral fluconazole step-down therapy. Two rezafungin for injection dosing regimens were evaluated as follows: Group 1 was administered 400 mg ×2 weekly doses with a third optional weekly dose of 400 mg for all subjects and a fourth optional weekly dose 400 mg dose for subjects with invasive candidiasis; Group 1 was administered

400 mg ×1 weekly dose followed by 200 mg ×1 weekly dose with a third optional weekly dose of 200 mg for all subjects and a fourth optional weekly dose of 200 mg for subjects with invasive candidiasis. The reference therapy caspofungin regimen was as follows: 70 mg ×1 day and 50 mg/day for 13 days with additional optional dosing 50 mg/day up to 21 days for all subjects and additional optional dosing 50 mg/day up to 28 days for patients with invasive candidiasis.

In Part A of this Phase 2 study, there were 107 subjects enrolled; 56.1% were male, most subjects were White (83%) with other identified races of Black or African American (11.2%) and Asian (3.7%). Ethnicity was primarily Not Hispanic/Latino (87.9%). Mean age was approximately 52 years. Diagnosis at study entry was 89.7% candidemia and 10.3% invasive candidiasis with reasonable balance across the treatment groups. The study demonstrated efficacy for rezafungin for injection comparable to standard of care at Day 14 for all endpoints. There are no notable imbalances in TEAEs across the study groups. Most adverse events were mild or moderate in severity. There were no notable imbalances in SAEs across the treatment groups and SAEs observed were not unexpected for the patient population. AEs of interest included those potentially representative of photosensitivity (results of Phase 1 photosensitivity study is pending) and neuropathy. One subject in a rezafungin for injection group had an AE of sunburn (Group 1) following substantial sun exposure. AEs in the rezafungin for injection groups potentially representing neuropathy were intensive care unit acquired weakness (Group 2, 1 subject, moderate severity), and tremor (Group 2, 1 subject, mild). An AE of intensive care unit acquired weakness also occurred in 1 subject receiving caspofungin (severe) and an AE of polyneuropathy (severe) occurred in 1 subject receiving caspofungin. These AEs of interest potentially representing study drug-related tremor/ataxia/neuropathy were followed until resolution; all resolved. The Investigator Brochure should be referenced for additional information.

4.5 CLINICAL PHARMACOLOGY

The PK of CD101 has been well-characterized in healthy subjects for doses up to 400 mg for 3 weeks in the 2 Phase 1 studies: CD101.IV.1.01 (SAD study) and CD101.IV.1.02 (MAD study).

4.5.1 Single Ascending Dose Pharmacokinetics (CD101.IV.1.01)

Pharmacokinetics was determined by analyzing plasma and urine samples for concentration of CD101 obtained from subjects who received CD101 Injection in each cohort at various time points after administration of the single dose of the study drug.

The plasma PK of CD101 was generally well-characterized following the 50, 100, 200, and 400 mg CD101 doses. Exposure to CD101 increased with increasing CD101 doses (Table 3). Time to reach C_{max} (ie, T_{max}) was observed at the end of infusion, as expected, at approximately 1 hour after the start of infusion for all doses. Elimination of CD101 appears multiphasic. AUC and C_{max} increased in a dose proportional manner and total body clearance was similar throughout the dose levels with $t_{1/2}$ values of >80 hours

through the first week of plasma collection (a longer terminal $t_{1/2}$ of 127-146 hours is calculated when incorporating data from later collection times). Total body clearance was approximately 4 mL/min across the CD101 doses, indicating linear kinetics for CD101 across the doses investigated. Volume of distribution (V_z and V_{ss}) ranged from 33 to 48 L. The fraction of dose excreted in urine was <1% at all dose levels, indicating minor contribution of renal clearance in CD101 excretion.

Table 3: Summary of Plasma CD101 Exposures Following Administration of 50, 100, 200, and 400 mg 1-hour Intravenous Infusion of CD101

Dose (mg)	C_{max} (µg/mL)	C_{144} (µg/mL)	AUC_{0-168} (µg·h/mL)	$t_{1/2}$ (hours)
50	2.76	0.481	145	86
100	4.84	0.854	254	92
200	10.9	2.01	592	91
400	22.7	3.83	1160	84

AUC_{0-168} = area under the curve from time 0 to 168 hours; C_{144} = plasma concentration at 144 hours post start of infusion; C_{max} = maximum plasma concentration; $t_{1/2}$ = half-life.

4.5.2 Multiple Ascending Dose Pharmacokinetics (CD101.IV.1.02)

Pharmacokinetics was determined by analyzing plasma and urine samples for concentration of CD101 obtained from subjects who received CD101 Injection in each cohort at various time points after administration of study drug.

The plasma PK of CD101 was also well characterized following 2 or 3 weekly doses of CD101: 100 mg (Day 1/ Day 8), 200 mg (Day 1/ Day 8), and 400 mg (Day 1/ Day 8/ Day 15). Exposures following the first dose were very comparable to that observed in the SAD study, with AUC and C_{max} generally increasing in a dose proportional manner (Table 4). Accumulation was minor, ranging from 14% to 34% (or 1.14 to 1.34) as measured by C_{max} ratio of last/first dose and 30% to 55% (or 1.30 to 1.55), as measured by the area under the curve from time 0 to 168 hours (AUC_{0-168}) ratio of last/first dose.

Table 4: Summary of Plasma CD101 Exposures Following Administration of 100 mg (Day 1/Day8), 200 mg (Day 1/Day8), and 400 mg (Day 1/Day15) Weekly 1-hour Intravenous Infusion of CD101

Dose (mg)	Day	C_{max} (µg/mL)	AUC_{0-168} (µg·h/mL)	Accumulation Ratio	
				C_{max}	AUC_{0-168}
100	1	5.67	299	1.14	1.30
	8	6.49	390		
200	1	10.6	570	1.17	1.43
	8	12.4	813		
400	1	22.7	1190	1.34	1.55
	15	30.5	1840		

AUC_{0-168} = area under the curve from time 0 to 168 hours; C_{max} = maximum plasma concentration.

4.6 SUMMARY OF KNOWN BENEFITS AND POTENTIAL RISKS

4.6.1 Potential Benefits

It is anticipated that subjects participating in this study who are randomized to the CD101 IV groups will experience at least similar therapeutic benefits as subjects randomized to the caspofungin group. Approximately two-thirds of the subjects enrolled in this study will be randomized to receive CD101 IV.

The therapeutic benefits of caspofungin and fluconazole for the treatment of fungal infections are documented in the prescribing information and published literature. Approximately one-third of the subjects enrolled in this study will be randomized to receive IV caspofungin with the option of oral fluconazole step down therapy.

4.6.2 Known Risks

Safety and PK data from Study CD101.IV.1.01 and Study CD101.IV.1.02 are presented in Section 4.4.

Nonclinical toxicology of CD101 is presented in Section 4.3 and described in the Investigator Brochure.

4.6.3 Potential Risks

Echinocandins are typically well tolerated (Eraxis [anidulafungin] Prescribing Information, 2013; Mycamine [micafungin sodium] Prescribing Information, 2013; Cancidas [caspofungin acetate] Prescribing Information, 2014). Potential drug class effects include risk of abnormal liver function tests, hepatitis, and hepatic failure. General and administration site events (infusion related reactions, peripheral edema, rigors, infusion site inflammation, and pyrexia) have been reported for echinocandins (Eraxis [anidulafungin] Prescribing Information, 2013; Mycamine [micafungin sodium] Prescribing Information, 2013; Cancidas [caspofungin acetate] Prescribing Information, 2014). Possible histamine-mediated symptoms have been reported in patients who received rapid infusions of echinocandins, including rash, urticaria, flushing, pruritus, dyspnea, hypotension, facial swelling, and vasodilation. Anaphylactic-like reactions have been reported with micafungin (Mycamine [micafungin sodium] Prescribing Information 2013).

Results from a phototoxicity study in rats indicate evidence of phototoxicity at elevated CD101 exposures (Section 4.3). Because of the safety margin to the human-equivalent exposure of subjects in this study, the possibility of the rat-specific histamine release affecting the results, and the mild reaction seen in rats at 3.6-fold above the human equivalent plasma level, Cidara believes that the risk to humans is low. Nevertheless, pending resolution of this issue through a Phase 1 human clinical study, Cidara has notified investigators of the findings and added wording to the Informed Consent Form (ICF) for subjects to use measures to reduce sun exposure while on study drug.

Based on a fertility study in male rats, there is the potential risk for decreased sperm motility, increased incidences of abnormal sperm morphology, and testicular seminiferous tubular epithelial degeneration. These findings were noted at 2.5-fold the exposure for Group 2. The risk to humans is unknown, thus the male contraception requirements in inclusion criterion 4 have been extended from first dose to 90 days with the inclusion of prohibited sperm donation within the period. This risk will be included in the ICF.

In a 3-month study in monkeys, there were observations of tremors, intention tremors, and histology consistent with axonal degeneration (potentially consistent with clinical presentation of neuropathy) first appearing at week 6 of dosing. These observations occurred at 11-fold the exposure for Group 2. Given the late timing and high exposure relative to the Group 2 dosing regimen, the risk to study subjects is assessed as low.

Because there may be unknown and potential risks with administration of CD101 IV, all subjects will be closely monitored for safety and tolerability by repeated assessment of clinical, vital signs, and clinical laboratory safety parameters and reporting of AEs.

4.6.4 Risk-Benefit Summary

Overall, based on risk/benefit analysis, the current study appears to be fully justified in the planned population.

4.7 JUSTIFICATION FOR DOSING REGIMEN

A population PK model has been developed for rezafungin (Bader 2018). Data from a subset of Phase 2 Part A data as well as data from a Phase 1 study was added to update the structural model and evaluate covariate effects. Preliminary data from the modeling is used to set doses for upcoming Phase 3 studies.

In brief, these data were best described using a 4-compartment model with 0-order drug input via the IV infusion and first-order, linear elimination. This model fit the observed data with very little bias and excellent precision.

Monte Carlo simulations for 2000 hypothetical patients were conducted to assess the probability of PK/PD target attainment using the weekly free-drug area under the rezafungin concentration-time curve from time 0 to 168 hours ($fAUC_{0\text{-}168}$) after each dose for the two dosing regimens tested in Part A; albumin, weight, and sex were bootstrapped (using random sampling and replacement) from the dataset of subjects and plasma protein binding of 97.4% was used.

Nonclinical studies of *C. albicans* infection models in mice have shown that a rezafungin free-drug *f*AUC:MIC is the PK/PD parameter most predictive of efficacy, and $fAUC_{0\text{-}168}$:MIC targets have been established in the mouse model for important pathogenic *Candida* spp. (refer to Investigator Brochure).

The PK/PD target attainment for the 2 regimens used in Part A (400 mg once weekly for 2 to 4 weeks and a 400 mg loading dose on Week 1 followed by 200 mg once weekly for a total of 2 to 4 weeks) relative to the reported MIC distribution (Pfaller 2017) is shown in Table 5 and Figure 4 for *C. albicans* and in Table 6 and Figure 5 for *C. glabrata*. Both regimens provided adequate PK/PD target attainment throughout 4 weeks of dosing, up to a MIC of 0.5 µg/mL for *C. albicans*, and up to an MIC of 16 µg/mL for *C. glabrata*. The 400 mg once weekly dosing regimen seems to provide some additional benefit in terms of target attainment, improving by 40 to 70% for an MIC=1, but not until Week 2 or beyond. However, most of the benefits of antifungal treatment occur in the first week of therapy, and the incremental improvement for the 400 mg once weekly dose regimen for Weeks 2 and 3 will likely be of little real clinical benefit in the treatment of candidemia or invasive candidiasis. In fact, in comparison to other echinocandins, the 400 mg loading dose on Week 1, followed by 200 mg once weekly dose regimen provides a significant advantage in terms of potential to cover pathogens with higher MICs (Table 7).

The data from Part A indicate that both rezafungin regimens were comparable to each other and to caspofungin for efficacy and safety. There were no adverse events that seemed to cluster in the 400 mg once weekly group to indicate any concern for increased toxicity with the higher dose. However, the Phase 1 results do indicate that there are infusion reactions that can occur in the higher dose rezafungin regimen that are an

echinocandin class effect and are related to the rate of infusion (mg/min). Thus, given there is no apparent clinical benefit to the 400 mg once weekly dose regimen over the regimen with a 400 mg loading dose on Week 1, followed by 200 mg once weekly, and that both options provide at least a three dilution MIC improvement in target attainment over the best of the currently approved echinocandins (Table 7), the regimen of a 400 mg loading dose on Week 1, followed by 200 mg once weekly for a total of 2 to 4 doses can be selected for safety and efficacy in the treatment of candidemia and/or invasive candidiasis.

Table 5: Predicted Pharmacokinetic-Pharmacodynamic Target Attainment for Rezafungin Regimens, Stratified by Week and Minimal Inhibitory Concentration, against *C. albicans*

Regimen[a]	Week	MIC (mg/L) [b]					
		0.06	0.12	0.25	0.5	1	2
400/400	1	100	100	100	98.8	35.1	0.05
	2	100	100	100	99.95	73.4	2.45
	3	100	100	100	100	84.3	7.1
	4	100	100	100	100	88.3	10.75
400/200	1	100	100	100	98.8	35.1	0.05
	2	100	100	100	92.55	14.95	0
	3	100	100	100	91.05	14.45	0
	4	100	100	100	90.55	15	

MIC = minimal inhibitory concentration.

a. Regimens defined by the weekly dose (eg, 400/200 represents 400 mg for the first dose, followed by 200 mg IV once weekly).

b. Shaded cells indicate PK-PD target attainment above 90%.

Figure 4: Predicted Pharmacokinetic-Pharmacodynamic Target Attainment for Rezafungin Regimens, against *C. albicans* relative to MIC Distribution

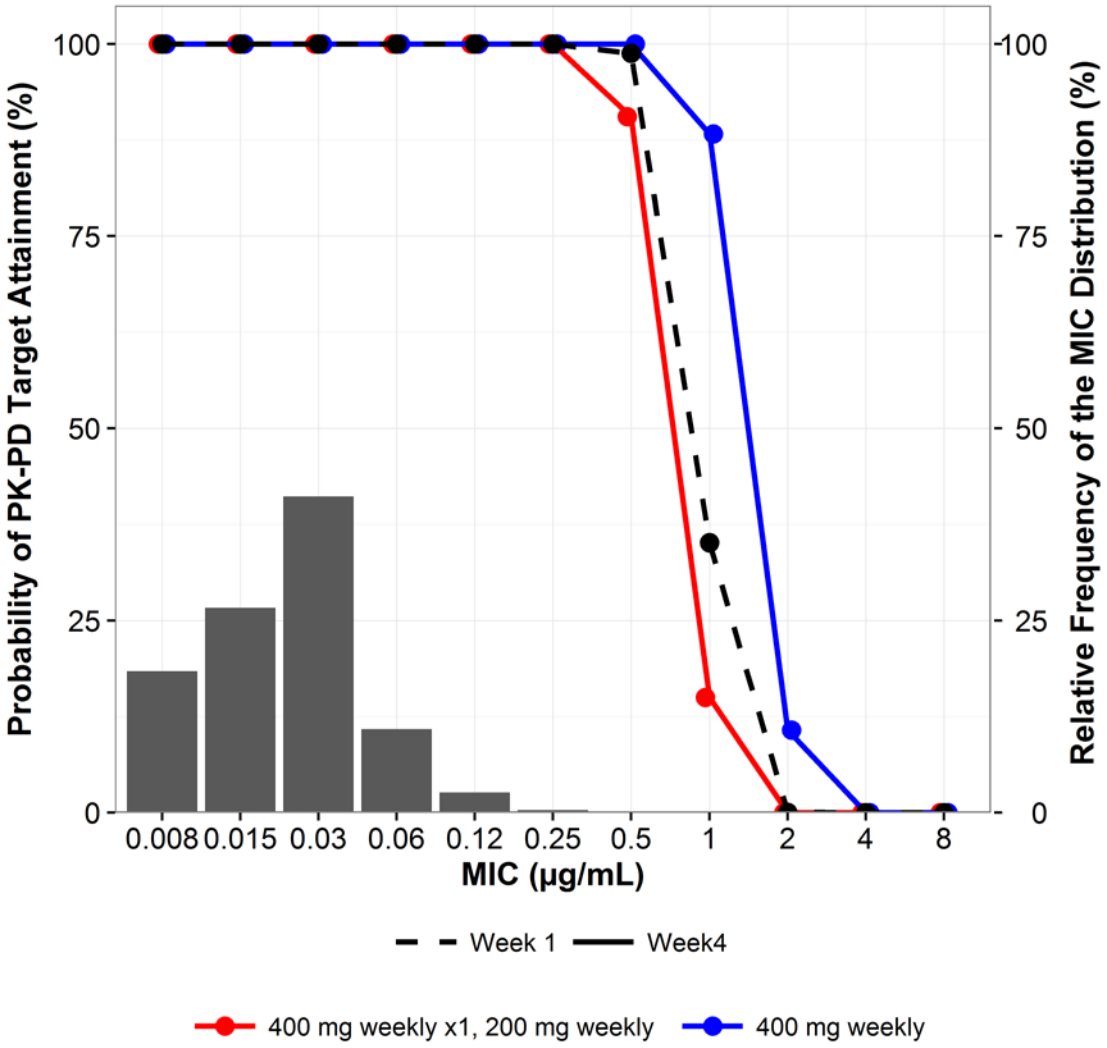


Table 6: Predicted Pharmacokinetic-Pharmacodynamic Target Attainment for Rezafungin Regimens, Stratified by Week and Minimal Inhibitory Concentration, against *C. glabrata*

Regimen[a]	Week	MIC (mg/L) [b]					
		0.12	0.5	2	4	8	16
400/400	1	100	100	100	100	100	100
	2	100	100	100	100	100	100
	3	100	100	100	100	100	100
	4	100	100	100	100	100	100
400/200	1	100	100	100	100	100	100
	2	100	100	100	100	100	100
	3	100	100	100	100	100	100
	4	100	100	100	100	100	98.65

MIC = minimal inhibitory concentration.

a. Regimens defined by the weekly dose (eg, 400/200 represents 400 mg for the first dose, followed by 200 mg once weekly).

b. Shaded cells indicate PK-PD target attainment above 90%.

Figure 5: Predicted Pharmacokinetic-Pharmacodynamic Target Attainment for Rezafungin Regimens, against *C. glabrata* relative to MIC Distribution

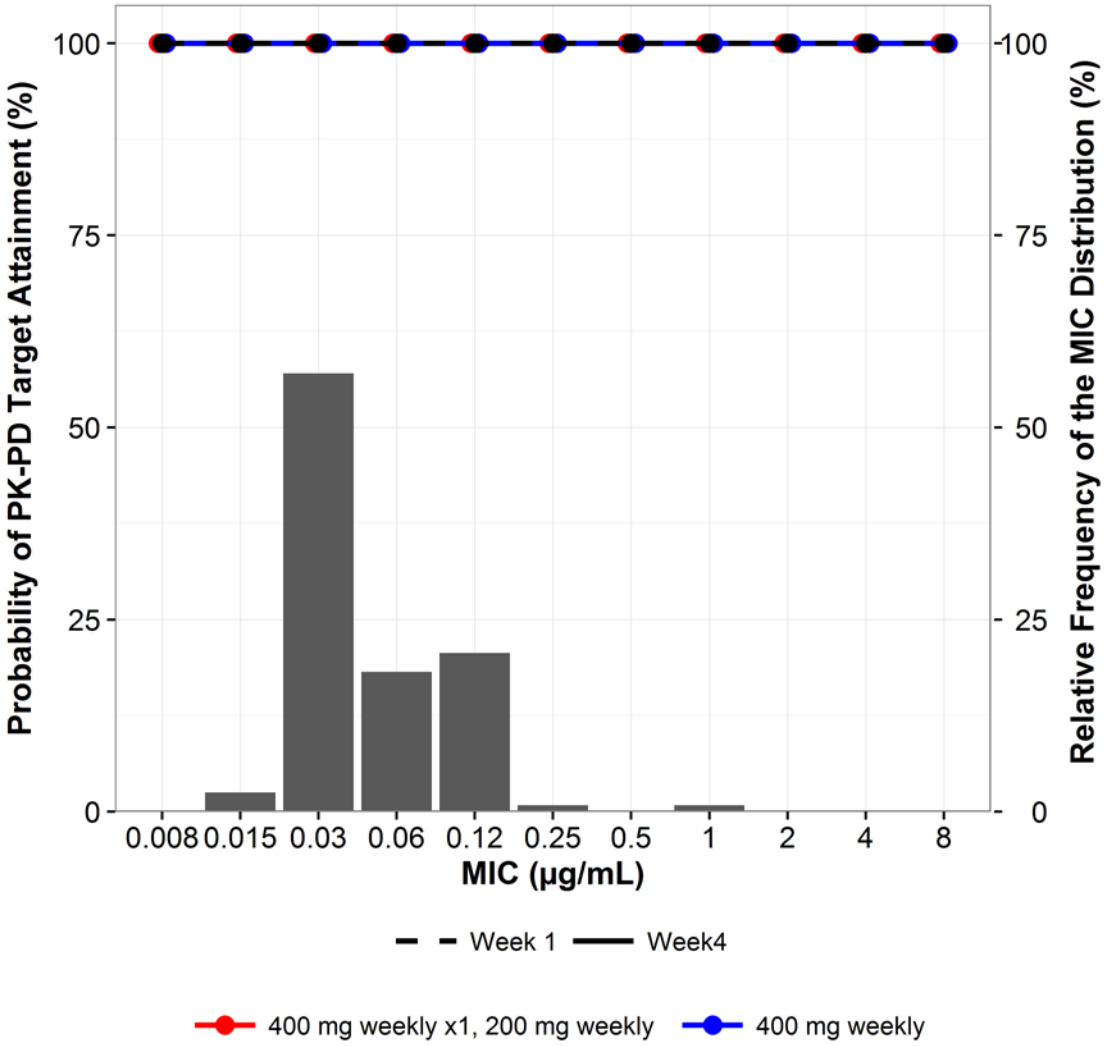


Table 7: Percent Probabilities of Pharmacokinetic-Pharmacodynamic Target Attainment by Anidulafungin, Caspofungin, and Micafungin against *Candida spp*.

MIC (mg/L)	Anidulafungin		Caspofungin		Micafungin		Rezafungin*	
	Candida albicans	*Candida glabrata*	*Candida albicans*	*Candida glabrata*	*Candida albicans*	*Candida glabrata*	*Candida albicans*	*Candida glabrata*
0.008	100[a,b]	100	100	100	99.4	100	100	100
0.015	99.1	100	100	100	71.2	100	100	100
0.03	100	99.2	100	100	10.1	97.5	100	100
0.06	39.8	54.3	97.9	100	0.10	49.9	100	100
0.12	0	0.95	76.7	100	0	3.4	100	100
0.25	0	0	35.7	100	0	40.1	100	100
0.5	0	0	12.1	97.0	0	0.15	90.55	100
1	0	0	4.4	73.2	0	0	15	100
2	0	0	1.35	33.9	0	0	0	100
4	0	0	0.25	11.3	0	0	0	100
8	0	0	0.05	4.35	0	0	0	100

Note: Data for other echinocandins (Bader 2017)

Abbreviations: MIC, minimal inhibitory concentration; MIC90, minimal inhibitory concentration required to inhibit 90% of isolates.

[a] Shaded cells indicate PK-PD target attainment values ≥90%.

[b] Cells with dotted outlines represent the MIC90 values for each agent against the respective *Candida spp*.

* 400/200/200/200 at wk 4

4.8 POPULATION TO BE STUDIED

In this study, adult subjects with candidemia and/or IC will be included.

4.9 STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles of the Declaration of Helsinki, and applicable regulatory and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) requirements.

4.10 JUSTIFICATION FOR USE OF CD101 IN CANDIDEMIA AND INVASIVE CANDIDIASIS

Candidemia is a fungal bloodstream infection usually affecting patients who are already ill with other comorbidities. Invasive candidiasis defines a number of different organ-specific infections with *Candida* spp. Candidemia and IC may present without the other syndrome or may exist together as part of the same pathophysiology of disseminated candidiasis. Risk factors for candidemia and IC include recent surgery, organ and bone marrow transplants, broad-spectrum antibiotic use, receipt of total parenteral nutrition, end stage renal disease, indwelling vascular catheters or other devices, etc. While candidemia is often associated with other forms of IC, including intra-abdominal abscess, peritonitis, or pleuritic involvement, candidemia without other overt organ involvement is the most common form of IC diagnosed. A recent study by the ESCMID Fungal Infection Study Group reported the incidence of candidemia as 6.9 per 1000 intensive care unit patients with mortality rates between 20% and 49% (Kett et al., 2011; Gudlaugsson et al., 2003; Arendrup et al., 2011). Candidemia and IC are serious and potentially life-threatening infectious complications that require aggressive and timely antifungal management.

The current IDSA and ESCMID guidelines recommend echinocandins as first-line therapy for candidemia and most forms of IC (Pappas et al., 2016; Cornely et al., 2012). There are currently 3 commercially authorized echinocandins in the US and the European Union: caspofungin, micafungin, and anidulafungin. These echinocandins are administered once daily via IV infusion and share similar PK parameters and safety profiles. CD101 is a novel echinocandin derived from another echinocandin (anidulafungin). CD101 has a more stable molecular structure compared to the other echinocandins, which results in a reduction in the formation of toxic metabolites and an improvement in the duration of exposure to active drug. This stability further translates into a better safety profile as demonstrated in both nonclinical and clinical studies, as well as a unique PK profile that allows for high dose, front-loaded exposures for improved fungal killing and once weekly IV dosing.

Both in vitro and in vivo data have demonstrated the potency and efficacy of CD101 against *Candida* and disseminated candidiasis (Section 4.2, Section 4.3, and Investigator Brochure). In all nonclinical efficacy studies performed for CD101 in neutropenic disseminated candidiasis, CD101 has performed as well as, or better than, currently approved echinocandin comparators. This Phase 2 double-blind, randomized, controlled trial comparing 2 dose regimens of CD101 against caspofungin is the first efficacy study in humans for CD101. The duration of antifungal therapy in standard practice depends on the time it takes to clear the *Candida* from infected blood or tissues, and thus patients with IC often require a longer duration of therapy than patients with candidemia alone. To that end, all subjects in this study must be administered study drug for at least 14 days followed by an optional third week (for subjects with either candidemia or IC) or fourth week (for subjects with IC only) of treatment if clinically indicated.

In PK and PD models, both of the CD101 dosing regimens proposed for the Phase 2 study demonstrate 100% target attainment of wild-type *C. albicans* and *C. glabrata* (*C. albicans* data is presented in Section 4.7). The 400-mg, once-weekly dosing regimen may have improved coverage of isolates with MICs >0.5 µg/mL, which is now of increasing prevalence in some institutions. Therefore, in this nonpowered study, both CD101 groups are expected to have equal efficacy with each other, as well as with the comparator. Since mild infusion reactions were observed in the Phase 1 studies, occurring most frequently in the third dose of the 400-mg dose group, it is possible that the lower dose regimen of CD101 may be better tolerated than the higher dose. This Phase 2 study is intended to assess, but not directly compare, the efficacy of both CD101 and the approved first-line comparator in the same patient population and to build confidence in the efficacy of CD101 for a larger powered Phase 3 study. Results from this study should help to discern any differences in safety and tolerability between the 2 CD101 dose groups and help to select the best CD101 dose and regimen for the Phase 3 study.

4.11 JUSTIFICATION OF THE PART B STUDY

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) with an interim analysis performed after approximately 40 to 60 subjects in the Microbiological Intent-to-Treat (mITT) population were enrolled and completed study drug therapy. The timing of this interim analysis enabled a smooth transition from the end of enrollment for Part A to the initiation of enrollment in Part B, and helped protect Part B subjects from unknown risks of low efficacy or safety findings prior to the start of the study extension.

As detailed in Section 4.10, efficacy is expected to be equal between the 2 regimens in this study. There may be some advantages for the Group 1 subjects due to higher exposures, especially for *Candida* strains with higher MICs, but due to the low prevalence of these organisms, the effect of the higher exposure of Group 1 on the overall efficacy estimates is expected to be minimal.

The purpose of Part B is to further assess the safety and efficacy of CD101. Assessment of blinded safety data and data unblinded for safety purposes in Part A indicated that there were no known episodes of flushing, infusion reactions, or any evidence of target organ toxicity in Part A, and thus the focus of continued CD101 assessment in Part B was Group 1. Part B was initiated directly after the close of enrollment for Part A and continued during the analysis of Part A data. Following evaluation of the unblinded results from Part A, it was determined that the best CD101 dose regimen for Phase 3 was the 400 mg loading dose on Week 1 followed by 200 mg once weekly for a total of 2 to 4 weeks (Group 2). Thus, with this amendment, enrollment in Group 1 will stop and Part B will continue enrollment of rezafungin for injection Group 2 and caspofungin enrolled in a 2:1 ratio. This extension is expected to at least double the size of the rezafungin for injection safety database.

5.0 STUDY PURPOSE AND OBJECTIVES

The primary objectives of this study are to:

- Evaluate the safety and tolerability of CD101 IV in the Safety population
- Evaluate overall success (mycological eradication and resolution of systemic signs attributable to candidemia and/or 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:

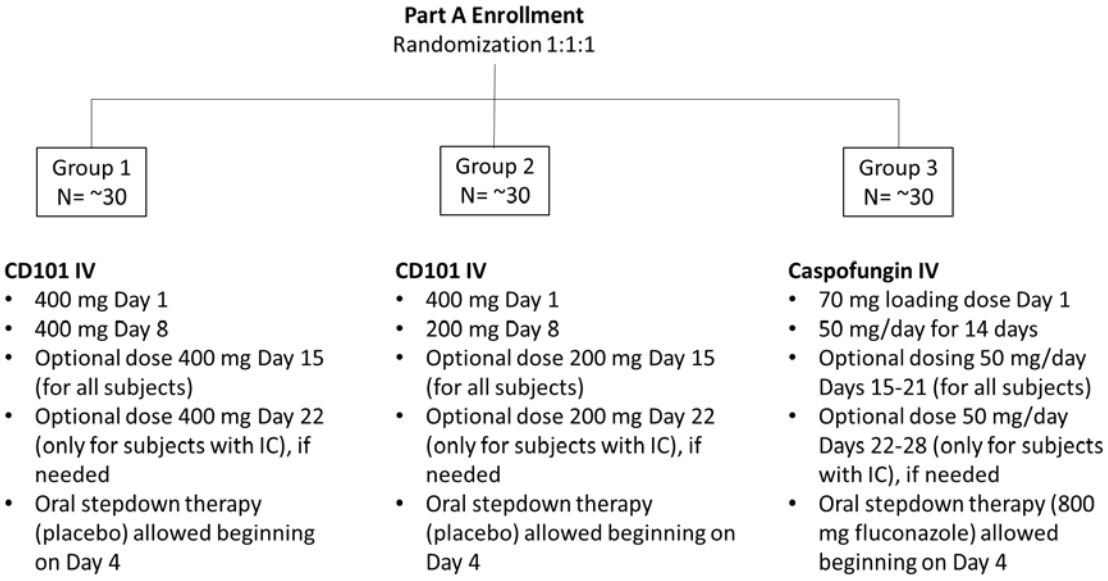
- Evaluate overall success (mycological eradication and resolution of systemic signs attributable to candidemia and/or IC) of CD101 IV at Day 5, Day 28 (±2 days; only for subjects with IC), and Follow-up (FU, Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) 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 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) 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 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) in the mITT population
- Evaluate the PK of CD101 IV

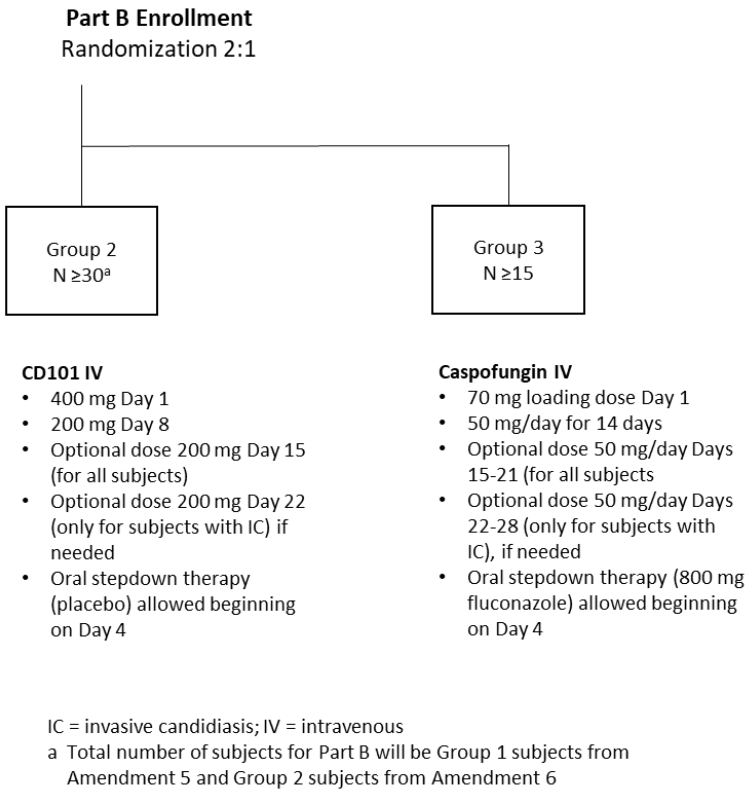
6.0 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a Phase 2, multicenter, prospective, randomized, double-blind study of CD101 IV or IV caspofungin followed by oral fluconazole step-down therapy for treatment of subjects with candidemia and/or IC. 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 (Figure 5, Figure 6, Figure 7, Table 6). Oral step-down therapy is allowed in all 3 treatment groups in Part A; oral placebo in the CD101 IV groups and oral fluconazole in the 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. In Part B, subjects will be randomized in a 2:1 ratio to receive CD101 IV treatment Group 1 or IV caspofungin (Figure 5, Figure 6, Figure 7, Table 6) until ≥45 additional subjects and no more than 120 subjects have been enrolled. (Note: Subjects enrolled under Amendment 5 and assigned to CD101 IV receive Group 1 treatment and subjects enrolled under Amendment 6 and assigned to CD101 IV treatment receive Group 2 treatment. Subjects enroll under the current, approved amendment at the site at the time of randomization; subjects enrolled to Amendment 5 continue study participation according to the same amendment regardless of subsequent approval of Amendment 6.) Total enrollment will depend on the enrollment rate for the 6- to 8-month period between the end of Part A and the staged start of the Phase 3 study, which is the trigger for the rolling close-out of Part B. 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.

Figure 6: Study Randomization and Treatment Regimens





IC = invasive candidiasis; IV = intravenous
a Total number of subjects for Part B will be Group 1 subjects from Amendment 5 and Group 2 subjects from Amendment 6

Subjects with candidemia only may be treated with study drug for a maximum of 21 days. Subjects with IC (with or without candidemia) may be treated with study drug for a maximum of 28 days. Subjects will be presumed to have IC if there is a positive culture fo*r Candida* spp. from a normally sterile site other than blood or if there is a positive sponsor-approved rapid in vitro diagnostic (IVD) or blood culture for *Candida* spp. combined with radiographic evidence of IC.

Subjects in the CD101 IV treatment Group 1 will receive CD101 IV 400 mg on Day 1 and Day 8, with an optional dose of 400 mg on Day 15 (for all subjects) and an optional dose of 400 mg on Day 22 (only for subjects with IC), if needed.Subjects in the CD101 IV treatment Group 2 will receive CD101 IV 400 mg on Day 1 and 200 mg on Day 8, with an optional dose of 200 mg on Day 15 (for all subjects) and an optional dose of 200 mg on Day 22 (only for subjects with IC), if needed. Subjects in the caspofungin group will receive IV caspofungin (a single 70 mg loading dose on Day 1 followed by 50 mg once daily) for ≥3 days up to a maximum of 21 days for subjects with candidemia only and up to a maximum of 28 days for subjects with IC (with or without candidemia). The optional doses of CD101 IV on Day 15 and Day 22 may be administered according to the subject's clinical response and the medical judgment of the Principal Investigator (PI).

After ≥3 days of IV therapy, subjects in the caspofungin group can be switched to oral step-down therapy of fluconazole (a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if criteria are met. In order to maintain the blind, subjects in the CD101 IV groups who have switched to oral step-down therapy will receive oral placebo (4 capsules on the first day followed by 2 capsules/day thereafter) and subjects in the caspofungin treatment group will receive IV placebo on Day 8, and on Days 15 and 22 if study drug is administered through these timepoints. The total IV plus oral treatment duration will be ≥14 days and up to a maximum of 28 days.

The dose and duration of any prior antifungal treatment taken within 4 weeks of randomization will be recorded at Screening. A retinal examination for evidence of a *Candida* eye infection, including endophthalmitis or chorioretinitis, will be performed during Screening or by Day 7 only on subjects with candidemia by blood culture, and should be repeated in subjects who were negative at baseline if the subject develops visual signs or symptoms of a *Candida* eye infection during the course of the study. Subjects who were negative at baseline and diagnosed with a *Candida* eye infection after initiating study drug should have an urgent ophthalmologic consultation (if not already done), should stop study drug, and be initiated on appropriate therapy for *Candida* eye infection per the local guidelines (Pappas et al., 2016; Cornely et al., 2012). If possible, all subjects diagnosed with endophthalmitis or chorioretinitis should remain in the study and all subsequent antifungal drugs, interventions, and outcomes for endophthalmitis or chorioretinitis should be recorded.

The Schedule of Assessments and Procedures is presented in Table 2. Study Day 1 is defined as the first day of study drug administration. Subsequent study days are defined by the number of consecutive calendar days thereafter. All subjects will be monitored for AEs and SAEs following signing of the ICF at Screening and throughout the study until the FU visit (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) for each treatment group. Vital signs (temperature, heart rate, blood pressure, respiratory rate) will be recorded daily while receiving IV study drug and at Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), End-of-Treatment (EOT) (+2 days allowed after last dose of study drug), and FU (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia). Hematology and chemistry laboratory tests will be performed at Screening; Days 2 and 4; Day 8, Day 14 (±1 day), EOT (+2 days allowed after last dose of study drug) and at the FU visit. Coagulation laboratory tests (prothrombin time/international normalized ratio [PT/INR] and either partial thromboplastin time [PTT] or activated partial thromboplastin time [aPTT]) will be performed at Screening. ECGs will be performed at Screening (before subject randomization) and EOT (+2 days allowed after the last dose of study drug).

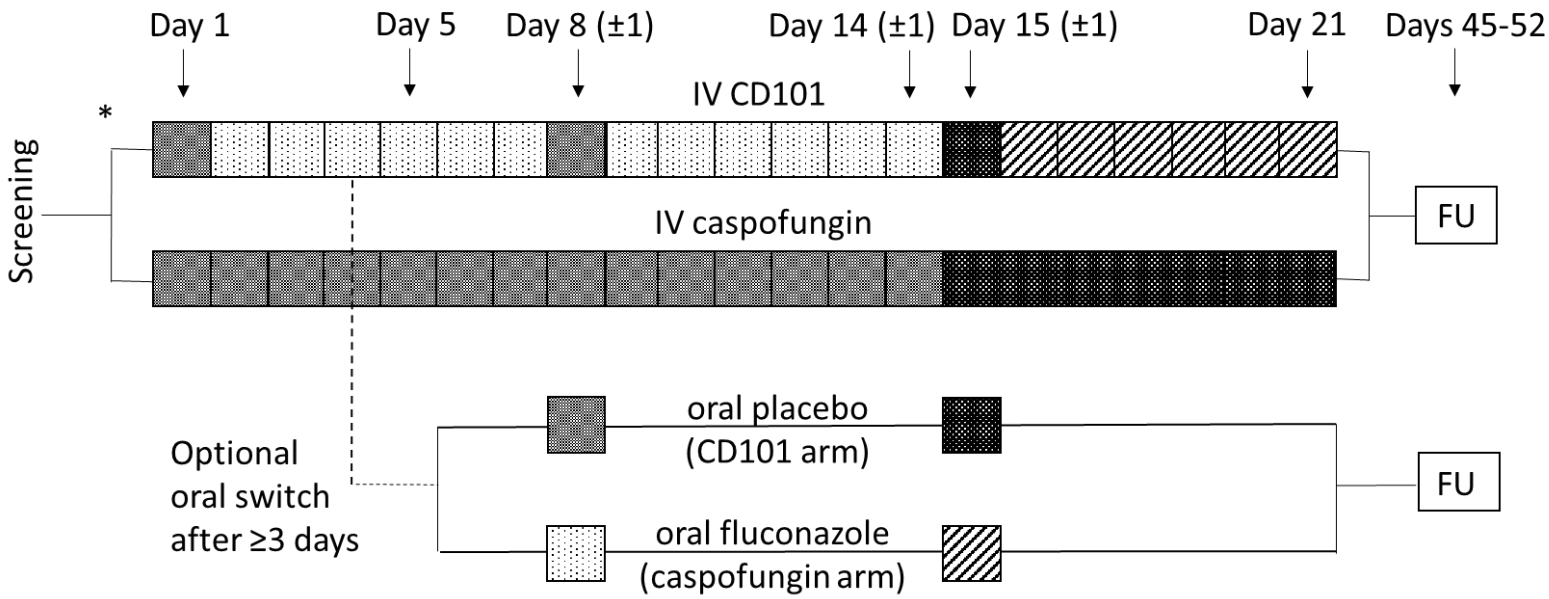
Mycological diagnosis of candidemia or IC sufficient for inclusion in the study will be established by a positive microbiological test for yeast o*r Candida* within 96 hours from time of collection of the sample until randomization. Acceptable positive microbiological tests for yeast o*r Candida* include ≥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. 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. Blood cultures should be performed daily (preferred) or every other day until 2 blood cultures drawn ≥12 hours apart are negative, without an intervening positive culture. Generally, blood cultures should involve 2 separate draws with ≥1 draw from a peripheral vein without an IV catheter. Two bottles should be filled from each draw site, totaling 4 bottles for each set of blood cultures. If possible, use 3 aerobic and 1 anaerobic bottle (if available at the site) for each blood culture set, although 2 aerobic and 2 anaerobic (if available) is also acceptable.

In Part A only, blood samples will be collected for PK analysis from the OPPOSITE arm of the infusion on Day 1 (within 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 safety labs if possible), Day 4 (random draw, with safety labs if possible), Day 8 (predose only), and Day 15 (predose only). 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. For the purpose of maintaining the blind, blood samples will be collected from all subjects, when possible, in all 3 treatment groups in Part A, but only PK samples from the CD101 IV

groups will be analyzed (using a validated assay) by an independent, central bioanalytical laboratory. In Part B, PK samples will not be collected.

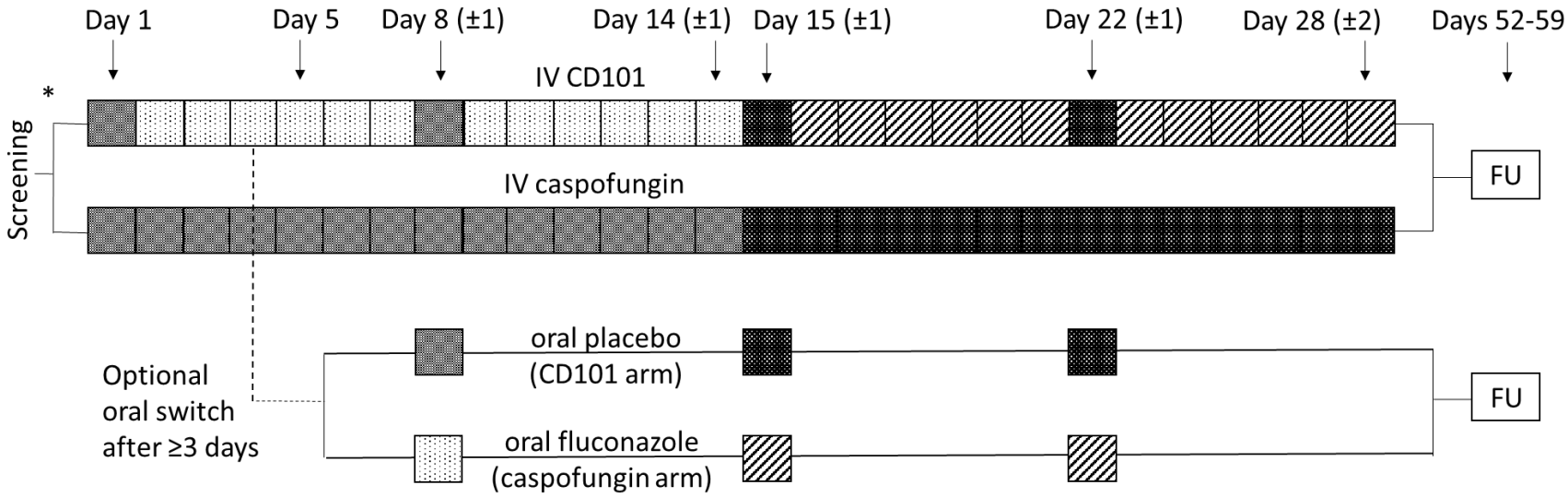
Overall success and mycological eradication will be assessed at Day 5, Day 14, Day 28 (±2 days; only for subjects with IC), and FU (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia). Clinical response will be assessed at Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), and FU (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia).

Figure 7: Study Design Diagram for Subjects with Candidemia Only



* Applies to CD101 Group 1 (Parts A and B) and Group 2 (Part A only)
Total IV plus oral therapy ≥14 days and ≤21 days
Total IV therapy ≥3 days and ≤21 days
Optional CD101 IV therapy allowed on Day 15 if require >14 days of therapy
Optional caspofungin IV therapy allowed on Days 15-21
Switch to oral step-down therapy allowed after ≥3 days IV therapy and up to Day 21
Day 8 IV therapy (required) PLUS oral therapy if on oral step-down therapy
Day 15 IV therapy (optional) PLUS oral therapy if on oral step-down therapy
Efficacy assessments on Days 5, 14, and FU (Days 45-52)
FU = follow-up visit; IV = intravenous

Figure 8: Study Design Diagram for Subjects with Invasive Candidiasis (with or without Candidemia)



* Applies to CD101 Group 1 (Parts A and B) and Group 2 (Part A only)
Total IV plus oral therapy ≥14 days and ≤28 days
Total IV therapy ≥3 days and ≤28 days
Optional CD101 IV therapy allowed on Day 15 and Day 22 if require additional therapy
Optional caspofungin IV therapy allowed on Days 15-28
Switch to oral step-down therapy allowed after ≥3 days IV therapy and up to Day 28
Day 8 IV therapy (required) PLUS oral therapy if on oral step-down therapy
Day 15 and Day 22 IV therapy (optional) PLUS oral therapy if on oral step-down therapy
Efficacy assessments on Days 5, 14, 28, and FU (Days 52-59)
FU = follow-up visit; IV = intravenous

6.2 NUMBER OF SUBJECTS

In Part A, subjects will be randomized (1:1:1) until there are approximately 30 subjects in the CD101 IV treatment Group 1, 30 subjects in the CD101 IV treatment Group 2, and 30 subjects in the comparator group in the mITT population. It is expected that approximately 114 subjects will need to be randomized to achieve 90 subjects in the mITT population (assuming 80% of randomized subjects will be included in mITT population).

In Part B, subjects will be randomized (2:1) until there are ≥30 subjects in the CD101 IV treatment and ≥15 subjects in the comparator group (≥45 additional subjects and no more than 120 subjects). (Note: Subjects enrolled under Amendment 5 and assigned to CD101 IV receive Group 1 treatment and subjects enrolled under Amendment 6 and assigned to CD101 IV treatment receive Group 2 treatment. Subjects enroll under the current, approved amendment at the site at the time of randomization; subjects enrolled to Amendment 5 continue study participation on the same amendment regardless of subsequent approval of Amendment 6.) Total enrollment will depend on the enrollment rate for the 6- to 8-month period between the end of Part A and the staged start of the Phase 3 study, which is the trigger for the rolling close-out of Part B.

6.3 MEASURES TAKEN TO MINIMIZE BIAS

Bias is minimized by subject randomization and blinding in both Part A and Part B (Section 6.5).

For the interim analysis, a few (≤5) efficacy and safety tables will be provided by an independent unblinded statistician without individual subject data to allow for continuation to Part B of the study. After the database for Part A is locked, summary tables of unblinded efficacy and safety data will be provided. Individual subjects will not be unblinded for either the interim analysis or the Part A analysis. (Note: An addendum to the Unblinding Plan for Part A allowed for unblinded safety review of adverse events of interest identified during blinded safety review; the addendum allowed for no more than 5% of subjects to be unblinded.) The data from Part B will only be unblinded and analyzed after database lock for Part B at completion of the study.

6.4 EXPECTED DURATION OF SUBJECT PARTICIPATION

Study participation will require from 45 to 52 days for subjects with candidemia only (or from 52-59 days for subjects with IC, with or without candidemia) after the first dose 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); safety, tolerability, and efficacy assessments up to Day 21 (for subjects with candidemia) or up to Day 28 (±2 days; only for subjects with IC); and a FU visit (Days 45 to 52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia).

6.5 METHOD OF TREATMENT ASSIGNMENT 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 will be assigned a subject number and randomized (2:1) to receive CD101 IV treatment or caspofungin on Day 1 just prior to dosing. Randomization will be stratified based on the method used at Screening to establish the diagnosis (blood culture/rapid 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 a computer-generated randomization schedule. A subject is considered randomized when the randomization transaction is recorded in the Interactive Web Response System (IWRS).

The data for the 40 to 60 subjects in the mITT population involved in the interim analysis will be locked prior to the unblinded interim analysis, and the database for Part A will be locked prior to the Part A analysis. The data from Part A will be unblinded after the database is locked for Part A, but likely prior to completion of Part B, and interim summary results and full Part A summary results will be reported when available.

All study personnel, including the Sponsor, PI, and site personnel involved in study conduct, and subjects will remain blinded to by-subject study medication assignment for both Part A and Part B until the study is completed, with the exception of the pharmacy monitor, unblinded program manager, clinical supplies, document manager, and quality (per the Sponsor Blinding Plan). Additionally, in Part A only, some personnel from vendors, including the PK analyst and an independent unblinded statistician, will be unblinded, but will not be involved in study conduct or the final analysis. An independent unblinded statistician will perform the analysis on the interim and final unblinded Part A data. (Note: An addendum to the Unblinding Plan for Part A allowed for unblinded safety review of adverse events of interest identified during blinded safety review; the addendum allowed for no more than 5% of subjects to be unblinded.) The Pharmacy Monitor will monitor drug preparation and drug accountability during the study and cases in which unblinding is required due to a safety or tolerability issue. 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. To maintain the blind, oral study drug pills must never be

crushed. 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 Section 8.6.

7.0 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

To be enrolled in this study, all subjects must meet all of the following inclusion criteria and none of the exclusion criteria.

7.1 SUBJECT INCLUSION CRITERIA

Subjects in must meet ALL of the following inclusion criteria to be enrolled:

1. Males or females ≥18 years.

2. Established mycological diagnosis of candidemia and/or IC from a sample taken ≤96 hours before randomization defined as:

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

    OR

    b. Positive test for *Candida* from a Sponsor-approved rapid IVD

    OR

    c. Positive Gram stain for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site

3. Willing to initiate or continue medical treatment to cure infections, including receipt of antibiotics and surgical procedures, if required. Subjects receiving only medications and measures for comfort, and not cure, should not be enrolled.

4. Female subjects of child-bearing potential <2 years postmenopausal must agree to and comply with using 1 barrier method (eg, female condom with spermicide) plus 1 other highly effective method of birth control (eg, oral contraceptive, implant, injectable, indwelling intrauterine device, vasectomized partner), or sexual abstinence while participating in this study. Male subjects must be vasectomized, abstain from sexual intercourse, or agree to use barrier contraception (condom with spermicide), and also agree not to donate sperm from first dose of CD101 (Day 1) until 90 days following last administration of study drug.

5. Willing and able to provide written informed consent. If the subject is unable to consent for himself/herself, a legally acceptable representative must provide informed consent on their behalf.

6. Presence of 1 or more systemic signs attributable to candidemia and/or IC (eg, fever, hypothermia, hypotension, tachycardia. tachypnea) (Section 7.1.2)

7.1.1 Rapid In Vitro Diagnostics for Candidemia and Invasive Candidiasis

The addition of rapid IVD for the identification of subjects with candidemia and/or IC is being employed to reduce the amount of prior empiric antifungal therapy being administered to potential study subjects. Rapid IVDs for *Candida* spp. used for inclusion in this study must be approved by the Sponsor prior to use in the study. Subjects may be enrolled based on a positive result at Screening from a Sponsor-approved rapid IVD, but a culture from blood or normally sterile tissue or fluid that is positive for *Candida* spp. will still be the required objective measure for candidemia or IC in the study analyses for efficacy. Subjects who are enrolled based on a positive rapid IVD test and have negative or missing blood culture at Screening and remain culture negative, may or may not have study therapy discontinued, but should continue to be followed in the study for safety assessments.

Potential subjects with 1 or more risk factors for candidemia and IC should have a Sponsor-approved rapid IVD for *Candida* spp. performed only if the site is drawing a blood sample for blood culture and if empiric antifungal therapy for candidiasis has been administered or will be administered within the subsequent day. Risk factors for candidemia and IC include (but are not limited to):

- Immunosuppression without frank neutropenia
- Central venous catheter
- Recent abdominal surgery
- Pancreatitis
- End stage renal disease
- Current daily administration of total parenteral nutrition
- Systemic inflammatory response syndrome while on broad spectrum antibiotics

Sites may choose to perform a sponsor-approved rapid IVD in potential subjects without the listed risk factors for candidemia and IC, but the potential subject still must have a blood culture drawn and empiric antifungal therapy administered. A call to the Medical Monitor is recommended for any questions about risk factors for candidemia and the appropriate subjects on which to perform a rapid IVD for *Candida* spp.

7.1.2 Systemic Signs of Candidemia and Invasive Candidiasis

It is a requirement that at least 1 systemic sign attributable to candidemia and/or IC be present at Screening for the subject to be eligible for enrollment. The Screening period for assessing systemic signs for inclusion in the study may include the 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 IVD, through enrollment. The possible signs of infection that might be

attributable to candidemia and/or IC at baseline include fever, hypothermia, hypotension, tachycardia, and tachypnea.

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

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

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

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

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

Tachypnea: Respiratory rate >20 breaths per minute

7.2 SUBJECT EXCLUSION CRITERIA

Subjects must NOT meet any of the following exclusion criteria to be enrolled:

1. Any of the following forms of IC:
   a. Septic arthritis in a prosthetic joint (septic arthritis in a native joint is allowed)
   b. Osteomyelitis
   c. Endocarditis or myocarditis
   d. Meningitis, endophthalmitis, or any central nervous system infection
2. Neutropenia (absolute neutrophil count ≤500/µL) at Screening or anticipated neutropenia during the study
3. Alanine aminotransferase or aspartate aminotransferase levels >10-fold the upper limit of normal
4. Severe hepatic impairment in subjects with a history of chronic cirrhosis (Child-Pugh score >9)
5. Received systemic treatment with an antifungal agent at approved doses for treatment of candidemia or IC for >48 hours (for example, >2 doses of a once daily antifungal agent or >4 doses of a twice daily antifungal agent) in the last 96 hours before randomization
   a. Exception: Receipt of antifungal therapy to which any *Candida* spp. isolated at Screening in qualifying cultures is not susceptible (Appendix 1)
6. Pregnant females
7. Lactating females who are nursing

8. Known hypersensitivity to CD101 IV, caspofungin, any echinocandin, or to any of their excipients

9. Previous participation in this or any previous CD101 study

10. Recent use of an investigational medicinal product within 28 days of the first dose of study drug or presence of an investigational device at the time of Screening

11. The PI considers that the subject should not participate in the study

12. Presence of an indwelling vascular catheter or device that cannot be removed and is likely to be the source of candidemia

7.3 REQUALIFICATION FOR ENTRY

Subjects not fulfilling the entry criteria and not randomized may be rescreened for participation if their eligibility characteristics have changed.

7.4 SUBJECT WITHDRAWAL CRITERIA

7.4.1 Withdrawal from Study Protocol

Subjects on study drug who wish to withdraw completely from this clinical study should be encouraged to complete the assessments at EOT. However, subjects may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the subject is otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely and this information should be recorded on the appropriate page(s) of the electronic case report form (eCRF). Subjects may be withdrawn from the study for any of the following reasons:

- Subject unable or unwilling to continue
- Subject elects to withdraw informed consent
- AE (whether or not related to study drug) that precludes further participation in the study in the judgment of the PI and/or Sponsor
- Protocol non-compliance
- Subject lost to follow up
- The PI considers that it is in the subject's best interest not to continue participation in the study

Subjects withdrawn from the study need not participate in the FU visit.

Following enrollment, subjects diagnosed with IC involving 1 or more organ systems and normally excluded from study participation (Exclusion Criterion #1, Section 7.2) do not need to exit the study. Documentation of the disease should be placed in the eCRF along with any further interventions related to the disease.

7.4.2 Early Discontinuation from Study Drug Administration

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), EOT assessments should be performed on the day of discontinuation. The reason for premature discontinuation of study drug administration should be recorded on the appropriate page(s) of the eCRF. Reasons for withdrawal from study drug may include, but are not limited to:

- Cultures negative for *Candida* spp.
    - Blood culture is positive for yeast at enrollment, but the final local blood culture results conclude the yeast is not *Candida* spp.
    - Subject is enrolled based on a rapid IVD test positive for *Candida* spp., but final local blood culture results from Screening or tissue/fluid culture results from a normally sterile site are negative for *Candida* spp.
- Safety
    - Subject unable or unwilling to continue or informed consent withdrawn
    - Occurrence of an AE that, in the opinion of the Investigator, warrants the subject's permanent discontinuation from study drug therapy. This includes development of a clinically significant laboratory abnormality that requires discontinuation from study drug (IV and IV/oral) therapy. In the event of discontinuation from study drug therapy due to the occurrence of an AE, the study site should notify the Medical Monitor as soon as possible
    - Suspected or confirmed pregnancy or nursing during the study drug administration period.
- Invasive Candidiasis

  Echinocandins are not appropriate therapy for *Candida* infections of the eye or central nervous system due to low drug distribution to these sites. In the event that a subject is diagnosed with endophthalmitis or chorioretinitis or a central nervous system infection with *Candida* species, study drug should be stopped and appropriate therapy should be started based on local guidelines (Pappas et al., 2016; Cornely et al., 2012).

Study drug may be continued in the event of diagnosis of other forms of IC listed in the exclusion criteria if the involvement of other organ systems was thought to be present at the time of enrollment and the diagnosis was delayed. If, on the other hand, the spread of *Candida* infection to other organ systems was thought to have occurred following enrollment and initiation of study drug, then the investigator should consider a change of therapy due to insufficient therapeutic effect of study drug. In all cases of other forms of IC, the investigator should consult local guidelines for the most appropriate management of disease and whether or not additional antifungal therapy may be warranted either during study drug administration or following completion of study drug therapy.

- Insufficient therapeutic effect

  An insufficient therapeutic effect may be determined prior to the planned EOT visit. This determination will require an assessment of clinical status including the synthesis of symptoms and signs data (both local and systemic) and available laboratory data. Subjects who are deemed to have an insufficient therapeutic effect should be discontinued from study drug therapy.

  If a subject has daily blood cultures positive for *Candida* spp. through Day 7 despite appropriate study drug administration then this should be considered an insufficient therapeutic effect and study drug should be discontinued and salvage therapy initiated. The subject should remain in the study through the FU visit to complete safety assessments and assess for mortality.

  Seven days is the maximum number of daily positive blood cultures allowed prior to a change in antifungal therapy. The investigator may determine that there is an insufficient therapeutic response prior to Day 7.

- Investigator discretion

  - Resistant Pathogen(s): In the event that an organism resistant to ≥1 of the potential study drugs is isolated, the Investigator will determine whether the subject remains on study drug therapy. The Investigator may decide to continue study drug therapy if, in the Investigator's opinion, there is clear and continuing clinical improvement while on therapy.

  - The Investigator may decide to prematurely discontinue study drug therapy and to initiate an alternative and appropriate therapy if, in the Investigator's opinion, the subject is not benefiting from study drug.

NOTE: The Medical Monitor should be contacted to discuss whether to continue or prematurely discontinue a subject on the study drug in the event that the subject requires systemic concomitant antifungal therapy.

In the event that salvage therapy is required due to either insufficient therapeutic effect or Investigator discretion, the Investigator should note that since the subject has failed echinocandin therapy, other echinocandins may not be the best choice for salvage therapy. If the subject is switched to oral stepdown therapy prior to study drug failure, then the Investigator should consider that subjects in the caspofungin arm will also have been taking fluconazole. In both circumstances, the Investigator should refer to the IDSA (Pappas et al., 2016) or ESCMID (Ullmann et al., 2012; Cornely et al., 2012) guidelines for treatment failure in candidemia, and will need to determine whether or not breaking the blind is necessary to make an informed choice of future antifungal therapies.

7.5 REPLACEMENT OF SUBJECTS

Randomized subjects who are withdrawn will not be replaced.

7.6 STUDY TERMINATION BY SPONSOR AND TERMINATION CRITERIA

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 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
- IRB/IEC decision to terminate or suspend approval for the investigation or the Investigator
- Investigator request to withdraw from participation
- Subject enrollment is unsatisfactory

8.0 STUDY DRUGS

In Part A, subjects were randomized in a 1:1:1 ratio to receive CD101 IV treatment Group 1, CD101 IV treatment Group 2, or IV caspofungin. In Part B, subjects will be randomized in a 2:1 ratio to receive CD101 IV treatment Group 2 or IV caspofungin. (Note: Subjects enrolled under Amendment 5 and assigned to CD101 IV receive Group 1 treatment and subjects enrolled under Amendment 6 and assigned to CD101 IV treatment receive Group 2 treatment. Subjects enroll under the current, approved amendment at the site at the time of randomization; subjects enrolled to Amendment 5 continue study participation on the same amendment regardless of subsequent approval of Amendment 6.) Oral step-down therapy is allowed in all treatment groups in Part A and Part B; oral placebo in the CD101 IV groups and oral fluconazole in the caspofungin group. The total IV plus oral treatment duration will be ≥14 days and up to a maximum of 28 days (Table 6).

In order to stop study drug for successful completion of therapy prior to 21 days, the following criteria must be met:

- ≥14 days of study drug
- The subject's clinical status is considered stable based on Investigator assessment
- All systemic signs attributable to candidemia and/or IC that were present at baseline have resolved
- For subjects with IC, there is documented or presumed eradication of IC
- If a blood culture is positive at Screening, 2 post-baseline blood cultures collected ≥12 hours apart are negative for *Candida* spp. without an intervening positive culture, and there are no subsequent blood cultures following the first qualifying negative culture that are positive for *Candida* spp.

Once these criteria are met, the total duration of study drug is at the discretion of the PI.

Subjects randomized to the CD101 IV treatment Group 1 will receive 1 dose of CD101 IV (400 mg) nominally over 60 (±10) minutes on Day 1 and Day 8 (Table 6). Subjects in Group 1 who require >14 days of IV therapy will receive an optional third dose of CD101 IV (400 mg) on Day 15. Subjects in Group 1 with IC (with or without candidemia) who require >21 days of IV therapy will receive an optional fourth dose of CD101 IV (400 mg) on Day 22. 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) nominally over 60 (±10) minutes on Day 1 and 200 mg on Day 8 (Table 6). Subjects in Group 2 who require >14 days of IV therapy will receive an optional third dose of CD101 IV (200 mg) on Day 15. Subjects in Group 2 with IC (with or without candidemia) who require >21 days of IV therapy will receive an optional fourth dose of CD101 IV (200 mg) on Day 22. Subjects in Group 1 will receive IV placebo on other study days in order to maintain the blind.

For both CD101 IV groups, the time may be increased as needed up to 180 (±10) minutes to manage symptoms of infusion reaction consistent with management of echinocandin class infusion reactions, whereby decreasing the rate of infusion often alleviates symptoms. (Note: infusion must be completed within the 4-hour stability limit, which starts at the time of reconstitution of rezafungin for injection lyophilized powder in the single-use vial.)

Intravenous study drug is administered 24 (±2) hours after study drug was administered on the previous day.

Subjects may receive oral step-down therapy after ≥3 days of IV therapy. 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 (±1 day), Day 15 (±1 day) for subjects who require >14 days of therapy, and Day 22 (±1 day) for subjects with IC (with or without candidemia) who require >21 days of therapy.

Subjects randomized to the caspofungin group will receive IV caspofungin (a single 70 mg loading dose on Day 1 followed by 50 mg once daily over 60 (±10) minutes) for ≥3 days and up to a maximum of 21 days for subjects with candidemia only and up to a maximum of 28 days for subjects with IC (with or without candidemia) (Table 6). Intravenous study drug is administered 24 (±2) hours after study drug was administered on the previous day.

Step-down therapy in the caspofungin treatment group will be oral fluconazole (a loading dose of 800 mg [4 capsules] 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 (±1 day), Day 15 (±1 day) for subjects who require >14 days of therapy, and Day 22 (±1 day) for subjects with IC (with or without candidemia) who require >21 days of therapy.

The total IV plus oral treatment duration will be ≥14 days and up to 28 days.

Table 8: Study Treatments

Study Day	CD101 IV Group 1 Group 2	Caspofungin Group
1	IV CD101 (400 mg)	IV caspofungin (a single 70 mg loading dose)
2-3 [a]	IV placebo	IV caspofungin (50 mg/day)
4-7	IV placebo if not stepped down **OR** oral step-down therapy (placebo) if already stepped down	IV caspofungin (50 mg/day) if not stepped down **OR** oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down
8 [b]	IV CD101 (400 mg Group 1, 200 mg Group 2) if not stepped down **OR** IV CD101 (400 mg Group 1, 200 mg Group 2) PLUS oral step-down therapy (placebo) if already stepped down	IV caspofungin (50 mg/day) if not stepped down **OR** IV placebo PLUS oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down
9-14 [c]	IV placebo if not stepped down **OR** oral step-down therapy (placebo) if already stepped down	IV caspofungin (50 mg/day) if not stepped down **OR** oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down
15 [b] (if needed)	IV CD101 (400 mg Group 1, 200 mg Group 2) if not stepped down **OR** IV CD101 (optional) [d] (400 mg Group 1, 200 mg Group 2) PLUS oral step-down therapy (placebo) if already stepped down **OR** No treatment	IV caspofungin (50 mg/day) if not stepped down **OR** IV placebo (optional) [d] PLUS oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down **OR** No treatment
16-21 [e] (if needed)	IV placebo if not stepped down **OR** oral step-down therapy (placebo) if already stepped down **OR** No treatment	IV caspofungin (50 mg/day) if not stepped down **OR** oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down **OR** No treatment

Table 8: Study Treatments

Study Day	CD101 IV Group 1 Group 2	Caspofungin Group
22 [b] (if needed, only for subjects with IC)	IV CD101 (400 mg Group 1; 200 mg Group 2) if not stepped down **OR** IV CD101 (optional) [f] (400 mg Group 1; 200 mg Group 2) PLUS oral step-down therapy (placebo) if already stepped down **OR** No treatment	IV caspofungin (50 mg/day) if not stepped down **OR** IV placebo (optional) [f] PLUS oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down **OR** No treatment
23-28 [g,h] (if needed, only for subjects with IC)	IV placebo if not stepped down **OR** oral step-down therapy (placebo) if already stepped down **OR** No treatment	IV caspofungin (50 mg/day) if not stepped down **OR** oral step-down therapy (fluconazole, a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter) if already stepped down **OR** No treatment

IC = invasive candidiasis; IV= intravenous

a. Subjects must receive IV therapy for ≥3 days before switching to oral step-down therapy.
b. The Day 8, Day 14, Day 15, and Day 22 visits have a window of ±1 day if subject already stepped down to oral therapy and discharged from the study site.
c. Total IV plus oral treatment duration must be ≥14 days.
d. Subjects who require >14 days of therapy may receive an optional third dose of IV study drug on Day 15, if needed.
e. Total IV plus oral treatment duration must be ≤21 days for subjects with candidemia only.
f. Subjects with IC (with or without candidemia) who require >21 days of therapy may receive a fourth dose of IV study drug on Day 22, if needed
g. The Day 28 visit has a window of ±2 days if subject already stepped down to oral therapy and discharged from the study site
h. Total IV plus oral treatment duration must be ≤28 days for subjects with IC (with or without candidemia).

8.1 CD101 FOR INJECTION

CD101 for Injection (100 mg) is supplied as a sterile lyophilized powder for reconstitution prior to dilution into infusion bags. The product is limited to investigational use only. Please refer to the current Investigator Brochure for additional information.

8.1.1 Directions for Use

One vial of CD101 for Injection will be reconstituted with 8 mL sterile water for injection (WFI) prior to diluting into infusion bags. Subject infusions must be completed within 4 hours of reconstitution of the lyophilized powder in the vial. Please refer to the Pharmacy Manual for detailed information on study drug preparation.

8.1.2 Drug Storage

Vials of CD101 for Injection and diluted infusion bags should be stored and used per the directions presented in the Pharmacy Manual.

8.2 CASPOFUNGIN

Please refer to the prescribing information provided in the Pharmacy Manual for additional information.

8.3 ORAL STEP-DOWN THERAPY

An oral step-down therapy is allowed in all treatment groups provided the following criteria are met:

- Able to take oral medication
- ≥3 days of IV study drug
- The *Candida* species isolated is susceptible to fluconazole
- The subject's clinical status is considered stable based on Investigator assessment
- If a blood culture is positive at Screening, 2 post-baseline blood cultures drawn ≥12 hours apart are negative for *Candida* spp., without an intervening positive culture, and the first of the 2 cultures was drawn ≥48 hours prior to oral study drug initiation
- No evidence of moderate or severe hepatic insufficiency (alanine aminotransferase or aspartate aminotransferase >3× the upper limit of normal)
- No history of hypersensitivity or any other contraindications to the use of fluconazole and in the Investigator's opinion, the subject can tolerate oral fluconazole therapy (refer to current fluconazole Prescribing Information)

The principal contraindications to fluconazole use are hepatic injury, anaphylaxis (hypersensitivity), drug-induced exfoliative skin disorders, and pregnancy. Medical staff should also beware of the potential of QT prolongation, especially when administered to subjects with known heart disease or with other drugs that cause this same side effect. Fluconazole should be administered with caution to subjects with potentially proarrhythmic conditions. The potential for drug-drug interactions with fluconazole is summarized in Section 8.7.

It is the responsibility of the PI to carefully read the list of requirements for the switch to oral fluconazole listed above, as well as the list of contraindications, warning and precautions, and drug-drug interactions in the US Package Insert or European Union Summary of Product Characteristics that are summarized here and in Section 8.3, in order to determine whether or not the subject may be eligible and safely started on oral fluconazole stepdown therapy.

For subjects with creatinine clearance >50 mL/min (Appendix 2), 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 treatment group and oral placebo

(4 capsules on the first day followed by 2 capsules/day thereafter) in the CD101 treatment groups.

To maintain the blind, oral study drug pills must never be crushed.

The total IV plus oral treatment duration will be ≥14 days and up to 28 days.

8.4 DOSE ADJUSTMENT

8.4.1 CD101 IV

Dosage adjustments are not allowed in the CD101 IV groups.

8.4.2 Caspofungin

Subjects in the caspofungin group with moderate hepatic impairment (Child-Pugh score of 7-9 with a history of chronic cirrhosis) 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 based on potential drug-drug interactions may be considered at the Investigator's discretion.

8.4.3 Fluconazole

Subjects in the caspofungin group with renal impairment who are switched to oral stepdown therapy may receive reduced doses of fluconazole.

For subjects with creatinine clearance ≤50 mL/min (Appendix 2), 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 mg [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.

8.5 COMPLIANCE

Treatment compliance for IV study drugs will be documented in the eCRF by recording the date, start time, stop time, and whether the dose of study drug was completely infused. For oral fluconazole (caspofungin group) or oral placebo (CD101 groups), treatment compliance will be documented by recording start date, end date, and pill counts.

8.6 BREAKING THE BLIND

This study is a double-blind design. The PI, study personnel, and subjects will not make any effort to determine which study drug therapy is being received. Unblinded pharmacy personnel or unblinded study personnel (ie, PK analyst in Part A only and statistician in Part A and Part B) may be utilized in this study.

The data for the 40 to 60 subjects in the mITT population involved in the interim analysis will be locked prior to the unblinded interim analysis, and the database for Part A will be locked prior to the Part A analysis. The data from Part A will be unblinded after the database is locked for Part A, but likely prior to completion of Part B, and interim summary results and full Part A summary results will be reported when available. Individual subjects will not be unblinded for either the interim analysis or the Part A analysis. Thus, no by-subject data will be made available to the Sponsor until after database lock for Part B. (Note: An addendum to the Unblinding Plan for Part A allowed for unblinded safety review of adverse events of interest identified during blinded safety review; the addendum allowed for no more than 5% of subjects to be unblinded.) The data from Part B will only be unblinded and analyzed after database lock for Part B at completion of the study.

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.

8.7 PREVIOUS AND CONCOMITANT MEDICATIONS AND SUBSTANCES

All systemic antifungal therapy administered within 4 weeks and all non-antifungal therapy administered within 1 week prior to randomization in will be documented in the CRF. Subjects who received systemic treatment with an antifungal agent at approved doses for treatment of candidemia for >48 hours before randomization will be excluded from the study.

Concomitant systemic antifungal agents, other than those listed as part of study drug therapy, are not permitted and their use, for any reason other than the subject being considered a treatment failure, must be discussed with the Medical Monitor before administration.

Use of concomitant cyclosporine should be limited to subjects for whom potential benefit outweighs potential risk of drug-drug interactions with caspofungin. All other concomitant medications necessary for the health and wellbeing of the subject are permitted.

Fluconazole is contraindicated in subjects with hypersensitivity to fluconazole and should be used with caution in subjects with hypersensitivity to other azoles. Fluconazole should not be co-administered with terfenadine, cisapride, astemizole, erythromycin, pimozide, quinidine, or any other drug metabolized via the cytochrome P450 (CYP)3A4 enzymatic pathway and may cause prolongation of the QT interval. Fluconazole should be administered with caution in patients with evidence of hepatic toxicity or liver dysfunction. Patients who have or develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe hepatic injury. Hepatic toxicity secondary to fluconazole is usually reversible.
Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor and thus all subjects on fluconazole who are concomitantly taking drugs that are also metabolized through these pathways should be monitored closely. Please refer to the US Package Insert or the European Union Summary of Product Characteristics for fluconazole for more information about the contraindications, warnings and precautions, and likely drug-drug interactions.

8.8 ACCOUNTABILITY PROCEDURES

The pharmacy or study personnel are responsible for ensuring that a current record of CD101 IV, caspofungin, fluconazole, and over encapsulated placebo inventory and accountability is maintained.

A Pharmacy Monitor will be responsible for checking drug accountability at the site. Inventory records must be readily available for inspection by regulatory authorities at any time. Each shipment of study drug will contain an acknowledgment of receipt section for site signature. Upon receipt of study drug, the pharmacy or study personnel will visually inspect the shipment and verify the number and condition of vials or capsules received. Refer to the Pharmacy Manual for additional information.

8.9 STUDY DRUG HANDLING AND DISPOSAL

Unless expressly disallowed by institution rules, used and unused vials of study drug (including CD101 and caspofungin) will be retained at the study site until study drug accountability has been performed by the Pharmacy Monitor. Upon completion of the study, termination of the study, or upon written authorization from the Sponsor, all retained unused and partially used study drug will be centrally destroyed. All records of disposal by a centralized destruction site will be maintained by the Sponsor.

9.0 STUDY PROCEDURES

Study procedures should be completed within the windows provided in the Schedule of Assessments and Procedures located in Table 2. However, if a subject is unable to attend

a visit within the specified windows, the PI (or qualified designee) should discuss appropriate scheduling with the Medical Monitor (or appropriate designee).

For Part A of this study, the blood sample for CD101 PK is a critical parameter and any postdose time point for blood sample needs to be collected within the specified window. All other procedures should be completed as close to the prescribed/scheduled time as possible. Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.1 SCREENING

Unless otherwise indicated, Screening assessments should be performed within 48 hours of randomization.

- Obtain signed informed consent prior to initiating any study-related assessments or procedures. Consent from a legally acceptable representative may be obtained if the subject is unable to consent for themselves

- Obtain a complete 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 (Pappas et al., 2016) and ESCMID (Ullmann et al., 2012; Cornely et al., 2012) guidelines.

- Record all systemic antifungal therapy administered within 4 weeks and all non-antifungal therapy (including other anti-infective therapy) administered within 1 week prior to randomization

- Clinical assessments

    - Conduct complete physical examination, including height and weight

    - Measure vital signs (temperature and the method used [oral, rectal, temporal, tympanic, or core], heart rate, blood pressure, and respiratory rate)

        – Record the 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

    - Perform 12-lead ECG before subject randomization

- Perform retinal examination for *Candida* eye infection by Day 7 only on subjects with candidemia by blood culture. This assessment is the standard of care for subjects with candidemia, and ideally would be performed by an ophthalmologist, if available.

- Assess presence or absence of systemic signs and symptoms and determine which are attributable to candidemia and/or IC. 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 sponsor-approved IVD, through enrollment.

- Laboratory assessments
  - Prior to the start of the Screening period, consider use of a Sponsor-approved rapid IVD for *Candida* spp. while drawing blood culture if the potential subject has known risk factors for candidemia and will be administered empiric antifungal therapy (Section 7.1.1)
    - All sites using rapid IVDs must label samples with subject identification number and date/time of blood draw and follow all necessary timing and procedures required for proper testing and interpretation of results
    - For commercial IVDs, sample handling and storage procedures should follow the package insert
  - A culture must be obtained as part of the standard of care for inclusion in the study. Established mycological diagnosis of candidemia sufficient for inclusion in the study will be established by either ≥1 blood culture positive for yeast or *Candida* OR 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 from a sample taken ≤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.
    - If the subject is suspected of having IC, then all reasonable attempts to obtain a culture from the suspected site of infection should be made as early as possible before empiric therapy.
    - Perform identification and susceptibility testing at local laboratory for *Candida* for any positive blood culture or any positive culture from normally sterile site
    - Record the species and susceptibilities for all bacteria isolated within 1 week prior to randomization from blood or any other normally sterile site

  - Send all fungal isolates cultured from blood or normally sterile tissue/fluid to the Central Laboratory

- Perform urine pregnancy test on female subjects of childbearing potential. Do not perform on women who are ≥2 years postmenopausal or surgically sterile.

- Obtain blood samples for hematology tests, coagulation laboratory tests (PT/INR and either PTT or aPTT), and serum chemistry tests (Appendix 3)

- Obtain a urine sample for urinalysis (UA) and microscopy (Appendix 3)

- Calculate Child-Pugh score only if the subject has a history of chronic cirrhosis (Appendix 4)
- Record modified Acute Physiology and Chronic Health Evaluation (APACHE) II parameters (Appendix 5) with Glasgow Coma Score (Appendix 6); note that the APACHE II score can be calculated after enrollment, but should use the vital signs and laboratory results from the Screening visit.

- If radiologic test performed, record radiologic test type with Findings and Interpretation only if radiologic test provides evidence of IC

- Assess, identify, and record any AEs following signing of the ICF
- Confirm subject qualification by inclusion/exclusion criteria

9.2 DAYS 1, 2, and 3

- Randomize subject just prior to dosing (Day 1 only)

- Administer study drug (Section 8.0 and Study Pharmacy Manual)

  - IV infusion of study drug over 60 (±10) minutes on Days 1, 2, and 3; 24 (±2) hours after study drug was administered on the previous day (for Days 2 and 3 only)

- Clinical assessments
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)

    - Record the 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 each day

  - Perform retinal examination for *Candida* eye infection once by Day 7 only on subjects with candidemia by blood culture. This assessment is the standard of care for subjects with candidemia, and ideally would be performed by an ophthalmologist, if available.

- Laboratory assessments
  - Obtain blood samples for hematology and serum chemistry tests (Day 2 only) (Appendix 3); in general, the laboratory values to be entered into the eCRF will be from the first laboratory samples drawn each day with routine morning laboratory samples
  - Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated
    - Obtain blood for culture daily (preferred) or every other day until 2 blood cultures drawn ≥12 hours apart are negative, without an intervening positive culture
    - 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
    - Perform identification and susceptibility testing for *Candida* for any positive culture requiring a change of antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)
    - All fungal isolates cultured from blood and normally sterile tissue/fluid 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
  - In Part A only, obtain blood samples for PK analysis 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) and Day 2 (random draw with date of sample same as Day 2 date of dose, with safety labs if possible)
- Record all concomitant medications including prescription, over the counter (OTC), and herbal medications
- 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
- Assess, identify, and record any AEs

9.3 DAYS 4 to 7

- Administer study drug (Section 8.0 and Study Pharmacy Manual)
  - IV infusion of study drug over 60 (±10) minutes, 24 (±2) hours after study drug was administered on the previous day

OR

- Oral step-down therapy if stepped down (Days 5, 6, and 7)
  - If on oral step-down therapy and discharged from study site, subject must mark date/time and number of capsules taken each day in Daily Subject Diary

- Clinical assessments
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate) only if receiving IV study drug
    - If hospitalized, record the 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.
    - Vital signs are required on Days 4 and 5 (temperature, heart rate, blood pressure, respiratory rate)
    - 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 to 7 if the subject is seen for clinical assessment or IV study drug infusion
  - Perform retinal examination for *Candida* eye infection once by Day 7 only on subjects with candidemia by blood culture. This assessment is the standard of care for subjects with candidemia, and ideally would be performed by an ophthalmologist, if available.
  - Assess presence or absence of systemic signs and determine which are attributable to candidemia and/or IC (Day 5 only)

- Laboratory assessments
  - Obtain blood samples for hematology and serum chemistry tests (Day 4 only) (Appendix 3); in general, the laboratory values to be entered into the eCRF will be from the first laboratory samples drawn each day with routine morning laboratory samples
  - Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated
    - Obtain blood for culture daily (preferred) or every other day until 2 blood cultures drawn ≥12 hours apart are negative, without an intervening positive culture
    - 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

  - Perform identification and susceptibility testing for *Candida* for any positive culture requiring a change of antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)

  - All fungal isolates cultured from blood and normally sterile tissue/fluid 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

- In Part A only, obtain blood samples for PK analysis on Day 4 (random draw with date of sample same as Day 4 date of dose, with safety labs if possible)

- Record all concomitant medications including prescription, OTC, and herbal medications
- 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

- Assess, identify, and record any AEs

9.4 DAY 8 (±1 day if already switched to oral step-down therapy and discharged from the study site)

- Administer study drug (Section 8.0 and Study Pharmacy Manual)
  - IV infusion of study drug over 60 (±10) minutes, 24 (±2) hours after study drug was administered on the previous day, if not stepped down

    OR

  - IV infusion of study drug over 60 (±10) minutes, PLUS oral step-down therapy if already stepped down

    — Note that oral study drug must be taken every day if the subject has stepped down to oral therapy.

    — If on oral step-down therapy and discharged from study site, subject must mark date/time and number of capsules taken each day in Daily Subject Diary

- Clinical assessments
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)

  - If hospitalized, record the 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

- Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study

- Laboratory assessments
  - Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated

    - Obtain blood for culture if demonstrating mycological eradication (if not already done) or if clinically indicated

    - 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

    - Perform identification and susceptibility testing for *Candida* for any positive culture requiring a change of antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)

    - All fungal isolates cultured from blood and normally sterile tissue/fluid 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

  - Obtain blood samples for hematology/serum chemistry tests (Appendix 3); in general, the laboratory values to be entered into the eCRF will be from the first laboratory samples drawn each day with routine morning laboratory samples

  - Obtain blood samples for PK analysis (predose only; Part A only)

- Record all concomitant medications including prescription, OTC, and herbal medications

- 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

- Assess, identify, and record any AEs

9.5 DAYS 9 to 13

- Administer study drug (Section 8.0 and Study Pharmacy Manual)
    - IV infusion of study drug over 60 (±10) minutes, 24 (±2) hours after study drug was administered on the previous day, if not stepped down

      OR

    - Oral step-down therapy if already stepped down
        - If on oral step-down therapy and discharged from study site, subject must mark date/time and number of capsules taken each day in Daily Subject Diary
- Clinical assessments
    - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate) only if receiving IV study drug
        - If hospitalized, record the 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
        - For subjects discharged from the hospital and in the community, vital signs (temperature, heart rate, blood pressure, respiratory rate) are only performed on Days 9 to 13 if the subject is seen for clinical assessment or IV study drug infusion
- Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study
- Laboratory assessments
    - Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated
        - Obtain blood for culture if demonstrating mycological eradication (if not already done) or if clinically indicated
        - 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

  - Perform identification and susceptibility testing for *Candida* for any positive culture requiring a change of antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)

  - All fungal isolates cultured from blood and normally sterile tissue/fluid 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

- Record all concomitant medications including prescription, OTC, and herbal medications
- 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
- Assess, identify, and record any AEs if subject has a study visit

9.6 DAY 14 (±1 day if already switched to oral step-down therapy and discharged from the study site)

- Administer study drug (Section 8.0 and Study Pharmacy Manual)
  - IV infusion of study drug over 60 (±10) minutes, 24 (±2) hours after study drug was administered on the previous day, if not stepped down

    OR

  - Oral step-down therapy if already stepped down

    — If on oral step-down therapy and discharged from study site, subject must mark date/time and number of capsules taken each day in Daily Subject Diary

- Clinical assessments
  - Conduct complete physical examination, including weight
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)

    – If hospitalized, record the 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

    - Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study

  - Assess presence or absence of systemic signs and symptoms and determine which are attributable to candidemia and/or IC

- Laboratory assessments
  - Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated
    - Review previous blood cultures drawn and obtain blood for culture if there is no evidence of mycological eradication (ie, 2 negative blood cultures drawn ≥12 hours apart without intervening positive blood cultures)
    - 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
    - Perform identification and susceptibility testing for *Candida* for any positive blood culture requiring a change in antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)
    - All fungal isolates cultured from blood and normally sterile tissue/fluid 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
  - Obtain blood samples for hematology/serum chemistry tests (Appendix 3); in general, the laboratory values to be entered into the eCRF will be from the first laboratory samples drawn each day with routine morning laboratory samples
  - In Part A only, 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

- PI to assess clinical response. Refer to Table 11 for definitions of clinical cure and failure
- Record all concomitant medications including prescription, OTC, and herbal medications
- 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

- Assess, identify, and record any AEs

9.7 DAY 15 (±1 day if already switched to oral step-down therapy and discharged from the study site)

- Administer study drug (Section 8.0 and Study Pharmacy Manual) if further therapy is clinically indicated
    - IV infusion of study drug over 60 (±10) minutes, 24 (±2) hours after study drug was administered on the previous day, if not stepped down and if needed

      OR

    - IV infusion of study drug over 60 (±10) minutes, PLUS oral step-down therapy, if already stepped down and if needed
        - Note that oral study drug must be taken every day if the subject has stepped down to oral therapy.
        - If on oral step-down therapy and discharged from study site, subject must mark date/time and number of capsules taken each day in Daily Subject Diary

      OR

    - No treatment
- Clinical assessments
    - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate) only if receiving IV study drug
        - If hospitalized, record the 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.
        - For subjects discharged from the hospital and in the community, vital signs (temperature, heart rate, blood pressure, respiratory rate) are only performed on Day 15 if the subject is seen for clinical assessment or IV study drug infusion
- Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study
- Laboratory assessments
    - Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated

- Obtain blood for culture if demonstrating mycological eradication (if not already done) or if clinically indicated
- 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
- Perform identification and susceptibility testing for *Candida* for any positive culture requiring a change in antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)
- All fungal isolates cultured from blood and normally sterile tissue/fluid 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

○ In Part A only, obtain blood samples for PK analysis (predose only); 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

- Record all concomitant medications including prescription, OTC, and herbal medications
- 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
- Assess, identify, and record any AEs

9.8 DAYS 16 to 21

- Administer study drug (Section 8.0 and Study Pharmacy Manual)

○ IV infusion of study drug over 60 (±10) minutes, 24 (±2) hours after study drug was administered on the previous day, if not stepped down and if needed

OR

○ Oral step-down therapy, if already stepped down and if needed

— If on oral step-down therapy and discharged from study site, subject must mark date/time and number of capsules taken each day in Daily Subject Diary

OR

○ No treatment

- Clinical assessments
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate) only if receiving IV study drug
    - If hospitalized, record the 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.
    - For subjects discharged from the hospital and in the community, vital signs (temperature, heart rate, blood pressure, respiratory rate) are only performed on Days 16 to 21 if the subject is seen for clinical assessment or IV study drug infusion
  - Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study
- Laboratory assessments
  - Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated
    - Obtain blood for culture if demonstrating mycological eradication (if not already done) or if clinically indicated
    - 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
    - Perform identification and susceptibility testing for *Candida* for any positive culture requiring a change in antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)
    - All fungal isolates cultured from blood and normally sterile tissue/fluid 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
- Record all concomitant medications including prescription, OTC, and herbal medications
- 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
- Assess, identify, and record any AEs

9.9 DAY 22 (±1 day if already switched to oral step-down therapy and discharged from the study site) - Only Subjects With Invasive Candidiasis

- Administer study drug (Section 8.0 and Study Pharmacy Manual) if further therapy is clinically indicated only for subjects with IC (with or without candidemia)
    - IV infusion of study drug over 60 (±10) minutes, 24 (±2) hours after study drug was administered on the previous day, if not stepped down and if needed

      OR

    - IV infusion of study drug over 60 (±10) minutes, PLUS oral step-down therapy, if already stepped down and if needed
        - Note that oral study drug must be taken every day if the subject has stepped down to oral therapy.
        - If on oral step-down therapy and discharged from study site, subject must mark date/time and number of capsules taken each day in Daily Subject Diary

      OR

    - No treatment
- Clinical assessments
    - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate) only if receiving IV study drug
        - If hospitalized, record the 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.
        - For subjects discharged from the hospital and in the community, vital signs (temperature, heart rate, blood pressure, respiratory rate) are only performed on Day 22 if the subject is seen for clinical assessment or IV study drug infusion
    - Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study
- Laboratory assessments
    - Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated

  - Obtain blood for culture if demonstrating mycological eradication (if not already done) or if clinically indicated

  - 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

  - Perform identification and susceptibility testing for *Candida* for any positive culture requiring a change in antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)

  - All fungal isolates cultured from blood and normally sterile tissue/fluid 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

- Record all concomitant medications including prescription, OTC, and herbal medications

- 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

- Assess, identify, and record any AEs

9.10 DAYS 23 to 27 - Only Subjects with Invasive Candidiasis

- Administer study drug (Section 8.0 and Study Pharmacy Manual) only for subjects with IC (with or without candidemia)

  - IV infusion of study drug over 60 (±10) minutes, 24 (±2) hours after study drug was administered on the previous day, if not stepped down and if needed

    OR

  - Oral step-down therapy, if already stepped down and if needed

    — If on oral step-down therapy and discharged from study site, subject must mark date/time and number of capsules taken each day in Daily Subject Diary

    OR

  - No treatment

- Clinical assessments
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate) only if receiving IV study drug

  - If hospitalized, record the 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.

  - For subjects discharged from the hospital and in the community, vital signs (temperature, heart rate, blood pressure, respiratory rate) are only performed if the subject is seen for clinical assessment or IV study drug infusion

- Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study

- Laboratory assessments
  - Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated

    - Obtain blood for culture if demonstrating mycological eradication (if not already done) or if clinically indicated

    - 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

    - Perform identification and susceptibility testing for *Candida* for any positive culture requiring a change in antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)

    - All fungal isolates cultured from blood and normally sterile tissue/fluid 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

- Record all concomitant medications including prescription, OTC, and herbal medications
- 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

- Assess, identify, and record any AEs

9.11 DAY 28 (±2 days if already switched to oral step-down therapy and discharged from the study site) - Only Subjects with Invasive Candidiasis

Perform Day 28 (±2 days) assessments and procedures 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.

- Administer study drug (Section 8.0 and Study Pharmacy Manual) only to subjects with IC (with or without candidemia)
    - IV infusion of study drug over 60 (±10) minutes, 24 (±2) hours after study drug was administered on the previous day, if not stepped down and if needed

      OR
    - Oral step-down therapy, if already stepped down and if needed
        - If on oral step-down therapy and discharged from study site, subject must mark date/time and number of capsules taken each day in Daily Subject Diary

      OR
    - No treatment
- Clinical assessments
    - Conduct complete physical examination, including weight
    - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)
        - If hospitalized, record the 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
    - Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study
    - Assess presence or absence of systemic signs and symptoms and determine which are attributable to candidemia and/or IC
- Laboratory assessments

- Obtain culture from blood and/or normally sterile tissue/fluid if demonstrating mycological eradication or if clinically indicated
  - Review previous blood cultures drawn and obtain blood for culture if there is no evidence of mycological eradication (ie, 2 negative blood cultures drawn ≥12 hours apart without intervening positive blood cultures)
  - 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
  - Perform identification and susceptibility testing for *Candida* for any positive culture requiring a change in antifungal therapy (ie, identification and susceptibility testing not required for *Candida* isolates cultured from specimens obtained without a required change in antifungal therapy)
  - All fungal isolates cultured from blood and normally sterile tissue/fluid 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

- PI to assess clinical response. Refer to Table 11 for definitions of clinical cure and failure
- Record all concomitant medications including prescription, OTC, and herbal medications
- 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
- Assess, identify, and record any AEs

9.12 END OF THERAPY (+2 days allowed after last dose of study drug)

Criteria for Completion of Study Drug Therapy (Section 8.0)**:**

In order to stop study drug for successful completion of therapy prior to 21 days (or prior to 28 days for subjects with IC), the following criteria must be met:

- ≥14 days of study drug
- The subject's clinical status is considered stable based on Investigator assessment
- All systemic signs attributable to candidemia and/or IC that were present at baseline have resolved
- For subjects with IC, there is documented or presumed eradication of IC

- If a blood culture is positive at Screening, 2 post-baseline blood cultures collected ≥12 hours apart are negative for *Candida* spp. without an intervening positive culture, and there are no subsequent blood cultures following the first qualifying negative culture that are positive for *Candida* spp.

Once these criteria are met, the total duration of study drug is at the discretion of the PI.

- Clinical assessments
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)
    - If hospitalized, record the 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
  - Perform 12-lead ECG
  - Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study
- Laboratory assessments
  - Obtain culture from blood and/or normally sterile tissue/fluid if clinically indicated.
    - All fungal isolates cultured from blood and normally sterile tissue/fluid 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
  - Obtain blood samples for hematology/serum chemistry tests (Appendix 3); in general, the laboratory values to be entered into the eCRF will be from the first laboratory samples drawn each day with routine morning laboratory samples
  - Obtain a urine sample for UA and microscopy (Appendix 3)
- Record all concomitant medications including prescription, OTC, and herbal medications
- 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

- Assess, identify, and record any AEs

9.13 FOLLOW-UP VISIT (DAYS 45-52 for Subjects with Candidemia Only or Days 52-59 for Subjects with Invasive Candidiasis, With or Without Candidemia)

- Clinical assessments
  - Conduct complete physical examination, including weight
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)
    - If hospitalized, record the 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
  - Repeat retinal examination for *Candida* eye infection only on subjects with candidemia by blood culture and only if the subject develops visual signs or symptoms of *Candida* eye infection during the course of the study
  - Assess presence or absence of systemic signs and symptoms of infection and determine which are attributable to candidemia and/or IC
- Laboratory assessments
  - Obtain blood samples for hematology and serum chemistry tests Appendix 3); in general, the laboratory values to be entered into the eCRF will be from the first laboratory samples drawn each day with routine morning laboratory samples
  - Obtain culture from blood, and if feasible from normally sterile tissue/fluid
    - Obtain culture from blood
    - 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 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
  - Perform urine pregnancy test on female subjects of childbearing potential. Do not perform on women who are ≥2 years postmenopausal or surgically sterile.

- PI to assess clinical response. Refer to Table 11 for definitions of clinical cure and failure
- Record all concomitant medications including prescription, OTC, and herbal medications
- 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
- Assess, identify, and record any AEs

10.0 ASSESSMENT OF SAFETY

10.1 SAFETY PARAMETERS

Safety will be assessed from the signing of the ICF at Screening to the FU visit through the evaluation of AEs, vital signs, ECGs, and clinical laboratory data (clinical chemistry panels and hematology and UA evaluations) according to the Schedule of Assessments and Procedures (Table 2) and Appendix 3.

10.2 ADVERSE EVENTS

AEs will be collected for all subjects from informed consent. The Investigator will assess all AEs and SAEs and will record the following information on the appropriate eCRF page:

- Date of onset
- Date of resolution or stabilization
- Severity
- Relationship to study drug
- Action taken with study medication

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory. The Investigator should employ best medical judgment in determining how to manage AEs and SAEs. Any questions regarding AE or SAE management should be directed to the Medical Monitor.

10.3 ADVERSE EVENT REPORTING

The Sponsor has requirements for expedited reporting of SAEs meeting specific criteria to worldwide regulatory authorities. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent.

All SAEs must be reported to the Medical Monitor by phone or email within 24 hours of the investigational site's knowledge of the event.

The study site will also transmit a Serious Adverse Event Report (SAER) to the safety vendor by facsimile or email within 24 hours. Contact details will be provided to all sites. An optional initial report can be made via telephone, but a completed SAER must still be faxed or emailed within 24 hours of the site's knowledge of the event. The Investigational site will be provided with SAER forms wherein the following information is requested.

- Subject identification, Investigator name, and site number
- SAE information: event term, onset date, severity, and causal relationship
- The outcomes attributable to the event (eg, death, a life-threatening AE, inpatient hospitalization, prolongation of existing hospitalization, a persistent or significant disability or incapacity, or other important medical event[s])
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The first and last dates of study drug administration. NOTE: as this is a double-blind study, SAERs should not indicate specific study drug assignments
- Indicate if the study drug was discontinued or the study drug administration schedule modified
- Supplemental information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates

In addition, relevant case report form pages should be appended to communicate relevant study drug and subject outcome information. The SAER should be faxed or emailed within 24 hours with as much of the above information as available at the time. The following minimum information is required for reporting an SAE: subject identification, reporting source, and an event or outcome. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. The Sponsor may contact the investigational site to solicit additional information or follow up on the event.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the subject's eCRF.

10.4 DEFINITIONS

10.4.1 Adverse Event

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, a clinically-significant

abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Events that are related to the disease under study, candidemia, should not be considered or recorded as AEs unless the event fits the definition for an SAE (Section 10.4.4), in which case the SAE form must be submitted for safety reporting in the appropriate timeframe and entered as an AE into the eCRF.

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms, or require medical intervention. However, each laboratory abnormality (eg, clinically significant changes detected on hematology, comprehensive metabolic panel, UA) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to interruption of study drug infusion or discontinuation, must be recorded as an AE, or SAE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments (eg, ECGs) that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE) as described in Section 10.4.1 (or Section 10.4.4).

10.4.2 Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

10.4.3 Life-Threatening Adverse Event or Life-Threatening Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘life threatening’’ if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

10.4.4 Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization for a planned or elective procedure or surgery for a pre-existing condition that has not worsened is not considered a serious adverse event.

10.4.5 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘unexpected’’:

- If it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed, or

- If an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended

- If it is not listed in the Prescribing Information (for marketed products)

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure listed only cerebral vascular accidents.

‘‘Unexpected,’’ as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.5 ADVERSE EVENT CLASSIFICATION

10.5.1 Relationship to Investigational Drug

The Investigator’s assessment of causality must be provided for all AEs (serious and non-serious) (Table 7). An Investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. Clinical failure that qualifies as an AE without evidence of study drug toxicity should be considered unrelated to study drug.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is thought to be unrelated to study drug administration, then an alternative explanation should be provided.

Table 9: Guidelines for Assessing Relationship of Event to Study Drug

Unrelated	There is little or no chance that the Investigational Product caused the AE; other conditions, including concurrent illnesses, progression or expression of the disease state, or a reaction to a concomitant medication best explain the event
Related	The association of the AE with the Investigational Product is unknown, however, the AE is not clearly due to another condition, or a reasonable temporal association exists between the AE and treatment administration and, based on the Investigator's clinical experience, the association of the AE with the Investigational Product seems likely

AE = adverse event.

10.5.2 Severity

All AEs will be graded for severity (Table 8).

The Investigator will use the terms: Mild, Moderate, or Severe to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

Table 10: Guidelines for Severity Assessments

Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Severe	Disabling; limiting self-care activities of daily living; urgent intervention indicated; death related to an AE

AE = adverse event.

10.5.3 Serious Adverse Event

Any adverse experience occurring at any dose of study medication that occurs between the time of informed consent and the FU visit (Days 45 to 52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Events that jeopardize the subject sufficiently that medical or surgical intervention may be required to prevent one of the above outcomes. Examples may include, but are not limited, to:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias that do not result in hospitalization
    - Seizures that do not result in hospitalization

10.5.3.1 SAE definition clarifications

- Death is an outcome of an AE, and not an AE in itself
- All deaths during study drug administration or up to the FU visit (Days 45 to 52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia), regardless of cause or relationship, must be reported
- "Occurring at any dose" does not imply that the subject is actively receiving study drug at the time of the event
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, had it occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If an AE prolongs hospitalization, it is an SAE.
- "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department (although an emergency department visit may define a medically important event, which is also considered an SAE).
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. In such cases, the diagnosis should be documented as the AE or SAE, rather than as the individual signs or symptoms.

10.6 ADVERSE EVENT FOLLOW-UP

All unresolved SAEs ("ongoing" at discharge) will be followed by the study staff until resolution or deemed stable.

10.7 ADVERSE EVENTS OF SPECIAL INTEREST

10.7.1 CD101 IV Intolerability

Events that, in the opinion of the Investigator, may represent intolerance of the IV infusion of IV study drug must be recorded as AEs on the eCRF. In general, these events will be temporally related to IV echinocandin infusion.

10.7.2 Phototoxicity

Results from a phototoxicity study in rats indicate evidence of phototoxicity at elevated CD101 exposures (Section 4.3). Although there is not yet any evidence of risk to humans, Investigators should advise subjects to avoid sun exposure without adequate protection and to report any AE potentially related to phototoxicity to the Sponsor.

10.7.3 Neuropathy and Tremors

In a CD101 3-month toxicity study in monkeys, there were observations of tremors, intention tremors, and histology consistent with Schwann cell hyperplasia/hypertrophy and axonal degeneration (potentially consistent with clinical presentation of neuropathy) first appearing at week 6 of dosing and at 11-fold the exposure for Group 2. Ataxia, axonal neuropathy, hypoesthesia, paresthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathies, peripheral sensorimotor neuropathy, polyneuropathy, toxic neuropathy, and tremors will be included in adverse events of special interest.

10.8 TOXICITY MANAGEMENT

The Investigator should employ best medical judgment in determining how to manage AEs. Any questions regarding AE management should be directed to the Medical Monitor.

10.9 RISKS FOR WOMEN OF CHILD-BEARING POTENTIAL OR DURING PREGNANCY

The risks of CD101 IV administration during pregnancy have not been evaluated. Pregnant or lactating females who are nursing are excluded from this study.

Subjects must be instructed to inform the Investigator *immediately* if they or their partner becomes pregnant during the study. Partners must complete informed consent to allow the investigator to follow them for the outcome of the pregnancy. In the event of a confirmed pregnancy, the following actions should be taken:

- Study drug should be discontinued immediately in all (and in only) female subjects
- The pregnancy should be reported within 24 hours of notification using the applicable Pregnancy Report Form

- The Investigator should counsel the subject regarding the possible effects of prior CD101 IV exposure on the fetus and the need to inform the study site of the outcome of the pregnancy

- The subject or subject's partner (if consented) should be monitored until the immediate postnatal period or until termination of the pregnancy. The outcome should be reported using the Pregnancy Outcome or Abnormal Pregnancy Outcome form.

Pregnancy is not an AE, in and of itself. However, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered an SAE and will be reported as described in the AE and SAE sections. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the Medical Monitor.

10.10 RISKS FOR MALES OF CHILDBEARING POTENTIAL

Recent results from a CD101 nonclinical rat fertility study indicated adverse effects on sperm morphology and motility without interference with reproduction at 2.5 times the exposure of rezafungin Group 2. The risks for CD101 effects on spermatogenesis in non-human primates and in humans have yet to be defined. Partner pregnancies of male subjects should be followed according to Section 10.9, when possible.

11.0 ASSESSMENT OF EFFICACY PARAMETERS

Mycological response will be programmatically determined at Day 5, Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), and FU (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) in the mITT population as defined in Table 9.

Table 11: Mycological Outcome Categories at Day 5, Day 14 (±1 day), Day 28 (±2 days; only for subjects with invasive candidiasis), and Follow-up Visit

Outcome	Definition
Success (eradication/ presumed eradication)	• If positive blood culture at baseline: ○ The last blood culture drawn on or prior to the day of assessment and another blood culture drawn at least 12 hours prior are both negative for *Candida* spp. AND ○ Any intervening blood cultures drawn between the 2 qualifying negative blood cultures are also negative for *Candida* spp. OR • If positive culture from a normally sterile site: ○ *Documented* mycological eradication: most recent culture on or prior to the day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is negative OR

Table 11: Mycological Outcome Categories at Day 5, Day 14 (±1 day), Day 28 (±2 days; only for subjects with invasive candidiasis), and Follow-up Visit

Outcome	Definition
	○ *Presumed* mycological eradication: follow-up culture is not available (eg, normally sterile baseline site of *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 invasive candidiasis that were present at baseline) and resolution or improvement of any baseline radiographic abnormalities due to invasive candidiasis AND • There was no change of antifungal therapy for the treatment of candidemia and/or invasive candidiasis AND • The subject is not lost to follow up on the day of assessment
Failure	• If positive blood culture at baseline: ○ The last blood culture drawn on or prior to the day of assessment or any blood culture drawn prior to and within 12 hours of the last blood culture is positive for *Candida* spp. OR ○ The most recent blood culture drawn at least 12 hours prior to the last blood culture is positive for *Candida* spp. OR • If positive culture from a normally sterile site: ○ *Documented* mycological persistence: most recent culture on or prior to the day of assessment from all normally sterile sites of baseline *Candida* infection (if accessible) is positive OR ○ *Presumed* mycological persistence: follow-up culture is not available (eg, normally sterile baseline site of *Candida* infection not accessible) in a subject without a successful clinical outcome or with continued (from baseline) radiographic abnormalities due to invasive candidiasis OR • The subject requires a change of antifungal therapy to treat candidemia OR • 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 • If positive culture from a normally sterile site: A sterile site tissue/fluid specimen was not available to culture or the result was not available AND an assessment of signs of invasive candidiasis was not available • Subject is lost to follow up on the day of assessment

The primary efficacy outcome is overall response and is determined programmatically from the mycological response and assessment of systemic signs attributable to candidemia and/or IC (Table 10). The signs that may be present at baseline and attributable to candidemia and/or IC include fever, hypothermia, hypotension, tachycardia, and tachypnea (Section 7.1.2). Subjects who require a change of antifungal therapy to treat candidemia and/or IC prior to a given day of the overall response assessment (Day 5, Day 14, or FU visit) 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 12: Overall Response Categories at Day 5, Day 14 (±1 day), Day 28 (±2 days; only for subjects with invasive candidiasis), and Follow-up Visit

Overall Response	Definition	
	Mycological Response	**Clinical 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 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 systemic signs was not completed for any reason

The Investigator will make an assessment of clinical response at Day 14 (±1 day), Day 28 (±2 days; only for subjects with IC), and FU, as detailed in Table 11. Subjects whose disease is progressing or who receive rescue antifungal therapy for candidemia prior to the Day 14 (±1 day) visit will be considered a clinical failure at the Day 14, Day 28 (±2 days; only for subjects with IC), and FU visits. Subjects who are a clinical cure at Day 14 (±1 day) and whose systemic signs or symptoms recur between Day 14 (±1 day) and Day 28 (±2 days; only for subjects with IC) or FU, and who receive antifungal therapy, will be considered a failure at Day 28 (±2 days; only for subjects with IC) or FU.

Table 13: Investigator's Assessment of Clinical Response at Day 14 (±1 day), Day 28 (±2 days; only for subjects with invasive candidiasis), and Follow-up Visit

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

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

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

12.0 ASSESSMENT OF PHARMACOKINETIC PARAMETERS (Part A only)

Blood PK samples will be drawn from the OPPOSITE arm of the infusion at the following specified time points.

Blood for PK analyses will be drawn 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.

For the purpose of maintaining the blind, blood samples will be collected from all subjects, when possible, in all 3 treatment groups in Part A, but only PK samples from the CD101 IV groups will be analyzed (using a validated assay) by an independent, central bioanalytical laboratory. When >1 assessment occurs at any time point, the PK blood sample will be given priority and taken at the correct protocol-specified time. Procedures for collection, storage, and shipping of PK samples are described in Appendix 7.

Plasma samples from all subjects who received CD101 IV will be analyzed by liquid chromatography- tandem mass spectrometry (LC-MS/MS) for the concentration of CD101. The plasma PK parameters of CD101 IV will be determined based upon the CD101 concentrations.

13.0 STATISTICAL METHODS

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

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables, will be provided by study drug (CD101 IV or caspofungin). All data will be summarized separately by study drug. Listings of individual subject data will also be produced. All analyses will be completed for Part A. Selected analyses will be completed only for Part B and for Part A and B combined.

To demonstrate preliminary efficacy and safety of CD101 and to confirm the correct CD101 dose regimen is utilized in Part B, an unblinded interim analysis will be performed after approximately 40 to 60 subjects in the mITT population have been enrolled and completed study drug therapy. This unblinded interim analysis of a few key efficacy and safety outcomes will be performed by an independent unblinded statistician. Interim efficacy and safety summary tables will be produced, but the identity of the group assignment for each individual subject will remain blinded until the completion of the study and the database for both Parts A and B are locked. Once Part A is completed, the database will be locked and a full unblinded analysis with all summary tables will be performed on Part A alone. As with the initial interim analysis and to help avoid bias, the full Part A analysis will be performed by an independent unblinded statistician, keeping the identity of the group assignment for each individual subject blinded until the completion of the study and the database for both Parts A and B are locked.

A Statistical Analysis Plan (SAP) will be prepared and finalized before the interim analysis. Any changes to the SAP from the time of the interim analysis to the final database lock of Part B will be documented in an addendum to the SAP. Any deviations from the final SAP/addendum will be described and justified in the study report. All statistical analyses will be performed using SAS®. All analyses will be completed for Part A. Selected analyses will be completed only for Part B and for Part A and B combined.

13.1 ANALYSIS POPULATIONS

Analysis populations are:

- Intent-to-Treat (ITT) population: all randomized subjects
- Safety population: all subjects who receive any amount of study drug
- The Microbiological Intent-to-treat (mITT) population: all subjects who had documented *Candida* infection based on Central Laboratory evaluation of a blood culture obtained within 96 hours of randomization, or from a specimen obtained from a normally sterile site, and received ≥1 dose of study drug
  -

13.2 ANALYSIS OF STUDY POPULATION AND SUBJECT CHARACTERISTICS

Demographics (including age, race, and gender), diagnosis (candidemia and/or IC), medical history including *Candida* risk factors, baseline assessments (including height, weight, BMI, modified APACHE II score, and Glasgow coma score), mycological data, systemic signs and symptoms, and administration of study drug will be summarized in the ITT and mITT populations. All analyses will be conducted for Part A only. The SAP will detail which analyses are conducted for Part B and for Parts A and B combined.

13.3 SAFETY ANALYSES

All subjects who receive any amount of study drug (Safety population) will be included in the safety analyses. All safety analyses will be conducted for Part A only and for Parts A and B combined.

Safety will be evaluated by presenting summaries of AEs, clinical laboratory evaluations (hematology evaluation, chemistry panel, and UA), vital signs, and ECGs. Safety variables will be tabulated by treatment group.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be collected for each subject from the signing of the ICF at Screening through the last study visit at FU (Days 45 to 52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia). A treatment-emergent adverse event (TEAE) is defined as an AE that occurs during or after study drug administration and up through the FU visit. The incidence of TEAEs will be presented by system organ class (SOC) and preferred term, by SOC, preferred term, and relationship to the study drug administration, and by SOC, preferred term, and severity. In addition, the incidence of serious TEAEs and TEAEs leading to discontinuation of study drug (IV and IV/oral) will be presented by SOC and preferred term.

Descriptive statistics for clinical laboratory test results, ECG parameters and vital signs, and for changes from baseline, will be presented by time point. Baseline is defined as the measurement closest to, but prior to, the administration of study drug. Incidences of potentially clinically significant clinical laboratory results, ECG parameters, and vital signs, as defined in the SAP, will also be summarized by time point.

13.4 EFFICACY ANALYSES

The number and percentage of subjects with an overall success (mycological eradication/presumed eradication and resolution of systemic signs of candidemia and/or IC that were present at baseline), failure, and indeterminate response at Day 14 in the mITT population will be presented. Exact 2-sided 95% CIs for the point estimates of overall success in each treatment group will be determined using the Clopper-Pearson method. Additional analysis of the primary efficacy outcome will be conducted. The number and percentage of subjects with each overall response (success, failure, indeterminate) will be determined separately for subjects with candidemia and with IC in the mITT population. Analyses will be conducted for Part A, Part B, and for Parts A and B combined.

The number and percentage of subjects with each overall response (success, failure, indeterminate) will be determined in those subjects in the mITT population who did not receive concomitant antifungal therapy in addition to study drug and will be determined in those subjects with and without a positive blood culture at baseline for *Candida* spp. For this analysis, a baseline culture is defined as one taken within 12 hours before randomization. Subjects will be included in the positive culture at baseline group if the baseline blood culture is negative, or not done and the first blood culture after receipt of study drug is positive. Exact 2-sided 95% CIs for the point estimates of success in each treatment group will be determined using the Clopper-Pearson method. Analyses will be conducted for Part A and for Parts A and B combined.

The number and percentage of subjects with an overall success, failure, and indeterminate response at Day 5, Day 28 (±2 days; only for subjects with IC), and at FU in the mITT population will be presented by treatment group. Exact 2-sided 95% CIs for the point estimates of success in each treatment group will be determined using the Clopper-Pearson method. Analyses will be conducted for Part A, Part B, and for Parts A and B combined.

An additional analysis of overall response at FU will be conducted in which subjects who received a non-study antifungal after Day 21 for the treatment of an infection other than the candidemia (or after Day 28 for the treatment of an infection other than IC) will be excluded. Analyses will be conducted for Part A and for Parts A and B combined.

Mycological outcome will be summarized by treatment group in the mITT population. The number and percentage of subjects with a success (mycological eradication/presumed eradication), failure, and indeterminate response at Day 5, Day 14, Day 28 (±2 days; only for subjects with IC) and at FU in the mITT population will be presented. Exact 2-sided 95% CIs for the point estimates of success in each treatment group will be determined using the Clopper-Pearson method. Analyses will be conducted for Part A, Part B, and for Parts A and B combined. Mycological outcome will also be analyzed in the subgroup of subjects with only a positive rapid in vitro diagnostic result and with only a positive baseline blood culture.

The number and percentage of subjects with a clinical cure, failure, and indeterminate response based on the Investigator's assessment at Day 14, Day 28 (±2 days; only for subjects with IC), and at FU in the mITT population will be presented by treatment group. Exact 2-sided 95% CIs for the point estimates of success in each treatment group will be determined using the Clopper-Pearson method. Analyses will be conducted for Part A, Part B, and for Parts A and B combined.

An additional analysis of Investigator's assessment of clinical response at FU will be conducted in which subjects who receive a non-study antifungal after Day 21 for the treatment of an infection other than the candidemia (or after Day 28 for the treatment of an infection other than IC) will be excluded. Analyses will be conducted for Part A and for Parts A and B combined.

The number and percentage of subjects who died up through the FU Visit (all-cause mortality) will be presented by treatment group. Kaplan-Meier methods will be utilized to analyze the time to the first negative blood culture (for those subjects enrolled with a positive blood culture). Time to negative blood culture will be defined as the time to the first of the 2 negative blood cultures drawn ≥12 hours apart, without an intervening positive culture. Subjects will be censored if they receive an alternative antifungal (ie, other than study drug) for the treatment of the candidemia, or if they are lost to follow up prior to having 2 negative blood cultures. Analyses will be conducted for Part A and for Parts A and B combined.

13.5 PHARMACOKINETIC ANALYSES (Part A only)

Plasma samples from subjects who received ≥1 complete dose of CD101 IV will be analyzed for the concentration of CD101 by a validated LC-MS/MS method in the PK Analysis population. Due to the sparse sampling for PK in this protocol, plasma concentrations will primarily be used to support population PK modeling in patients. PK parameter assessment will be reported separately for the PK Analysis population and may include: C_{max}, T_{max}, $AUC_{0\text{-}168}$, and area under the CD101 concentration time curve from time zero to infinity [$AUC_{0\text{-}\infty}$], if applicable.

13.6 DETERMINATION OF STUDY SAMPLE SIZE

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 caspofungin groups in Part A to provide an initial, substantive analysis of safety, tolerability, and estimate efficacy.

In Part A, subjects will be randomized (1:1:1) until there are approximately 30 subjects in the CD101 IV treatment Group 1, 30 subjects in the CD101 IV treatment Group 2, and 30 subjects in the comparator group in the mITT population. It is expected that approximately 114 subjects will need to be randomized to achieve 90 subjects in the mITT population (assuming 80% of randomized subjects will be included in the mITT population).

In Part B, subjects will be randomized (2:1) until there are ≥30 subjects in the CD101 IV treatment groups at any dose and ≥15 subjects in the comparator group (≥45 additional subjects and no more than 120 subjects). Total enrollment will depend on the enrollment rate for the 6- to 8-month 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.

In Part A, assuming a 73% overall success rate, the sample size of 30 subjects in each CD101 IV group will yield a 95% CI of 53.8% to 87.5%. 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%.

13.7 HANDLING OF DROPOUTS AND MISSING, UNUSED, AND SPURIOUS DATA

Every effort will be made to collect all data at specified times. For the primary and secondary efficacy outcomes, subjects with missing outcome data are considered to have an indeterminate response. Subjects with an indeterminate response are included in the denominator of the response calculation and thus, are treated in the same manner as failures in the analysis. Substitutions for other missing data will be specified in the SAP.

13.8 TERMINATION CRITERIA

Enrollment and withdrawals from the study and from study drug will be summarized by treatment group.

13.9 DEVIATION REPORTING

Protocol deviations will be summarized by treatment group. 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.

14.0 INVESTIGATOR REQUIREMENTS

14.1 PROTOCOL ADHERENCE

The Investigator must adhere to the protocol as detailed in this document (Appendix 8) and agree that the Sponsor must approve any change to the protocol before seeking approval from the IRB/IEC. The Investigator will be responsible for enrolling only those subjects who have met the protocol inclusion and exclusion criteria.

14.2 ELECTRONIC CASE REPORT FORMS

The eCRF will be supplied by the contract research organization or designee for the recording of all information and study data as specified by this protocol. All eCRFs must be completed by trained study personnel. The Investigator is responsible for ensuring that the eCRF data are entered and completed in a timely manner.

Once all data queries and issues have been resolved for each subject, the Investigator will electronically sign each subject's eCRF to attest to the accuracy of the data.

The data from Part A will be locked separately from the data from Part B.

14.3 SOURCE DOCUMENT MAINTENANCE

Source documents are defined as documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, study- or subject-specific e-mail correspondence, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspections by the Sponsor and by regulatory authorities. The original signed ICF for each participating subject shall be filed with records kept by the Investigator, and a copy shall be given to the subject.

14.4 STUDY MONITORING REQUIREMENTS

An authorized Sponsor representative will conduct site visits to inspect study data, subjects' medical records, and eCRFs in accordance with International Conference on Harmonisation (ICH) guidelines, GCPs, and the foreign regulations and guidelines, as applicable. A monitor will be utilized for monitoring ongoing drug accountability and adherence to protocol procedures.

The Investigator will allow representatives of the Sponsor and regulatory authorities to inspect facilities and records relevant to this study.

14.5 STUDY COMPLETION

The Sponsor requires the following data and materials before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from Screening throughout the study until the FU visit (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia)

- eCRFs (including data queries) properly completed by appropriate study personnel and signed and dated by the Investigator

- Copies of complete drug accountability records (drug inventory log and an inventory of returned or destroyed clinical material)

- Copies of protocol amendments and IRB/IEC approval and notification, if appropriate

- A summary of the study prepared by the Investigator (an IRB/IEC summary letter is acceptable)

15.0 QUALITY CONTROL AND QUALITY ASSURANCE

Written standard operating procedures (SOPs) will be followed to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control will be applied to each stage of data handling. Regular monitoring, as defined in ICH GCP, Section 1.8, "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)", will be conducted throughout the conduct of the study.

The purpose of monitoring is to verify that:

- Rights and well-being of the human subjects are protected

- The reported study data are accurate, complete, and verifiable from source documents

- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements

- Monitoring is an integral role in the quality control of a clinical trial and is designed to verify the quality of the study

To fulfill the Quality Assurance requirements of GCP, audits will be conducted to assess and assure the reliability and integrity of a study's quality control systems and recognized standards.

The purpose of an audit is to:

- Ensure participant safety

- Assure compliance to study protocol procedures, regulatory requirements, and SOPs

- Assure data quality

16.0 PROTECTION OF HUMAN SUBJECTS

This study will be conducted in compliance with the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use E6 GCP: Consolidated Guidelines, the ethical principles of the Declaration of Helsinki, FDA GCP guidelines, and any additional national or IRB/IEC-required procedures.

16.1 INFORMED CONSENT

This study will be conducted in compliance with ICH E6 GCP: Consolidated Guidelines pertaining to informed consent. Subjects will give written consent to participate in the study at the first visit, prior to initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. If a subject is unable to provide written informed consent, the subject's legally acceptable representative may provide written consent, as approved according to institution-specific guidelines. The ICF must be signed and dated by the subject, or the subject's legally acceptable representative, prior to study participation. A copy of the ICF must be provided to the subject or the subject's legally acceptable representative. If applicable, it will be provided in certified translation for non-English-speaking subjects. Signed ICFs must remain in the subject's study file and be available for verification by Sponsor at any time.

16.2 IRB/IEC APPROVAL

This protocol, the ICF, and all relevant supporting data must be submitted to the IRB/IEC for approval. The protocol, ICF, and any advertisement used to recruit study subjects must be approved by the IRB/IEC. Approval by the IRB/IEC of the protocol and ICF must be obtained before the study may be initiated.

The Investigator is responsible for informing the IRB/IEC of any changes made to the protocol, and to advise them, at least once a year, about the progress of the study. The Investigator is also responsible for notifying the IRB/IEC of any significant AEs that occur during the study.

17.0 DATA HANDLING AND RECORD KEEPING

Training sessions, regular monitoring of Investigators by Sponsor-designated personnel, instruction manuals, data verification, crosschecking, and data audits will be performed to ensure quality of all study data. Investigator meetings will be performed to prepare Investigators and other study personnel for appropriate collection of study data.

The Sponsor will review and validate study data as defined in the monitoring plan.

It will be the responsibility of the Investigator to ensure that the essential documents are available at the Investigator or institutional site. Any or all of these documents may be subject to, and should be available for, monitoring by the Sponsor or inspection by the regulatory authorities as defined in the monitoring plan.

17.1 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

The Investigator agrees by his/her participation that the results of this study may be used for submission to national or international registration. If required, these authorities will be provided with the name of the Investigator and his or her address, qualifications, and extent of involvement. It is understood that the Investigator is required to provide Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by any regulatory authorities, by Sponsor and by the IRB/IEC as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Medical information obtained from subjects during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

17.2 STUDY DRUG ACCOUNTABILITY

All supplies of CD101 IV, caspofungin, and fluconazole required for completion of this study will be provided by the Sponsor. It is the responsibility of the unblinded Pharmacy staff or unblinded study staff to ensure that a current record of drug inventory and drug accountability is maintained. Inventory and accountability records must be readily available for inspection by the unblinded monitor and are open to inspection at any time by applicable regulatory authorities.

17.3 RETENTION OF RECORDS

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product and shipment and delivery of the drug for investigational use is discontinued. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements of specific ICH- and non-ICH countries, or by an agreement with the Sponsor. The Sponsor will inform the Investigator/institution as to when these documents no longer need to be retained.

18.0 FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

19.0 PUBLICATION POLICY

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. Authorship on any publication of the results from this study will be based on contributions to study design, enrollment, data analysis, and interpretation of results.

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21.0 APPENDICES

APPENDIX 1: CLINICAL AND LABORATORY STANDARDS INSTITUTE (CLSI) AND EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING (EUCAST) BREAKPOINTS FOR *CANDIDA SPP*:

The following table provides susceptibility breakpoints for both CLSI and EUCAST and should be used as guidance in determining susceptibility of different *Candida* species to potential empiric antifungal drugs. Not all species or antifungal drugs are referenced here and local determination of susceptibility and resistance may be used when appropriate.

		MIC Breakpoints (mg/L)									
Antifungal Agent	Standard	*C. albicans*		*C. glabrata*		*C. krusei*		*C. parapsilosis*		*C. tropicalis*	
		S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B	EUCAST	1	1	1	1	1	1	1	1	1	1
	CLSI	-	-	-	-	-	-	-	-	-	-
Anidulafungin	EUCAST	0.03	0.03	0.06	0.06	0.06	0.06	0.002	4	0.06	0.06
	CLSI	0.25	0.5	0.12	0.25	0.25	0.5	2	4	0.25	0.5
Caspofungin	EUCAST										
	CLSI	0.25	0.5	0.125	0.25	0.25	0.5	2	4	0.25	0.5
Fluconazole	EUCAST	2	4	0.002	32	-	-	2	4	2	4
	CLSI	2	4	32 (SDD)	32	-	-	2	4	2	4
Itraconazole	EUCAST	0.06	0.06	IE	IE	IE	IE	0.12	0.12	0.12	0.12
	CLSI	0.125	0.5	0.125	0.5	0.125	0.5	0.125	0.5	0.125	0.5
Micafungin	EUCAST	0.016	0.016	0.03	0.03	IE	IE	0.002	2	IE	IE
	CLSI	0.25	0.5	0.06	0.12	0.25	0.5	2	4	0.25	0.5
Posaconazole	EUCAST	0.06	0.06	IE	IE	IE	IE	0.06	0.06	0.06	0.06
	CLSI	-	-	-	-	-	-	-	-	-	-
Voriconazole	EUCAST	0.125	0.125	IE	IE	IE	IE	0.125	0.125	0.125	0.125
	CLSI	0.125	0.5			0.5	1	0.125	0.5	0.125	0.5

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; IE = insufficient evidence; R = resistant; S = susceptible; SDD = susceptible dose dependent

Source: Alastruey-Izquierdo et al., 2015.

APPENDIX 2: CREATININE CLEARANCE

In the event the local laboratory does not calculate creatinine clearance based on the most recent serum creatinine value, estimate the patient's creatinine clearance using the serum creatinine value provided by the local laboratory, actual body weight, and the appropriate Cockcroft-Gault formula. If necessary, convert serum creatinine values from µmol/L to mg/dL by dividing by 88.4. For example, 100 µmol/L divided by 88.4 equals 1.131 mg/dL:

Males:

$$\text{creatinine clearance} = \frac{(140 - [\textit{insert age in years}]) \times [\textit{insert weight in kg}]}{72 \times [\textit{insert serum creatinine in mg/dL}]}$$

Females:

$$\text{creatinine clearance} = \mathbf{0.85} \times \frac{(140 - [\textit{insert age in years}]) \times [\textit{insert weight in kg}]}{72 \times [\textit{insert serum creatinine in mg/dL}]}$$

APPENDIX 3: SAFETY LABORATORY TESTS

Hematology	Serum Chemistry
hemoglobin	blood urea nitrogen
hematocrit	bilirubin (total and direct)
total and differential leukocyte count	alkaline phosphatase
red blood cell count	aspartate aminotransferase
platelet count	alanine aminotransferase
Coagulation	albumin
Prothrombin time/ International Normalized Ratio	sodium
Partial thromboplastin time or activated partial thromboplastin time	potassium
Urinalysis	chloride
pH	glucose
specific gravity	creatinine
protein [a]	total protein
glucose	calcium
ketones	bicarbonate
bilirubin [b]	procalcitonin [c]
blood [a]	
nitrite [a]	**Additional Tests**
urobilinogen [b]	Urine pregnancy test for females of childbearing potential. Do not perform on women who are ≥2 years postmenopausal or surgically sterile.
leukocyte esterase [a]	

a. If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.
b. Urobilinogen and bilirubin are optional tests.
c. Procalcitonin is an optional test to be performed only at Screening

APPENDIX 4: CHILD-PUGH SCORE

Calculate the Child-Pugh score only if the subject has a history of chronic cirrhosis.

The Child-Pugh score employs 5 clinical measures of liver disease. Each measure is scored 1 to 3, with 1 indicating the least severe and 3 indicating the most severe score. The sum of the 5 measures is the total Child-Pugh point score.

Parameter	**Points**		
	1	**2**	**3**
Ascites	None	Medically controlled	Poorly controlled
Encephalopathy [a]	None	Medically controlled	Poorly controlled
Total bilirubin (mg/dL)	<2	2 – 3	>3
Albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
International Normalized Ratio **OR** PT prolongation in seconds	<1.7 <4	1.7 – 2.3 4 – 6	>2.3 >6

a. If sedated, use last known encephalopathy status before sedation.

APPENDIX 5: MODIFIED ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE) II SCORE

Point Value	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**	**Total**
Glasgow Coma Score	Score = 15 minus actual Glasgow Coma Score									
Temperature (rectal, ºC)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9	
Mean Arterial Pressure (mmHg) [a]	≥160	130-159	110-129		70-109		50-69		≤49	
Heart Rate (bpm)	≥180	140-179	110-139		70-109		55-69	40-54	≤39	
Respiration Rate	≥50	35-49		25-34	12-24	10-11	6-9		≤5	
Alveolar-Arterial Oxygen Gradient (if FiO_2 ≥50%) OR PaO_2 (mmHg) OR Oxygen Saturation, %	≥500	350 to 499	200 to 349		<200 >70 ≥92	61-70 88-91		55-60 85-87	<55 85	
Arterial pH OR Serum HCO_3 (mEq/L) - (venous- if ABG not performed)	≥7.7 ≥52	7.6-7.69 41-51.9		7.5-7.59 32-40.9	7.33-7.49 22-31.9		7.25-7.32 18-21.9	7.15-7.24 15-17.9	<7.15 <15	
Serum Na^+ (mMol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110	
Serum K^+ (mMol/L)	≥7.0	6.0-6.9		5.5-5.9	3.5-5.4	3.0-3.4	2.5-2.9		<2.5	
Serum creatinine (mg/dL)	≥3.5	2.0-3.4	1.5-1.9		0.6-1.4		<0.6			
Acute renal failure [b]	×2 creatinine point score if patient has acute renal failure									
Hematocrit, %	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20	
WBC, (10^9 cells/L or mm^3)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1	
Severe organ failure (liver, heart, or lung) or immunocompromised [c]	Add 5 points if patient is medical (no surgery) or postoperative for emergency surgery Add 2 points if patient is postelective surgery									
Age (years) points	≤44=0, 45-54=2, 55-64=3, 65-74=5, ≥75=6									
									Sum of all rows	

Source: Modified from Knaus et al., 1985.

a. Mean arterial pressure = (systolic blood pressure + 2 diastolic blood pressure)/3
b. Acute Renal Failure = a 0.5 mg/dL increase in serum creatinine if the baseline serum creatinine was ≤1.9 mg/dL, a 1.0 mg/dL increase in serum creatinine if the baseline serum creatinine was 2.0 to 4.9 mg/dL, and a 1.5 mg/dL increase in serum creatinine if the baseline serum creatinine was ≥5.0 mg/dL.
c. Organ insufficiency or immunocompromised state must have been evident **prior** to this hospital admission and conform to the following criteria:
   - **Liver** – biopsy proven cirrhosis and documented portal hypertension; episodes of past upper gastrointestinal bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.
   - **Cardiovascular** – New York Heart Association Class IV.
   - **Respiratory** – Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (ie, unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency.
   - **Renal** – receiving chronic dialysis.
   - **Immunocompromised** – the patient has received therapy that suppresses resistance to infection (eg, immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, eg, leukemia, lymphoma, AIDS).

APPENDIX 6: GLASGOW COMA SCORE

Sedating and paralytic agent use may confound the assessment of the Glasgow Coma Score. If sedation is reduced and patients awakened daily to perform neurologic assessments, assess the score during the period when the patient is not sedated. If daily awakenings are not performed, please record the score as if the patient did not have sedating or paralytic agents preventing response.

Neurologic Response		**Score**
Best Eye Response (E)	Spontaneous-open with blinking at baseline	4
	Opens to verbal command, speech or shout	3
	Opens to pain (not applied to face)	2
	None	1
Best Verbal Response (V)	Oriented	5
	Confused conversation, but can answer questions	4
	Inappropriate responses, words discernible	3
	Incomprehensible speech	2
	None	1
Best Motor Response (M)	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion, decorticate posture	3
	Extensor (rigid) response, decerebrate posture	2
	None	1
Total Score		

Source: Teasdale and Jennet, 1974.

APPENDIX 7: PHARMACOKINETIC SAMPLE PROCESSING AND SHIPMENT (Part A only)

Plasma PK sample collection and processing procedure

1. Draw blood into a 4 mL lavender top potassium ethylenediaminetetraacetic acid (K_2EDTA) Vacutainer tube. Label the tube.

2. Mix the blood with the anticoagulant by gently inverting the tube 8 to 10 times, and then immediately place the tube on wet ice. It is preferable to leave the sample on wet ice for 5 to 10 minutes before centrifuging.

3. Centrifuge the blood samples for approximately 10 minutes at approximately 1006g in a centrifuge within approximately 60 minutes after blood sample collection.

4. Immediately following centrifugation, gently remove the plasma from the packed cells and aliquot into 2 transfer vials. Into the first, aliquot ≥0.5 mL of plasma, and, into the second, aliquot the rest.

5. Replace the caps on the transfer vials and freeze the samples immediately at approximately -20°C or colder.

6. Note: No more than 60 minutes should elapse between blood collection and freezing the plasma samples.

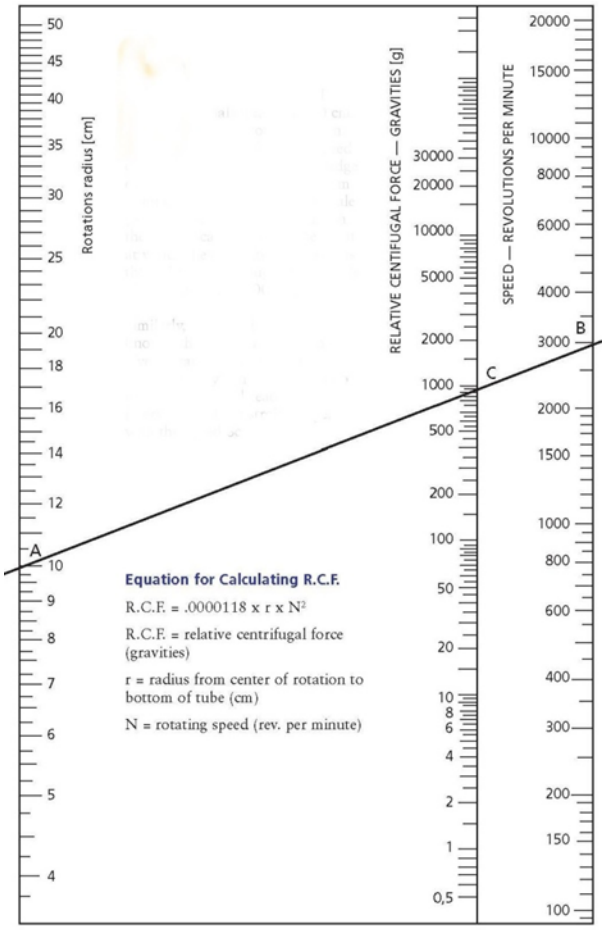
7. Keep the samples frozen at approximately -20°C or colder until shipment.

8. Ship the primary sample on dry ice; retain the frozen backup sample until receipt of instructions regarding its shipment.

Note: Wet ice is defined as a mixture of ice and water.

Pharmacokinetic Sample Shipment

Procedures for the shipping of PK samples, including contact information, is provided in the Pharmacokinetics Manual.



Radius (cm)	G-Force	RPM
10	1006	3000
12	1006	2738
14	1006	2535
16	1006	2371
18	1006	2236
20	1006	2121
22	1006	2022
24	1006	1936
26	1006	1860
28	1006	1793

APPENDIX 8: INVESTIGATOR SIGNATURE

I have read and understand protocol CD101.IV.2.03 and the Investigator Brochure. I agree to the following:

1. To conduct the trial in compliance with GCP, with applicable regulatory requirement(s), with the protocol agreed to by the Sponsor and given approval/favorable opinion by the IRB/IEC

2. To comply with procedures for data recording and reporting

3. To permit monitoring, auditing, and inspection by the Sponsor, its designated representatives, and regulatory authorities

4. To retain the essential documents in the Investigator/institution files until the Sponsor informs the Investigator or institution that these documents are no longer needed

INVESTIGATOR SIGNATURE:

_____ _____
[Investigator Signature] Date

_____
[Investigator Name]

_____
[Site Number]

_____
[Site Name]

_____
[Site Address]