SCYNEXIS, Inc.

Clinical Trial Protocol

A Phase 3, Multicenter, Prospective, Randomized, Double-blind Study of Two Treatment Regimens for Candidemia and/or Invasive Candidiasis: Intravenous Echinocandin followed by Oral Ibrexafungerp versus Intravenous Echinocandin followed by Oral Fluconazole (MARIO)

SCYNEXIS Protocol Number: SCY-078-302

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2.0 Protocol Approvals

PROTOCOL NUMBER: SCY-078-302

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SCYNEXIS, Inc. Approval:

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Investigator Agreement Statement

PROTOCOL NUMBER: SCY-078-302

A Phase 3, Multicenter, Prospective, Randomized, Double-blind Study of Two Treatment Regimens for Candidemia and/or Invasive Candidiasis: Intravenous Echinocandin followed by Oral Ibrexafungerp versus Intravenous Echinocandin followed by Oral Fluconazole (MARIO)

I understand that all documentation provided to me by SCYNEXIS, Inc. or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's Brochure, case report forms, and other scientific data. This study will not commence without the prior written approval of a properly constituted Institutional Review Board or Ethics Committee. No changes will be made to the study protocol without the prior written approval of SCYNEXIS, Inc. and the Institutional Review Board/Ethics Committee, except where necessary to eliminate an immediate hazard to the patient. All patients will provide a written informed consent prior to participation. If the patient is not able to provide written consent due to the severity of their illness and I consider the patient's condition to be life-threatening or highly debilitating without participation in this clinical study, I will obtain written consent from a legal representative (LAR) of the patient. Once the patient is able to provide oral or written consent, I will obtain appropriate consent. If the patient is capable of giving consent but does not give consent to continue, the patient will be withdrawn from the trial.

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol, and in compliance with International Conference on Harmonization (ICH) guidelines, Good Clinical Practices (GCP), Safety Reporting obligations and any applicable local requirements.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Printed)

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3.0 Abbreviations

ABBREVIATION	DEFINITION
ACM	All-cause mortality
AE	Adverse event
ALT	Alanine Aminotransferase
ABG	Arterial Blood Gas
AP	Alkaline phosphatase
APACHE	Acute Physiology and Chronic Health Evaluation
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the concentration-time curve from 0 to 24 hours
BAT	Best Available Therapy
β-hCG	β-human chorionic gonadotropin
BID	Twice daily
BUN	Blood Urea Nitrogen
C	Celsius
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum concentration
CPK	Creatine phosphokinase
CRO	Contract Research organization
CT	Computed tomography
CTFG	Clinical Trials Facilitation and Coordination Group
CYP	Cytochrome P450
DRC	Data Review Committee
eCRF	Electronic case report form
EDC	Electronic data capture
EKG	Electrocardiogram
EOIV	End of intravenous echinocandin therapy
EMA	European Medicines Agency
EOT	End-of-Treatment (end of all antifungal therapy)
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
F	Fahrenheit
FDA	Food and Drug Administration
FN-MITT	Fluconazole Non-Susceptible Modified Intent-to-Treat
FS-MITT	Fluconazole Susceptible Modified Intent-to-Treat
FU	Follow up
GCP	Good Clinical Practices
GGT	Gamma glutamyl transferase
GSI	Glucan synthesis inhibitors

ABBREVIATION	DEFINITION
GvHD	Graft Versus Host Disease
HDL	High density lipoprotein
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IP	Intraperitoneally
IRB/EC	Institutional Review Board/Ethics Committee
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
MIC	Minimum inhibitory concentration
µg	Microgram
µM	Micromolar
mg	Milligram
mL	Milliliter
MRI	Magnetic resonance imaging
NIM	Non inferiority margin
NOAEL	No-observed-adverse-effect-level
NSAID	Non-steroidal Anti-inflammatory Drug
P-gp	P-glycoprotein 1
PI	Principal Investigator
PK	Pharmacokinetics
Pop PK	Population Pharmacokinetics
PP	Per-protocol population
PPI	Proton Pump Inhibitor
PVG	Pharmacovigilance Group
QD	Once daily
qSOFA	Quick Sequential (sepsis related) Organ Failure Assessment
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SGPT	Serum glutamate pyruvate transaminase

ABBREVIATION	DEFINITION
SGOT	Serum glutamic oxaloacetic transaminase
SOC	Standard of Care
TEAE	Treatment-emergent adverse event
ULN	Upper Limit of Normal
US	United States
VVC	Vulvovaginal Candidiasis
WBC	White blood cell
WHO	World Health Organization

4.0 Protocol Synopsis

TITLE: A Phase 3, Multicenter, Prospective, Randomized, Double-blind Study of Two Treatment Regimens for Candidemia and/or Invasive Candidiasis: Intravenous Echinocandin followed by Oral Ibrexafungerp versus Intravenous Echinocandin followed by Oral Fluconazole (MARIO)

STUDY OBJECTIVES

Primary Objective:

- To demonstrate that treatment of Invasive Candidiasis/Candidemia with intravenous (IV) echinocandin followed by oral ibrexafungerp is non-inferior to IV echinocandin followed by oral fluconazole (or Best Available Therapy [or BAT]).

Key Secondary Objective:

- To demonstrate that treatment of Invasive Candidiasis/Candidemia with IV echinocandin followed by oral ibrexafungerp is non-inferior to IV echinocandin followed by oral fluconazole (or BAT), based on Global Response (clinical, radiological, and mycological response, as confirmed by the Data Review Committee [DRC]) at Day 14.

Other Secondary Objectives:

- To compare the efficacy of the treatment regimens, based on:
  - Global Response at Day 30 and End of Therapy (EOT) as determined by the PI and DRC,
  - Clinical Response as determined by the Principal Investigator (PI) and DRC,
  - Mycological Response as determined by the DRC,
  - no recurrence as determined by the DRC, and
  - fungal-free survival as determined by the DRC.
- To evaluate the safety of the regimens.
- To evaluate the pharmacokinetics (PK) of ibrexafungerp.

STUDY ENDPOINTS

Primary Endpoint:

All-cause Mortality (ACM) at Day 30 in the ITT population.

The percentage of subjects with Successful Global Response, as determined by the DRC at EOT (European Union [EU] only).

Key Secondary Endpoint:

The percentage of subjects with Successful Global Response, as determined by the DRC (based on clinical response as determined by the PI, mycological response and radiological response [when applicable]) at Day 14.

Secondary Endpoints:

Efficacy Endpoints

- The percentage of subjects with Successful Global Response at Day 30 and EOT as determined by the PI and the DRC.

- The percentage of subjects with Successful Clinical Response at Day 14, Day 30 and EOT as determined by the PI and the DRC.
- The percentage of subjects with Successful Mycological Response at Day 14, Day 30 and EOT as determined by the DRC.
- The percentage of subjects with no recurrence at 2 weeks and 6 weeks after EOT as determined by the DRC.
- The percentage of subjects alive with Successful Global Response at EOT and no recurrence at 6 weeks after EOT as determined by the DRC.

Safety Endpoints

- Frequency of treatment-emergent adverse events (TEAEs), drug-related adverse events, discontinuations due to AEs, serious adverse events (SAEs), and safety laboratory assessments.

PK Endpoint

- Description of ibrexafungerp plasma concentrations.

STUDY PHASE: 3

STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled, comparative study to evaluate the efficacy, safety and tolerability of oral ibrexafungerp compared to oral fluconazole (or BAT) step-down treatment following IV echinocandin in the treatment of adult subjects (≥18 years old) with invasive candidiasis and/or candidemia. The pharmacokinetics of ibrexafungerp will also be described.

Eligible subjects will receive treatment with IV echinocandin and will then be switched to double-blind, double-dummy oral therapy (either ibrexafungerp or fluconazole) as soon as step-down criteria are met. The study will be multi-national. Approximately 220 subjects are planned to be randomized in the study.

Study Visits

Study Day 1 is the day of first dose of IV echinocandin treatment and may occur before the Screening visit. The study will consist of a Screening visit which includes randomization [from 4 days prior to start of IV echinocandin, i.e. Day -4 to before end of IV echinocandin (EOIV)], an end of IV treatment (EOIV) visit, Oral Treatment Day 1 visit, Oral Treatment Days 2 and 7 visits (PK subset only), an end of antifungal treatment (EOT) visit, Day 14 and Day 30 visits (counted as IV + oral), a 2-Week Follow-up (FU) visit (14 days after EOT) and a 6-Week FU visit (42 days after EOT). The EOIV and Oral Treatment Day 1 visit should ideally occur on the same day. The Day 14 and Day 30 visits may occur before, on, or after EOT. Other study visits may also be combined if they occur on the same day or within the protocol specified window period. EOT is end of all protocol specified treatments, including IV and oral.

Subject Enrollment

Subjects with a diagnosis of candidemia and/or invasive candidiasis will be invited to participate in the study either prior to or while they are receiving an IV echinocandin. After having signed an informed consent form, subjects will be assigned a study number. Following screening, subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized. Screening and randomization should occur as soon as possible after the diagnosis of candidemia and/or invasive candidiasis has been made. It is anticipated that most subjects may be on IV echinocandin at the time of randomization.

However, randomization may occur before or after the initiation of IV echinocandin which is Study Day 1.

Study Treatments

All randomized subjects will receive IV echinocandin therapy followed by step-down oral treatment or other Best Available Therapy (BAT), as described below. Eligible subjects will be randomized at a 1:1 ratio to one of two treatment regimens: IV echinocandin followed by oral ibrexafungerp, or IV echinocandin followed by oral fluconazole or BAT. The IV component of these treatment regimens will consist of an IV echinocandin (caspofungin, micafungin or anidulafungin administered as per local label instructions) given as open-label therapy. The oral component of the regimen (ibrexafungerp or fluconazole) will be administered as double-blind, double-dummy treatment, unless the *Candida* spp. isolate is identified as suspected or confirmed non-susceptible to fluconazole (i.e., *C.glabrata, C.krusei* or *C.auris,* or subjects with breakthrough infections whilst receiving azole prophylaxis treatment). These subjects will receive open label ibrexafungerp (if originally randomized to receive oral ibrexafungerp as step-down) or BAT (if originally randomized to receive oral fluconazole as step-down).

Treatment Duration and Switch from IV to Oral Therapy

In line with current treatment guidelines, the antifungal treatment duration will depend on subjects' invasive candidiasis condition and response to therapy (e.g., for candidemia antifungal treatment should continue for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia) with an anticipated treatment duration ranging from 14 days to 6 weeks (IV + oral antifungal treatment).

Subjects will receive IV echinocandin treatment until the criteria for switching to oral antifungal treatment are met.

The switch from IV echinocandin to oral antifungal should occur as soon as the criteria for switching is met (they are clinically stable, able to tolerate oral medication, are hemodynamically stable, blood cultures should be negative for at least 48 hours (candidemia) , the *Candida* species is known, and no mucositis or Graft Versus Host Disease (GvHD) affecting the gut with severity > Grade 3) and ideally within 5 days of start of the IV echinocandin. While on IV echinocandin, subjects should be assessed daily to determine if they meet the criteria for step-down therapy.

Study Assessments

The study will include efficacy, safety, tolerability and PK assessments. Efficacy will be assessed primarily in terms of ACM. In addition, Global Response [a composite assessment of clinical, radiological and mycological assessments (primary for EU only)], Clinical Response, Mycological Response, absence of recurrence, and survival with no recurrence will also be assessed as secondary endpoints. Safety and tolerability will be assessed by including parameters such as physical examinations, vital signs, AEs and safety laboratory tests (hematology and blood chemistry). Blood samples will also be collected for PK analysis. The Independent Data Monitoring Committee (IDMC) will review available, unblinded, safety data at least once a year during the conduct of the study i.e., from the first subject's enrollment in this study until the last subject has completed the safety follow-up visit, and when approximately 70% of subjects have completed the safety follow-up visit. Other IDMC reviews may be conducted for safety reasons as required. Details will be provided in the IDMC Charter.

STUDY POPULATION: The study population will include adult subjects ≥ 18 years of age, with a diagnosis of invasive candidiasis (including candidemia).

KEY INCLUSION CRITERIA

Subjects must fulfill all of the following **KEY** criteria at Screening to be eligible for participating in the study:

1. Subject is a male or female adult ≥ 18 years of age on the day the study informed consent is signed.
2. Subject has a diagnosis of candidemia and/or invasive candidiasis, defined as evidence of *Candida* spp. in **either** a bloodstream or tissue/fluid culture from a normally sterile site (excluding eye, cardiac tissue, bone tissue, central nervous system or prosthetic device) collected within ± 4 days (96 hours) of initiation of IV echinocandin accompanied by any related clinical sign and/or symptom (e.g., fever [on one occasion > 38°C], hypotension, or local signs of inflammation, etc.).

KEY EXCLUSION CRITERIA

A subject will be excluded from participation in the study if he or she meets any of the following **KEY** exclusion criteria:

1. Subject has any of the following forms of invasive candidiasis at Screening:
   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,
   e. Chronic disseminated candidiasis,
   f. Urinary tract candidiasis due to ascending *Candida* infection secondary to unresolved obstruction or non-removeable device in the urinary tract,
   g. Patients with a sole diagnosis of mucocutaneous candidiasis, i.e., oropharyngeal, esophageal, or genital candidiasis; or *Candida* lower urinary tract infection or *Candida* isolated solely from respiratory tract specimens,
   h. Patients with concurrent invasive fungal infection other than *Candida* spp., e.g., cryptococcosis, mold infection or endemic fungal infection,
   i. Patients who failed a previous antifungal therapy for the same infection,
   j. Subject has an uncontrolled fungal disease source (e.g., indwelling vascular catheter or device that cannot be removed or an abscess that cannot be drained) that is likely to be the source of the candidemia or invasive candidiasis.
2. Subject has abnormal liver test parameters: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 10-fold the upper limit of normal (ULN).
3. Subject has severe hepatic impairment due to a history of chronic cirrhosis (Child-Pugh score > 9).
4. Subject has received more than 48 hours of non-echinocandin antifungal therapy for the treatment of invasive candidiasis (including candidemia) within 96 hours preceding initiation of IV echinocandin.
   Exception: Receipt of antifungal therapy to which any *Candida* spp. isolated in qualifying culture is not susceptible.
5. Baseline QTcF ≥ 500 msec, history or family history of Torsades de Pointes or other conditions that would put the subject at undue risk for development of ventricular arrythmias (including Torsades de Pointes).

STUDY DRUGS:

The study drugs administered for the double-blinded oral treatment component of the study will be provided by the Sponsor and will consist of oral ibrexafungerp (250 mg tablets and matching placebo tablets) and oral fluconazole (200 mg tablets or capsules and matching placebo tablets or capsules). Ibrexafungerp (250 mg tablets) required for administration during the open-label oral treatment component will be provided by the sponsor.

STUDY TREATMENTS

Study Treatment Groups

All randomized subjects will receive IV echinocandin therapy followed by step-down blinded oral treatment or, in case of isolates non-susceptible to fluconazole either open label ibrexafungerp or other BAT. Subjects will be invited to participate in the study and asked to sign the informed consent form either prior to or while they are receiving an IV echinocandin. Randomization will occur as soon as the subject is confirmed to meet eligibility criteria.

Eligible subjects will be randomized at a 1:1 ratio to one of two treatment regimens:

- IV echinocandin followed by oral ibrexafungerp, or
- IV echinocandin followed by oral fluconazole or BAT.

Open-Label IV Component

The IV component of the study treatment for both study groups will consist of IV echinocandin (caspofungin, micafungin or anidulafungin) given in an open-label fashion and as per local label instructions. Subjects will receive IV echinocandin treatment until the criteria for switching to oral antifungal treatment are met. The switch from IV echinocandin to oral antifungal should occur as soon as the criteria for switching is met and ideally within 5 days of start of the IV echinocandin. While on IV echinocandin, subjects should be assessed daily to determine if they meet the criteria for step-down therapy. For subjects enrolled with candidemia, at least one post-baseline culture should be collected during IV echinocandin treatment.

Switch to Oral Therapy

Unless there is a documented reason why switching to oral therapy is not adequate for the subject, subjects should be switched to the randomly assigned oral study drug as soon as:

- They are clinically stable (e.g. no worsening of signs and symptoms associated with invasive candidiasis).
- They are able to tolerate oral medication.
- They are hemodynamically stable (i.e. do not require use of vasopressors).
- Blood cultures should be negative for at least 48 hours (patients with candidemia).
- The *Candida* species causing the infection is known.
- They have no mucositis or GvHD affecting the gut with severity > Grade 3.

Subjects with Isolates Assumed or Known Susceptible to Fluconazole – Switch to Double-Blinded Arm Oral Therapy (Group 1)

Subjects harboring an infection caused by *Candida* species commonly susceptible to fluconazole (e.g., *C. albicans, C. tropicalis, C. parapsilosis*, etc.) will receive antifungal treatment with either oral ibrexafungerp or oral fluconazole, depending on the treatment strategy that they were randomized to in a double-blind, double-dummy fashion.

The oral component of the study treatment will consist of one of the following:

- Ibrexafungerp Group: oral ibrexafungerp 750 mg BID (twice daily; total daily dose = 1500 mg) on Days 1 and 2, followed by oral ibrexafungerp 750 mg QD (once daily; total daily dose = 750 mg) from Day 3 onwards + placebo matching fluconazole, or
- Fluconazole Group: loading dose of 800 mg QD Day 1, followed by 400 mg QD from Day 2 onwards. This may be adjusted at 12 mg/kg (loading dose) and 6 mg/kg (maintenance dose) rounded to the closest 200 mg for underweight or overweight subjects (e.g., for a 70 kg person, the daily dose will be ~ 400 mg QD) + placebo matching ibrexafungerp.
  For subjects with renal impairment, the fluconazole dose adjustments in the table below are recommended per fluconazole label.

Creatine clearance (ml/min)	Percent of recommended dose
>50	100%
≤50 (no dialysis)	50%
Regular dialysis	100% after each dialysis 50% on non-dialysis days

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance in adults:

Males: $\frac{\text{Weight (kg) x (140-age)}}{\text{72 x serum creatinine (mg/100 mL)}}$

Females: 0.85 x value obtained by above formula

The IV echinocandin will be discontinued upon initiation of oral study drug. The study drug should be initiated within 24 hours after the last administration of IV echinocandin.

Subjects will receive systemic antifungal treatment (including both the IV and oral components of the treatment) for approximately 14 days to 6 weeks.

Subjects with Isolates Non-Susceptible to Fluconazole – Open-Label Arm (Group 2)

When subjects with infections due to *Candida* species that are frequently not susceptible to fluconazole (i.e., *C. auris, C. krusei, C. glabrata*) or other *Candida* spp. isolates with documented non-susceptibility to fluconazole based on minimum inhibitory concentration (MIC) determination, or subjects with breakthrough infections whilst receiving azole prophylaxis treatment meet criteria for switching to oral antifungal therapy, their randomization assignment will be unblinded and they will receive either open-label oral ibrexafungerp or open label BAT, according to the initial randomly assigned treatment regimen.

If after randomization, the baseline *Candida* isolate (collected prior to randomization) is identified as being not-susceptible to fluconazole (e.g., *Candida albicans* with a fluconazole MIC ≥ 8 µg/mL), the subject will be discontinued from the Double-Blinded Arm and will be transferred to the Open-Label Arm offering open-label oral ibrexafungerp or BAT, according to their original randomization schedule. Subjects randomized to double-blind ibrexafungerp would be transferred to open-label ibrexafungerp, subjects randomized to double-blind fluconazole would be transferred to open-label BAT. BAT should be administered in accordance with the locally approved label for the applicable drug.

STUDY BLINDING, RANDOMIZATION AND STRATIFICATION:

Group 1

This arm is a randomized, double-blind, double-dummy study. All subjects, sponsor personnel, and study team members will be blinded to treatment assignments.

Due to the different dosing schedules and number of tablets/capsules needed for both oral ibrexafungerp and fluconazole treatment, subjects will receive active and matching placebo tablets/capsules in a double-dummy fashion to maintain treatment blinding.

Group 2

Due to the variable nature of BAT for subjects with non-susceptible fluconazole isolates, a double-blind approach is not logistically feasible.

The Data Review Committee will be blinded to any study drug assignment for both Group 1 and Group 2 subjects.

A total of approximately 220 subjects will be randomly assigned at a 1:1 ratio to one of the two study treatment groups (110 per treatment group). Randomization of subjects will be managed electronically through an Interactive Web Response System (IWRS).

Subjects will be stratified according to geographic region (North America-Europe, China and Other), scores on the Acute Physiology and Chronic Health Evaluation (APACHE II) instrument (≤ 20 or > 20) and absolute neutrophil count (≤ 500 or > 500 per cubic millimeter) at Day 1 (1st dose of IV echinocandin) or closest day prior to Day 1. Randomization will be performed in centrally balanced, permuted blocks within each stratum in a 1:1 ratio.

STUDY EVALUATIONS

Efficacy Procedures

- Targeted physical examination to evaluate the signs and symptoms of infection.
- Mycological testing including blood cultures, cultures of non-blood sites of infection.
- Radiological assessments for qualifying invasive candidiasis.
- Survival (collected as ACM).
- Assessment of Clinical Response, Mycological Response and Global Response.
- Assessment of Recurrence or Emergent Infections.

Pharmacokinetic Procedures:

Blood samples for PK analysis of ibrexafungerp in plasma will be collected from subjects who provide consent to participate in the PK sampling. Up to 7 blood samples may be collected at the following visits and sampling windows: Oral Days 1 and 2 (one sample collected between 3-6 hours after either the 1st or 2nd daily dose), Oral Day 7 (one sample collected before dosing and one sample 3-6 hours after dosing) and one sample collected 36 to 60 hours after the last dose, when feasible. Additional blood PK samples will be collected on Day 14 and Day 30 before dosing for subjects still receiving study treatment or when clinically indicated.

Safety Procedures:

Safety will be evaluated throughout the study by complete physical examinations, vital signs and temperature, clinical safety laboratory assessments and monitoring of AEs.

STATISTICAL ANALYSIS

Sample Size Determination

This trial will randomize approximately 220 subjects into one of two treatment regimens at a 1:1 ratio. A sample size of 110 subjects per treatment group will provide > 90% power (two-sided $\alpha = 0.05$) to declare non-inferiority (within a 20% non-inferiority margin [NIM]) of IV echinocandin followed by oral ibrexafungerp compared to IV echinocandin followed by oral fluconazole assuming a true 30-day ACM rate of 27% in both treatment groups. IV echinocandin followed by ibrexafungerp will be considered non-inferior to IV echinocandin followed by oral fluconazole if the upper limit of the 2-sided 95% CI for the difference in response rates between ibrexafungerp and fluconazole is less than 20%.

Analysis Populations

The populations for the study are:

- Intent-to-Treat (ITT) Population: The ITT Population will include all randomized subjects. This will be the population for the primary endpoint.
- Modified Intent-to-Treat (MITT) Population: The MITT Population will include all subjects from the ITT population who received oral step-down therapy.
- Fluconazole Susceptible (FS-MITT) Population: The FS-MITT population will include all subjects in the MITT population who are treated under the double-blinded portion of the study.
- Fluconazole Non-Susceptible (FN-MITT) Population: The FN-MITT population will include all subjects in the MITT population who received open-label step-down therapy.
- Per-protocol (PP) Population: The PP population will include all subjects in the ITT population who meet key inclusion and exclusion criteria and do not have major protocol deviations.
- PK Population: The PK population will include all enrolled subjects who provide at least one PK sample and no deviations significant enough to affect the interpretability of PK data.
- Safety Population: The Safety Population will include all subjects who receive at least one dose of on-study antifungal treatment (either IV or oral).

Efficacy Analyses

Efficacy will be assessed primarily in terms of ACM. In addition, Global Response (primary for EU only), Clinical Response, Mycological Response, absence of recurrence, and survival with no recurrence will also be assessed. The primary analysis will be conducted in the ITT population.

All-Cause Mortality

ACM will be defined as death during the prespecified period of evaluation, regardless of attribution. Subject status (alive or deceased) as well as date of death will be documented. If the subject is deceased, the investigator's assessed relationship to the fungal infection will also be recorded. If an autopsy is conducted, key findings should be collected in the eCRF.

Recurrence

Recurrence is defined as a diagnosis of invasive candidiasis and/or candidemia in subjects who previously achieved a Successful Global Response. Recurrence of the *Candida* infection is required to be with the same species and involving the same site that was initially identified at Screening. The DRC will be responsible for determining recurrence.

Treatment Outcome (Clinical Response, Mycological Response, Radiological Response, and Global Response)

Treatment outcome will be assessed as follows:

Clinical Response

Success:

- Resolution of all attributable clinical symptoms and physical findings.
- Partial resolution of attributable clinical symptoms and physical findings.

Failure:

- No resolution of any attributable clinical symptoms and physical findings and/or worsening, including subjects requiring any other systemic antifungal agent due to worsening after stepping down to the assigned oral antifungal.
- Not done or missing.

(Alternative approaches to handling missing data and intercurrent events will be specified in the SAP).

Mycological Response (by the DRC)

Success: Mycological response as defined by Eradication or Presumed Eradication

- Eradication: clearance of *Candida* from the bloodstream or invasive candidiasis source (clearance for candidemia is defined as 2 negative blood cultures drawn at least 24 hours apart).
- Presumed Eradication: subjects who have no follow-up cultures available but who have a clinical outcome of Success (i.e., improved based on objective, non-culture related parameters (e.g. clinical signs and symptoms or radiological findings).

Failure: Mycological response as defined by Persistence or Presumed Persistence

- Persistence: Persistent isolation of *Candida* species from blood specimens or specimens from other sterile sites.
- Presumed Persistence: subjects who have no follow-up cultures available but who have a clinical outcome of failure.

Radiological Response for qualified infections (by the DRC)

Success:

- Complete resolution of attributable radiological findings.
- Partial resolution of attributable radiological findings (e.g., remaining findings not indicative of progressive or active infection).

Failure:

- No resolution of any attributable radiological findings and/or worsening.

Note: Missing radiological outcomes will not be considered failures if the clinical and mycological outcomes are successful.

Global Response

Success: Defined as Successful Clinical Response plus Successful Mycological Response plus Successful Radiological Response (when applicable) and did not receive alternative (rescue)

antifungal therapy for invasive candidiasis or candidemia treatment initiated within 48 hours of Day 30 or EOT visits or any time prior to FU timepoints.

Failure: All subjects that did not meet criteria for success.

Primary Efficacy Analysis

The primary efficacy variable for the study is the percentage of subjects with 30-day ACM. The primary efficacy assessment will be performed for the ITT population. Sensitivity analyses will also be conducted for the MITT, FS-MITT, FN-MITT, and PP Populations. Other sensitivity analyses will be specified in the SAP. To assess non-inferiority, an estimate of the difference in mortality rates will be calculated along with a 95% confidence using the method of Mietinnen and Nurminen. Intravenous echinocandin followed by ibrexafungerp will be considered noninferior to IV echinocandin followed by oral fluconazole if the upper limit of the 2-sided 95% CI for the difference in response rates between the ibrexafungerp group and the fluconazole group is less than 20%. If non-inferiority is concluded, an assessment of superiority will also be performed. Superiority will be concluded if the entire 95% confidence interval is below zero. A logistic regression analysis may be performed to identify predictors of mortality. Point estimates and the corresponding 95% confidence intervals for the odds ratios for the identified risk factors may also be calculated.

Survival will also be summarized by treatment group using Kaplan-Meier plots.

Secondary Efficacy Analysis

All categorical secondary efficacy variables will be analyzed using the same approach as for the primary efficacy variable where appropriate. The secondary efficacy assessment will be performed for the ITT, MITT, FS-MITT, FN-MITT, and PP Populations.

Pharmacokinetics

The PK analyses will be performed for the PK population. For the subset of subjects undergoing PK analysis, sparse PK samples collected during treatment (Oral Days 1, 2, 7 and 36 to 60 hours after the last dose) will be analyzed by Population PK (Pop PK) analysis using NONMEM to estimate PK parameters [e.g. maximum concentration (C_{max}) and area under the concentration-time curve (AUC)]. Additional PK samples will be collected on Study Days 14 and 30 for subjects still receiving study treatment. A stand-alone Population PK report will be prepared to describe the PK analyses from this part of the study.

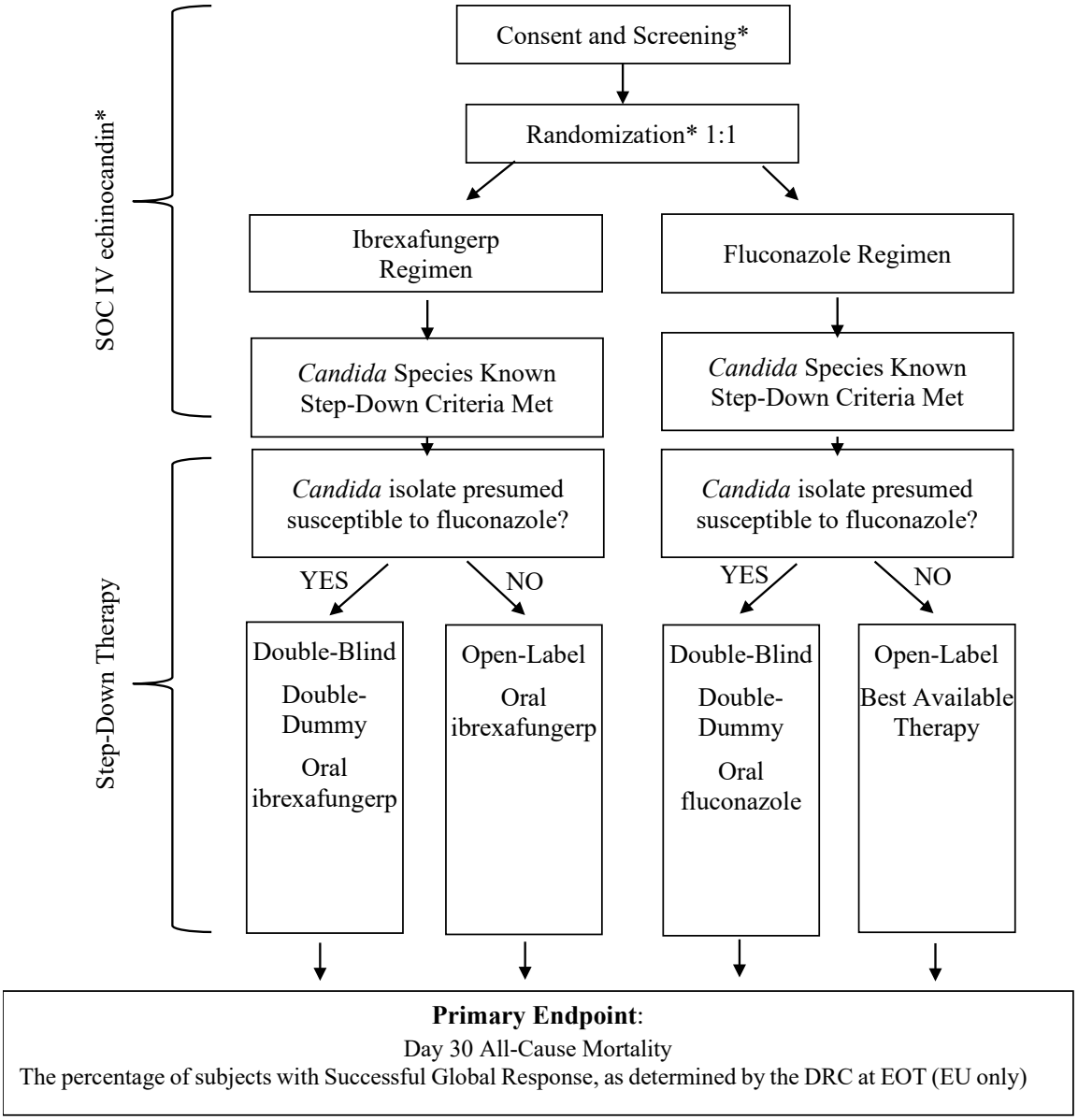
Safety

The safety analysis will be performed for the Safety Population.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class, preferred term and treatment group, and ordered by decreasing frequency for all subjects. Separate tabulations will list events according to seriousness, severity, and possible association with investigational therapy, if applicable. Subjects who discontinued treatment because of AEs and those who had a serious AE will be summarized.

Clinical laboratory data will be summarized using descriptive statistics and shifts from baseline (with categories for below, within, and above the normal range). Vital signs and body weight will also be summarized. Results will be summarized for each timepoint and for changes in each variable from baseline.

5.0 Schematic of Study Design



*Consent and Randomization may occur after subject has begun IV echinocandin.

6.0 Background Information and Scientific Rationale:

6.1 Background Information

Ibrexafungerp (formerly "SCY-078") is a member of a new class of antifungal agents, the triterpenoids. It is a semi-synthetic triterpene derivative of the natural product enfumafungin. Ibrexafungerp is a structurally distinct glucan synthesis inhibitor (GSI) that inhibits the synthesis of the fungal cell wall polymer β-(1,3)-D-glucan. Time-kill studies have demonstrated that ibrexafungerp has fungicidal *in vitro* activity against *Candida* spp. isolates similar to that observed with the echinocandins.

Ibrexafungerp is being developed as the first oral and intravenous (IV) GSI for the treatment and prevention of fungal diseases caused by *Candida*, *Aspergillus* and other fungal species with the potential to provide the therapeutic advantages of both an IV and oral formulation.

While four classes of antifungal agents are currently available to treat these infections, only flucytosine and azoles are available for oral therapy. Concerns about flucytosine toxicity and rapid emergence of resistance on therapy limits its use in candidiasis. The emergence of resistance to azoles and, more recently, to echinocandins and the toxicity associated with polyenes signals the need for new agents that are well tolerated and that retain activity against resistant strains.

The echinocandins are fungicidal against *Candida* compared to triazoles that are fungistatic and have consistently demonstrated better outcomes when used for initial treatment.[1,2] Like the echinocandins, ibrexafungerp is fungicidal and blocks the same enzyme, beta glucan synthase, although likely at a different binding site. Ibrexafungerp retains activity *in vitro* and *in vivo* against both azole-resistant and the majority of clinical isolates containing *FKS* gene mutations, which confer echinocandin resistance.

Unlike echinocandins, ibrexafungerp is orally bioavailable. With demonstrated *in vitro* and *in vivo* activity against *Candida* spp., *Aspergillus* spp. and other fungal genera, ibrexafungerp would represent the first oral non-azole treatment alternative for these infections.

Fungal diseases caused by *Candida* spp., *Aspergillus* spp., *Pneumocystis*, dimorphic fungi, etc., represent a growing threat, particularly to patients with compromised immune systems. Invasive fungal diseases caused by *Candida* and *Aspergillus* species are of principal concern. *Candida* is the most common cause of health care-associated bloodstream fungal infections in the United States and is estimated to result in an additional 3 to 13 days of hospitalization.[3,4] The overall mortality rate of invasive candidiasis remains ~ 30% despite therapy. The Centers for Disease Control and Prevention (CDC) surveillance data have reported that approximately 7% of all *Candida* bloodstream isolates tested are resistant to fluconazole and some *Candida* strains are increasingly resistant to first-line and second-line antifungal treatment agents, including azoles and echinocandins.[5] Centers specialized in the treatment of immune-compromised patients report increased frequency of non-*albicans* species of *Candida* with higher incidence of resistance. For example, in a survey conducted at the MD Anderson Cancer Center, Houston, Texas, U.S. (2005–

2013), out of 146 isolates of *C. glabrata* evaluated, 30 (20.5%) were resistant to fluconazole, 15 (10.3%) to caspofungin, and 10 (6.8%) to multiple drugs.[6] Roughly, 30% of patients with bloodstream infections (candidemia) due to drug-resistant *Candida* die during their hospitalization.

Antifungal activity

The spectrum and potency of activity of ibrexafungerp has been evaluated by numerous independent laboratories against an extensive panel of clinically relevant yeast and mold isolates using the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) methods. Overall, the epidemiological studies have demonstrated that ibrexafungerp has potent, broad-spectrum activity against the majority of the clinical isolates tested. These studies have laid the foundation in support of the use of ibrexafungerp for the treatment of invasive fungal diseases.

Activity against *Candida* spp.

Ibrexafungerp has been evaluated against >2000 *Candida* isolates, including all clinically relevant species, more than 600 *C. glabrata* isolates and more than 400 *C. auris* isolates. These *in vitro* studies have demonstrated the broad range of anti-*Candida* spectrum of activity of ibrexafungerp. Additionally, ibrexafungerp demonstrated *in vitro* activity against pre-formed biofilms, which is a relevant feature when addressing catheter-related *Candida* infections. Studies conducted with azole- and echinocandin-resistant strains have shown that ibrexafungerp retains activity (i.e., no significant change in minimum inhibitory concentration [MIC] when compared to wild type) against >90% of azole-resistant strains and >70% of *Candida* strains with *FKS* mutations commonly associated with echinocandin resistance. Interestingly, although ibrexafungerp and the echinocandins share a similar mechanism of action (β-[1,3]-D-glucan synthesis inhibition), their clearly different molecular structure provides them with some differentiating characteristics in terms of microbiological activity.

Ibrexafungerp was evaluated *in vitro* against approximately 190 clinical isolates of echinocandin-resistant strains of *Candida* spp., with most isolates having mutations in the *FKS* gene. Overall, ibrexafungerp was active against the majority of the echinocandin-resistant strains tested. Significantly, ibrexafungerp was active against approximately 70% of the isolates containing the most commonly reported *FKS* mutation associated with echinocandin resistance in *C. glabrata* (S663P in *FKS2* and S645P in *FKS1*). Selection of ibrexafungerp resistance *in vitro* occurs at a low frequency. A deletion at position F659 in *FKS2* of *C. glabrata* was the predominant mutation observed in these studies; notably, ibrexafungerp did not select for mutations at positions S663 or S645. These results suggest that ibrexafungerp inhibits glucan synthase in a manner different from that of echinocandins.

The *in vitro* studies also included a number of multidrug-resistant isolates. Consistent with the data described above, ibrexafungerp was active against >70% of these isolates. Ibrexafungerp has also demonstrated activity against life-threatening and multidrug-resistant *C. auris* strains recently

highlighted as an urgent threat by the CDC due to the global emergence of this fungal disease with limited therapeutic options and high mortality. In recent studies, ibrexafungerp demonstrated potent *in vitro* activity against >400 different *C. auris* isolates and results showed potent activity of ibrexafungerp against all strains at concentrations indicative of potential clinically-relevant effect.[7]

While the majority of surveillance and resistance studies included isolates obtained from patients with invasive infections, ibrexafungerp demonstrated potent activity against vaginal *Candida* isolates and was also shown to be active against pre-formed biofilms *in vitro*.

Non-clinical models of invasive fungal diseases

The antifungal efficacy of ibrexafungerp has been evaluated in several murine models of disseminated candidiasis and aspergillosis. In a disseminated *C. albicans* model, ibrexafungerp was more active than fluconazole at all doses. The plasma area under the concentration-time curve (AUC) necessary to achieve target efficacy in these models was estimated to be 15.4 ± 2.2 μM•h (11.2 μg•hr.mL). Murine models of ibrexafungerp in disseminated candidiasis caused by *C. glabrata*, *C. auris,* and *C. tropicalis* indicated activity across multiple *Candida* species.

The penetration of ibrexafungerp at the site of infection in a mouse model of intraabdominal candidiasis was evaluated. Mice were infected intraperitoneally (IP) with *C. albicans* (SC5314) in a sterile stool matrix. To evaluate tissue penetration, a single oral dose of ibrexafungerp (30mg/kg) or a single IP dose of micafungin (5 mg/kg) was administered to mice on day 3 post-inoculation. To evaluate the effects of repeated dosing, mice were treated with 2 days of ibrexafungerp (15 mg/kg, BID) or micafungin (5 mg/kg, QD), and drug accumulation was analyzed at 24, 48, and 72 hours after the last dose. The results of this study indicated that ibrexafungerp rapidly distributed into tissues after a single dose and efficiently accumulated within the lesions. Concentrations of ibrexafungerp within the necrotic center of the liver abscesses were nearly 100-fold higher than the corresponding serum concentrations. Robust and long-lasting lesion penetration of ibrexafungerp was observed after two days of treatment, with ibrexafungerp being retained within necrotic core at 48 and 72 hours after the last dose. In comparison, micafungin concentration within lesions was low at 48 hours and completely undetectable at 72 hours after two days therapy.

Preclinical safety

In pregnant rabbits, oral ibrexafungerp administered during pregnancy was associated with fetal malformations at exposures generally greater than the estimated human exposure at the intended doses in this study. Oral ibrexafungerp administered to pregnant rats during pregnancy was not associated with fetal harm. The potential significance of these observations in rabbits to humans is not known. However, as a precaution, ibrexafungerp should not be used in pregnancy because it may cause fetal harm.

Long-term toxicology studies have been conducted in rats and dogs. In the six-month study in rats, no new toxicities or target organs of toxicity were identified (compared to the results of the shorter-term studies). Daily administration of oral ibrexafungerp for 26 weeks in rats, at the highest dose was associated with marked, but reversible, lung, stomach lining, and peripheral nerve abnormalities. The potential significance of these observations in rats to humans is not known. The no-observed-adverse-effect-level (NOAEL) was established at 40 mg/kg, a dose which corresponds to an $AUC_{0\text{-}24}$ on Day 182 of 80500 ng•hr/mL (males and females combined). This exposure provides an animal-to-human multiple of approximately 3-fold, relative to the human exposure of 28160 ng•hr/ml from the dosing regimen where ibrexafungerp is given at 750 mg BID for two days followed by 750 mg QD thereafter in healthy volunteers.

Likewise in the nine-month study in dogs, no new toxicities or target organs of toxicity were identified (compared to the results of the shorter-term studies), and the NOAEL was established at 100 mg/kg, a dose which corresponds to an $AUC_{0\text{-}24}$ on Day 273 of 36400 ng•hr/mL (males and females combined). This exposure provides an animal-to-human multiple of approximately 1.3-fold relative to the exposure to humans.

The data available from all of the *in vitro* and *in vivo* studies conducted to date provide significant support for the use of ibrexafungerp in the treatment of invasive fungal diseases.

Clinical experience

To date, approximately 1495 subjects (420 healthy subjects and 16 subjects with liver impairment in Phase 1 studies without any underlying fungal indication and 1059 subjects with invasive pulmonary aspergillosis, candidiasis or VVC in phase 1, 2 and 3 studies) have been exposed to ibrexafungerp in 31 clinical trials.

Ibrexafungerp was generally well tolerated following single oral doses of up to 1600 mg and multiple oral doses of up to 800 mg/day for 28 consecutive days in Phase 1 studies. Reported adverse events (AEs) after oral administration have been generally transient and primarily mild to moderate in intensity. The most frequently reported AEs have been mild gastrointestinal events (nausea, vomiting, diarrhea and abdominal pain).

A Phase 2 study of oral ibrexafungerp as step-down therapy from IV echinocandin in patients with invasive candidiasis has been completed. This was a multicenter, randomized, open-label study in which, following three to ten days of IV echinocandin therapy, 21 subjects received either

ibrexafungerp 500 mg QD with a 1000 mg loading dose (6 patients), ibrexafungerp 750 mg QD with a 1250 mg loading dose (7 patients) or standard of care (SOC) treatment (8 patients with either oral fluconazole 400 mg QD with an 800 mg loading dose or IV micafungin 100 mg QD for up to 28 days). Ibrexafungerp was well tolerated in this study with an AE profile typical of this population and comparable to the SOC. The results from this study also indicated that the higher dose of ibrexafungerp tested (750 mg QD) is predicted to achieve the target exposure at steady state in the majority of patients.

A preliminary efficacy review of the 74 subjects who completed therapy under Protocol SCY-078-301, a Phase 3 study of open-label oral ibrexafungerp in patients with refractory invasive fungal diseases, was conducted by an external expert panel (Data Review Committee, DRC). These 74 patients suffered from a variety of conditions, including esophageal candidiasis, intra-abdominal abscesses, spondylodiscitis and oropharyngeal candidiasis, with the most common fungal species being *C. glabrata*, *C. krusei*, and *C. albicans*. Ibrexafungerp treatment ranged from seven to 90 days. Per DRC evaluation at end of treatment, 46 patients achieved a Complete or Partial Global Response and 18 patients a stable-disease response. Only 6 patients showed no response, and 4 patients' outcomes were considered indeterminate.

In another open-label study evaluating the efficacy of oral ibrexafungerp in patients with *Candida auris* infection, Protocol SCY-078-305. The outcome of 10 completed patients in study SCY-078-305 was recently assessed. Analysis found that 80% (8 out 10) patients experienced a complete response, and one patient died of an underlying condition unrelated to the treatment and one patient was considered indeterminate.

Two cases with significant elevation of hepatic enzymes [one was a serious adverse reaction (SAR)] have been reported in the clinical development program, both events resolved without intervention. Similarly, two SARs of acute kidney injury (AKI) have been reported. The association of hepatic dysfunction and AKI with ibrexafungerp is however not proven and there is no preclinical data to indicate an association either. Hepatic and renal function are being monitored in the study. Two SAEs of hallucinations and two SAEs of pneumonitis have been reported from clinical trial programs. Hallucinations and Pneumonitis were considered as potential risks requiring monitoring.

Available data on ibrexafungerp use in pregnant women are insufficient to draw conclusions about any drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Women of childbearing potential are required to use two approved contraceptive methods as described in the protocol and informed consent document.

Ibrexafungerp has the potential to be an important addition to the anti-fungal treatment arsenal by providing potent activity against the full spectrum of *Candida* species, including difficult to treat organisms, and affording the added flexibility of oral step-down and earlier hospital discharge.

For additional information on ibrexafungerp, please refer to the Investigator's Brochure (IB).

6.2 Rationale for the Study

The primary objective of the study is to demonstrate that treatment of Invasive Candidiasis/ Candidemia with intravenous (IV) echinocandin followed by oral ibrexafungerp is non-inferior to IV echinocandin followed by oral fluconazole (or BAT).

Rationale for Study Population

The study population will consist of subjects with invasive candidiasis and/or candidemia, defined as evidence of *Candida* in either a bloodstream or tissue culture from a normally sterile site accompanied by related clinical signs and symptoms. This population is considered adequate to evaluate the effect of an antifungal treatment regimen.

Rationale for IV Treatments Administered and IV Treatment Duration

IV echinocandins (anidulafungin, caspofungin, or micafungin) will be administered as per local label instructions. To allow the participation of institutions with different standard local practices in terms of echinocandin choice, either micafungin, caspofungin, or anidulafungin will be allowed in the study, as they all have demonstrated comparable activity in previous trials and most hospitals have only one on formulary.[8]

In a study by Vazquez et al. (2014), a shorter duration of IV echinocandin of 5 days was shown to have similar response rates when compared to a standard, longer IV infusion strategy prior to oral switch in patients that met prespecified criteria.[9] In recent years, the rapid de-escalation from an echinocandin to oral therapy (azoles) as soon as possible, has become the standard of care in many institutions[10]. Further shortening of the intravenous therapy duration before transition to oral therapy, if specific parameters are met, is justified to further simplify treatment and reduce costs of treatment without loss of efficacy. Consequently, a 5 day cumulative echinocandin treatment may suffice for subjects to be switched to the step-down oral antifungal therapy if specific parameters are met, e.g., as soon as the subject is clinically stable, is able to tolerate oral medication, is hemodynamically stable (i.e., does not require vasopressors), blood cultures should be negative for at least 48 hours (candidemia), the *Candida* species causing the infection is known, and they have no mucositis or GvHD affecting the gut with severity > Grade 3.

Rationale for Oral Therapy

The proposed oral comparator for this study, fluconazole, is consistent with current treatment guidelines.[11] Subjects who have isolates that are frequently not susceptible to fluconazole including all *C. glabrata, C. krusei,* and *C. auris* isolates, or other *Candida* spp. isolates with documented non-susceptibility to fluconazole based on MIC determination, will be treated in an open-label arm with open-label ibrexafungerp at the same dosing regimen given to subjects who participate in the double-blind arm or BAT.

Oral fluconazole will be administered as per recommended dose for this indication (loading dose of 800 mg QD Day 1, followed by 400 mg QD from Day 2 onwards. This may be adjusted at 6 mg/kg rounded to the closest 200 mg for underweight or overweight subjects). Oral ibrexafungerp

will be given as 750 mg BID (total daily dose = 1500 mg) on Days 1 and 2, followed by oral ibrexafungerp 750 mg QD (total daily dose = 750 mg) from Day 3 onwards.

Ibrexafungerp: Based on the cumulative *in vivo* animal efficacy data and animal and human safety data, the target plasma exposure for clinical efficacy in invasive candidiasis is 15.4 μM•hr (11.2 μg•hr/mL). This exposure has been well tolerated in toxicology pre-clinical studies as well as in clinical trials. A simulation using a population PK model was performed based on pooled data from healthy volunteers and patients. This simulation was used to predict the percentage of patients with AUCs greater than or equal to this target exposure and the simulated plasma time course of the planned oral dosing regimen for ibrexafungerp, which consists of a two-day loading dose regimen of 750 mg BID administered on Day 1 and Day 2 followed by an oral maintenance dose of 750 mg QD starting on Day 3. The results of the simulation indicate that ibrexafungerp given 750 mg BID for two days followed by 750 mg QD results in over 80% of the population reaching or exceeding the exposure target of $AUC_{0\text{-}24} \geq 11.2$ μg•hr/mL. The exposure achieved by this dose regimen was further confirmed in a Phase 1 study (SCY-078-111) in 16 healthy volunteers in which oral ibrexafungerp was administered at doses of 750 mg BID on Days 1 and 2 followed by 750 mg QD on Days 3 – 7. The geometric mean $AUC_{0\text{-}24}$ on Day 1 was 16 μg•hr/mL, indicating that target exposures were achieved within the first day. In the same study, steady state was reported by Day 4 and the $AUC_{0\text{-}24}$ on Day 7 was 28 μg•hr/mL, urine concentrations of ibrexafungerp of 10 of 16 subjects were above 0.5 μg /mL at Day 7.

Additionally, based on a simulation using the population PK model, ibrexafungerp can be administered as 750 mg BID on Day 1 and Day 2 followed by 375 mg BID starting on Day 3. This alternative dosing regimen results in the same exposure (AUC) and C_{avg} with a minor reduction in C_{max}, in comparison to the primary dosing regimen described above. This dose regimen adjustment (375 mg BID) will be allowed in the study in case of moderate to severe nausea associated with the 750mg QD regimen.

Rationale for Study Endpoints

The primary efficacy endpoint of the study is ACM at Day 30. This objective criterion has been previously used to evaluate the treatment effect of antifungal agents in invasive fungal diseases. Global Response was selected as primary endpoint for EU only based on European Medicines Agency (EMA) feedback. Per EMA, Global Response at end of treatment is the preferred primary endpoint, considering that ACM can be influenced by the underlying condition.

Secondary efficacy endpoints include Global Response, Clinical Response and Mycological Response at several timepoints (Day 14, EOT, Day 30) as determined by a DRC. The assessment of Clinical, Mycological and Global responses are well-recognized criteria often used to assess the efficacy of antifungal therapies in invasive candidiasis setting.

These endpoints are considered adequate to demonstrate the non-inferiority of the IV echinocandin followed by oral ibrexafungerp treatment strategy when compared against the current SOC treatment (IV echinocandin followed by oral fluconazole) in this patient population.

7.0 Study Objectives

7.1 Primary Objective

To demonstrate that treatment of Invasive Candidiasis/Candidemia with IV echinocandin followed by oral ibrexafungerp is non-inferior to IV echinocandin followed by oral fluconazole (or BAT).

7.2 Key Secondary Objective

To demonstrate that treatment of Invasive Candidiasis/Candidemia with IV echinocandin followed by oral ibrexafungerp is non-inferior to IV echinocandin followed by oral fluconazole (or BAT) based on Global Response (clinical, radiological and mycological response, as confirmed by the Data Review Committee [DRC]) at Day 14.

7.3 Other Secondary Objectives

- To compare the efficacy of the treatment regimens, based on:
  - Global Response at Day 30 and End of Therapy (EOT) as determined by the PI and Data Review Committee (DRC),
  - Clinical Response as determined by the PI and DRC,
  - Mycological Response as determined by the DRC,
  - No recurrence as determined by the DRC, and
  - Fungal-free survival as determined by the DRC.
- To evaluate the safety of the regimens.
- To evaluate the pharmacokinetics (PK) of ibrexafungerp.

8.0 Study Endpoints

8.1 Primary Endpoint

ACM at Day 30 in the ITT population.

The percentage of subjects with Successful Global Response, as determined by the DRC at EOT (EU only).

8.2 Key Secondary Endpoint

The percentage of subjects with Successful Global Response, as determined by the DRC (based on clinical response as determined by the PI, mycological response and radiological response [when applicable]) at Day 14.

8.3 Secondary Endpoints

Efficacy Endpoints

- The percentage of subjects with Successful Global Response at Day 30 and End of Treatment (EOT) as determined by the PI and the DRC.
- The percentage of subjects with Successful Clinical Response at Day 14, Day30 and EOT as determined by the PI and the DRC.
- The percentage of subjects with Successful Mycological Response at Day 14, Day30 and EOT as determined by the DRC.
- The percentage of subjects with no recurrence at 2 weeks and 6 weeks after EOT as determined by the DRC.
- The percentage of subjects alive with Successful Global Response at EOT and no recurrence at 6 weeks after EOT as determined by the DRC.

Safety Endpoints

Frequency of treatment-emergent adverse events (TEAEs), drug-related adverse events, discontinuations due to AEs, serious adverse events (SAEs), and safety laboratory assessments.

PK Endpoint

Description of ibrexafungerp plasma concentrations.

9.0 Study Design

9.1 Overall Description of the Study

This is a Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled, comparative study to evaluate the efficacy, safety, tolerability and pharmacokinetics of oral ibrexafungerp compared to oral fluconazole step-down treatment following IV echinocandin in the treatment of adult subjects (≥18 years old) with invasive candidiasis and/or candidemia.

Eligible subjects will receive treatment with an IV echinocandin and will then be switched to double-blind, double-dummy oral therapy (either ibrexafungerp or fluconazole) as soon as step-down criteria are met. It is anticipated that subjects may have received IV echinocandin prior to screening/randomization. The study will be conducted globally. Approximately 220 subjects (110 per treatment group) are planned to be randomized in the study.

Study Visits

Study Day 1 is the first day of IV echinocandin treatment and may occur before the Screening visit. The study will consist of a Screening visit which includes randomization [from 4 days prior to start of IV echinocandin, i.e. Day -4 to before end of IV echinocandin (EOIV)], an end of IV treatment (EOIV) visit, Oral Treatment Days 1 visit, Oral Treatment Days 2 and 7 visits (PK subset only), an end of antifungal treatment (EOT) visit, Day 14 and Day 30 visits (IV + Oral), a 2-Week FU visit (14 days after EOT) and a 6-Week FU visit (42 days after EOT). The EOIV and Oral

Treatment Day 1 should ideally occur on the same day. The Day 14 and Day 30 visits may occur before, on, or after EOT. Other study visits may also be combined if they occur on the same day or within the protocol specified window period. The 2-Week and 6-Week follow-up visits may be done telephonically, remotely or via home visits in accordance with local regulations and practicalities, except if an in person visit to the center is clinically indicated by adverse event screening, assessment of persistent or new signs and symptoms of invasive fungal disease, or to follow up on the course of the underlying disease. EOT is end of all protocol specified treatments, including IV and oral.

Subject Enrollment

Subjects with a diagnosis of candidemia and/or invasive candidiasis will be invited to participate in the study, either prior to or while they are receiving an IV echinocandin. After having signed an informed consent form, subjects will be assigned a study number. Following screening, subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized. Screening and randomization should occur as soon as possible after the diagnosis of candidemia and/or invasive candidiasis has been made. It is anticipated that most subjects may be on IV echinocandin at the time of randomization. However, randomization may occur before or after the initiation of IV echinocandin which is Study Day 1.

Study Treatments

All randomized subjects will receive IV echinocandin therapy followed by step-down treatment or other Best Available Therapy (BAT) as described below. Eligible subjects will be randomized to the Double-Blinded Arm at a 1:1 ratio to one of two treatment regimens: IV echinocandin followed by oral ibrexafungerp or IV echinocandin followed by oral fluconazole or BAT. The IV component of these treatment regimens will consist of an IV echinocandin (caspofungin, micafungin or anidulafungin administered as per local label instructions) given as open-label therapy while the oral component for randomized subjects with fluconazole susceptible isolates (ibrexafungerp or fluconazole) will be administered as double-blind, double-dummy treatment and subjects with fluconazole non-susceptible isolates will receive open-label oral ibrexafungerp or Best Available Therapy (BAT).

Randomization will occur as soon as eligibility has been confirmed. It is expected that the *Candida* species causing the infection is known prior to step-down. Subjects harboring an infection caused by *Candida* species commonly susceptible to fluconazole (e.g., *C. albicans*, *C. tropicalis*, *C. parapsilosis*, etc.) will be stepped down into the Double-Blinded Arm (ibrexafungerp or fluconazole depending on the treatment regimen they were randomized to).

Subjects with infections due to *Candida* species that are frequently not susceptible to fluconazole (i.e., *C. auris*, *C. krusei*, *C. glabrata*) or other *Candida* spp. isolates with documented non-susceptibility to fluconazole based on minimum inhibitory concentration (MIC) determination or subjects with breakthrough infections whilst receiving azole prophylaxis treatment will not be randomized into the Double-Blinded Arm but will receive either open-label oral ibrexafungerp or

open-label BAT after initial IV echinocandin therapy, according to their initial randomization study drug assignment.

If after randomization, the baseline *Candida* isolate (collected prior to randomization) is identified as being not-susceptible to fluconazole (e.g., *Candida albicans* with a fluconazole MIC ≥ 8 μg/mL), the subject will be discontinued from the Double-Blinded Arm and will be transferred to the Open-Label Arm offering open-label oral ibrexafungerp or BAT. Subjects randomized to double-blind ibrexafungerp would be transferred to open-label ibrexafungerp, subjects randomized to double-blind fluconazole would be transferred to open-label BAT.

Treatment Duration and Switch from IV to Oral Therapy

In line with current treatment guidelines, the antifungal treatment duration will depend on subjects' invasive candidiasis condition and response to therapy (e.g., for candidemia antifungal treatment should continue for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia) with an anticipated treatment duration ranging from 14 days to 6 weeks (IV plus oral treatment).

Subjects will receive IV echinocandin treatment until the criteria for switching to oral antifungal treatment are met.

The switch from IV echinocandin to oral antifungal should occur as soon as the criteria for switching is met (they are clinically stable, able to tolerate oral medication, are hemodynamically stable, blood cultures should be negative for at least 48 hours (candidemia), the *Candida* species is known, and no mucositis or GvHD affecting the gut with severity > Grade 3) and ideally within 5 days of start of the IV echinocandin. While on IV echinocandin, subjects should be assessed daily to determine if they meet the criteria for step-down therapy. For subjects enrolled with candidemia, at least one post-baseline culture should be collected during IV echinocandin treatment.

Study Assessments

The study will include efficacy, safety, tolerability and PK assessments. Efficacy will be assessed primarily in terms of ACM. In addition, Global Response (a composite assessment of clinical, radiological and mycological assessments, [primary for EU only]), Clinical Response, Mycological Response, absence of recurrence, and survival with no recurrence will also be assessed as secondary endpoints. Safety and tolerability will be assessed by including parameters such as physical examinations, vital signs, AEs and safety laboratory tests (hematology and blood chemistry). Blood samples will also be collected from consenting subjects for PK analysis.

The IDMC will review available, unblinded, safety data at least once a year during the conduct of the study i.e., from the first subject's enrollment in this study until the last subject has completed the safety follow-up visit, and when approximately 70% of subjects have completed the safety follow-up visit. Additional IDMC meetings may be held as required for safety data reviews. Details will be provided in the IDMC Charter.

9.2 Study Blinding, Randomization and Stratification

Group 1

This arm is a randomized, double-blind, double-dummy study. All subjects, sponsor personnel, and study team members will be blinded to treatment assignments.

Due to the different dosing schedules and number of tablets/capsules needed for both oral ibrexafungerp and fluconazole treatment, subjects will receive active and matching placebo tablets/capsules in a double-dummy fashion to maintain treatment blinding.

Group 2

Due to the variable nature of BAT for subjects with non-susceptible fluconazole isolates, a double-blind approach is not logistically feasible.

The Data Review Committee will be blinded to any study drug assignment for both Group 1 and Group 2 subjects.

A total of approximately 220 subjects will be randomly assigned at a 1:1 ratio to one of the two study treatment groups (110 per treatment group). Randomization of subjects will be managed electronically through an Interactive Web Response System (IWRS).

Subjects will be stratified according to geographic region (North America-Europe, China and Other), scores on the Acute Physiology and Chronic Health Evaluation (APACHE II) instrument (≤ 20 or > 20) and absolute neutrophil count (≤ 500 or > 500 per cubic millimeter) at Day 1 (1st dose of IV echinocandin) or closest day prior to Day 1. Randomization will be performed in centrally balanced, permuted blocks within each stratum in a 1:1 ratio.

10.0 Study Population

The study population will include adult subjects ≥ 18 years of age, with a diagnosis of invasive candidiasis (including candidemia).

10.1 Inclusion Criteria

Subjects must fulfill all of the following criteria at Screening to be eligible to participate in the study:

1. Subject is a male or female adult ≥ 18 years of age on the day the study informed consent is signed.
2. Subject has a diagnosis of candidemia and/or invasive candidiasis, defined as evidence of *Candida* spp. in **either** a bloodstream or tissue/fluid culture from a normally sterile site (excluding eye, cardiac and bone tissue, central nervous system or prosthetic device) collected within ± 4 days (96 hours) of initiation of IV echinocandin accompanied by any related clinical sign and/or symptom (e.g., fever [on one occasion > 38°C], hypotension, or local signs of inflammation, etc.).

3. Subject is willing to initiate or continue medical treatment to cure infections, which includes receiving antibiotics and undergoing surgical procedures, if required.
4. Female subjects of childbearing potential < 2 years post-menopausal must agree to and comply with using one barrier method (e.g., female condom with spermicide) plus one other highly effective method of birth control (Section 12.4), or sexual abstinence from signing the consent form until at least 7 days after end of treatment. Male subjects must be vasectomized, abstain from sexual intercourse, or agree to use barrier contraception (Section 12.4), and also agree not to donate sperm from signing the consent form until at least 7 days after end of treatment.
5. Subject and/or legal representative is able to understand and sign a written informed consent form (ICF), which must be obtained prior to treatment and any study-related procedures. Informed consent via electronic signature will be allowed (Exception for Germany - no subject who requires a legal representative, will be eligible for participation).
6. Subject and/or legal representative is able to understand and sign a consent or authorization form, which shall permit the use, disclosure and transfer of the subject's personal health information (e.g., in the United States Health Information Portability and Accountability Act Authorization form).
7. Subject and/or legal representative is able to understand and follow all study-related procedures including study drug administration.

10.2 Exclusion Criteria

A subject will be excluded from participation in the study if he or she meets <u>any</u> of the following exclusion criteria:

1. Subject has any of the following forms of invasive candidiasis at Screening:
   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.
   e. Chronic disseminated candidiasis.
   f. Urinary tract candidiasis due to ascending *Candida* infection secondary to unresolved obstruction or non-removeable device in the urinary tract.
   g. Patients with a sole diagnosis of mucocutaneous candidiasis, i.e., oropharyngeal, esophageal or genital candidiasis; or *Candida* lower urinary tract infection or *Candida* isolated solely from respiratory tract specimens.
   h. Patients with concurrent invasive fungal infection other than *Candida* spp., e.g., cryptococcosis, mold infection or endemic fungal infection.

i. Patients who failed a previous antifungal therapy for the same infection.

j. Subject has an uncontrolled fungal disease source (e.g., indwelling vascular catheter or device that cannot be removed or an abscess that cannot be drained) that is likely to be the source of the candidemia or invasive candidiasis.

2. Subject has abnormal liver test parameters: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 10-fold the upper limit of normal (ULN).
3. Subject has severe hepatic impairment due to a history of chronic cirrhosis (Child-Pugh score > 9).
4. Subject has received more than 48 hours of non-echinocandin antifungal therapy for the treatment of invasive candidiasis (including candidemia) within 96 hours preceding initiation of IV echinocandin.

   Exception: Receipt of antifungal therapy to which any *Candida* spp. isolated in qualifying culture is not susceptible.
5. Patients with baseline QTcF ≥ 500 msec, history or family history of Torsades de Pointes or other conditions that would put the subject at undue risk of development of ventricular arrhythmias (including Torsades de Pointes).
6. Subject is receiving or anticipates to require treatment with the prohibited medications (including prescription and over-the-counter medications, supplements, and herbal products) listed in Section 20.1 (Appendix A).
7. Subject has a known history of allergy, hypersensitivity or serious reaction to ibrexafungerp, any of the azole or echinocandin class of antifungal or to any of the components of the formulations.
8. Subject has received treatment with ibrexafungerp in a previous invasive fungal infection trial.
9. Subject is currently participating in another interventional treatment trial with an investigational agent, has participated in any other investigational study within 30 days (or within 5.5 half-lives of the investigational product, whichever is longer) before signing the ICF, or is using an investigational device at the time of Screening.
10. Subject has any other condition or laboratory abnormality evidencing a major organ system disease that, in the judgment of the PI, would put the subject at unacceptable risk for participation in the study or may interfere with the assessments included in the study.
11. Subject is an employee of SCYNEXIS, Inc., the investigator or the Contract Research Organization involved in the study, or is an immediate family member (partner, offspring, parent, sibling, or sibling's offspring) of an employee involved in the study.
12. Subject is unlikely to comply with protocol requirements.
13. Subject is expected to die from a non-infectious cause within 30 days from the day the study ICF is signed.
14. Subject is pregnant or breastfeeding or plans to become pregnant.

10.3 Discontinuation Criteria

A subject may be discontinued from the study or study drug for any of the following reasons:

- Withdrawal of consent by the subject or subject's legally acceptable representative
- Investigator or Sponsor decision that withdrawal is in the subject's best interest
- Occurrence of an AE that, in the opinion of the investigator, warrants discontinuation of the subject from the study drug
- Lost to follow-up (every attempt should be made to contact the subject)
- Elevations in liver function tests, confirmed by repeat tests (at least 72 hours apart), as follows (the medical monitor must be contacted to discuss these findings before discontinuation of study drug, subjects may be allowed to remain on the study treatment if causes other than study drug are likely the cause of elevated liver function tests):
    - ALT or AST > 10 x ULN
    - ALT or AST > 5 x ULN **and** (total bilirubin > 2 x ULN)
    - ALT or AST > 5 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

The reason for a subject's discontinuation of treatment or withdrawal from the study will be clearly documented in the source documents and on the electronic case report form (eCRF). At the time of discontinuation, all EOIV procedures should be performed for subjects who discontinue from the study after randomization but before receiving oral therapy (i.e., who discontinue on or before the EOIV visit). All EOT procedures should be performed for subjects who discontinue from the study on or before the EOT Visit and all 6-Week FU procedures should be performed for subjects who discontinue from the study after the EOT Visit but on or before the 6-Week FU Visit.

Subjects withdrawn from the study regimen for any reason will receive antifungal therapy as deemed appropriate by the investigator. All subjects should be evaluated for survival status at Day 30 and followed up until the 6-Week FU Visit for safety and outcome assessments, with the exception of subjects who withdraw consent to collect further information or are lost to follow-up. If withdrawal from study therapy is a consequence of clinical failure, these subjects will be considered as such for the efficacy analysis but must be followed up for assessment of survival status at Day 30 and for safety for 30 days after discontinuation of antifungal therapy.

10.4 Replacement of Discontinued Subjects

Subjects who discontinue early from randomized treatment will not be replaced.

11.0 Study Treatments

11.1 Study Treatment Groups

All randomized subjects will receive IV echinocandin therapy followed by step-down blinded oral treatment or, in the case of isolates non-susceptible to fluconazole, either open-label ibrexafungerp or other Best Available Therapy (BAT). Eligible subjects will be randomized at a 1:1 ratio to one of two treatment regimens:

- IV echinocandin followed by oral ibrexafungerp, or
- IV echinocandin followed by oral fluconazole or BAT

The IV component of these treatment regimens will be given as open-label therapy while the oral component for all randomized subjects with fluconazole susceptible isolates (ibrexafungerp or fluconazole) will be administered as double-blind, double-dummy treatment (Group 1) and subjects with fluconazole non-susceptible isolates will receive open-label oral ibrexafungerp or BAT (Group 2).

11.1.1 Open-Label IV Component

The IV component of the study treatment for both study groups will consist of IV echinocandin (caspofungin, micafungin, or anidulafungin) given in an open-label fashion and as per local label instructions. Subjects will receive IV echinocandin treatment until the criteria for switching to oral antifungal treatment are met. The switch from IV echinocandin to oral antifungal should occur as soon as the criteria for switching is met and ideally within 5 days of start of the IV echinocandin. While on IV echinocandin, subjects should be assessed daily to determine if they meet the criteria for step-down therapy.

11.1.2 Randomization and Switch to Oral Therapy

Randomization will occur as soon as the subject is confirmed to meet eligibility criteria. It is expected that the *Candida* species causing the infection is known prior to step-down.

Unless there is a documented reason why switching to oral therapy is not adequate for the subject, subjects should be switched to the randomly assigned oral study drug as soon as:

- They are clinically stable (e.g. no worsening of signs and symptoms associated with invasive candidiasis).
- They are able to tolerate oral medication.
- They are hemodynamically stable (i.e., do not require use of vasopressors).
- Blood cultures should be negative for at least 48 hours (candidemia).
- The *Candida* species causing the infection is known.
- They have no mucositis or GvHD affecting the gut with severity > Grade 3.

The IV echinocandin will be discontinued upon initiation of oral study drug. The study drug should be initiated within 24 hours after the last administration of IV echinocandin, with a minimum of 6 hours between the last IV dose and the first oral dose.

Subjects will receive systemic antifungal treatment (including both the IV and oral components of the treatment) for approximately 14 days to 6 weeks.

Drug administration via naso-gastric (NG), percutaneous endoscopic gastrostomy (PEG) and Jejunostomy (J) tubes is allowed. Administration instructions are provided in the study specific product manual.

11.1.3 Subjects with Isolates Assumed or Known Susceptible to Fluconazole – Switch to Double-Blinded Arm Oral Therapy (Group 1)

Subjects harboring an infection caused by *Candida* species commonly susceptible to fluconazole (e.g., *C. albicans*, *C. tropicalis*, *C. parapsilosis*, etc.) will be stepped down into the Group 1 Double-Blinded Arm (ibrexafungerp or fluconazole) depending on the treatment regimen that they were randomized to. The oral component of the study treatment for all randomized subjects will consist of one of the following, as detailed in Table 1 and Table 2:

Table 1 Double-Blinded Ibrexafungerp Dosing Details

	ORAL Treatment Days	Ibrexafungerp Dosing Regimen	Total Ibrexafungerp Daily Dose	Placebo Matching Fluconazole
Ibrexafungerp Loading Dose	ORAL Day 1	**750 mg BID**** 750 mg (3 tablets x 250 mg) AM 750 mg (3 tablets x 250 mg) PM	1500 mg	**QD** 4 capsules
Ibrexafungerp Loading Dose	ORAL Day 2	**750 mg BID**** 750 mg (3 tablets x 250 mg) AM 750 mg (3 tablets x 250 mg) PM	1500 mg	**QD*** 2 capsules
Ibrexafungerp Maintenance Dose	ORAL Day 3 to EOT	**750 mg QD***** 750 mg (3 tablets x 250 mg)	750 mg	**QD*** 2 capsules

Abbreviations: AM = morning; BID = twice a day; EOT = end of treatment; PM = evening; QD = once a day

* Placebo Matching fluconazole – dose may be adjusted at 6 mg/kg rounded to the closest 200 mg for underweight or overweight subjects. The maximum dose of placebo matching fluconazole is 800 mg QD.

** Ibrexafungerp – In the event of moderate to severe nausea associated with the loading doses, the doses may be split into multiple doses spread over the dosing period.

*** Ibrexafungerp - A regimen adjustment to 375 mg (1 ½ tablet x 250 mg) BID will be allowed for subjects with moderate to severe nausea associated with study drug administration.

Table 2 Double-Blinded Fluconazole Dosing Details

	ORAL Treatment Days	Fluconazole Dosing Regimen	Placebo Matching Ibrexafungerp
Fluconazole Loading Dose Period	ORAL Day 1	**QD** 800 mg (4 capsules x 200 mg)	**BID**** 3 tablets AM, 3 tablets PM
Fluconazole Maintenance Period	ORAL Day 2	**QD*** 400 mg (2 capsules x 200 mg)	**BID**** 3 tablets AM, 3 tablets PM
Fluconazole Maintenance Period	ORAL Day 3 to EOT	**QD*** 400 mg (2 capsules x 200 mg)	**QD***** 3 tablets

Abbreviations: AM = morning; BID = twice a day; EOT = end of treatment; PM = evening; QD = once a day
* Fluconazole – dose may be adjusted at 6 mg/kg rounded to the closest 200 mg for underweight or overweight subjects. The maximum dose of fluconazole is 800 mg QD.
** Placebo Matching ibrexafungerp - In the event of moderate to severe nausea associated with the loading doses, the doses may be split into multiple doses spread over the dosing period.
*** Placebo Matching ibrexafungerp - A regimen adjustment to 375 mg (1 ½ tablet x 250 mg) BID will be allowed for subjects with moderate to severe nausea associated with study drug administration.

For subjects with renal impairment, the fluconazole dose adjustments in the table below are recommended per fluconazole label.

Creatine clearance (ml/min)	Percent of recommended dose
>50	100%
≤50 (no dialysis)	50%
Regular dialysis	100% after each dialysis 50% on non-dialysis days

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance in adults:

Males: $$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Females: 0.85 x value obtained by above formula

11.1.4 Subjects with Isolates Non-Susceptible to Fluconazole – Open-Label Arm (Group 2)

When subjects with infections due to *Candida* species that are frequently not susceptible to fluconazole (i.e., *C. auris*, *C. krusei*, *C. glabrata*) or other *Candida* spp. isolates with documented non-susceptibility to fluconazole based on MIC determination, or subjects with breakthrough infections whilst receiving azole prophylaxis treatment, meet criteria for switching to oral antifungal therapy, their randomization assignment will be unblinded and they will receive either

open-label oral ibrexafungerp or open label BAT, according to the initial randomly assigned treatment regimen.

If after randomization, the baseline *Candida* isolate (collected prior to randomization) is identified as being not-susceptible to fluconazole (e.g., *Candida albicans* with a fluconazole MIC ≥ 8 μg/mL), the subject will be discontinued from the Double-Blinded Arm and will be transferred to the Open-Label Arm offering open-label oral ibrexafungerp or BAT. Subjects randomized to double-blind ibrexafungerp would be transferred to open-label ibrexafungerp, subjects randomized to double-blind fluconazole would be transferred to open-label BAT (Tables 3 and Table 4). Administration of BAT should be according to the locally approved label for the applicable drug.

Table 3 Open-Label Ibrexafungerp Dosing Details

	ORAL Treatment Days	**Ibrexafungerp Dosing Regimen**	**Total Ibrexafungerp Daily Dose**
Ibrexafungerp Loading Dose Period	ORAL Days 1 - 2	**750 mg BID** 750 mg (3 tablets x 250 mg) AM 750 mg (3 tablets x 250 mg) PM	1500 mg
Ibrexafungerp Maintenance Dose Period	ORAL Day 3 to EOT	**750 mg QD*** 750 mg (3 tablets x 250 mg)	750 mg

Abbreviations: AM = morning; BID = twice a day; EOT = end of treatment; PM = evening; QD = once a day
* A regimen adjustment to 375 mg (1 ½ tablet x 250 mg) BID will be allowed for subjects with moderate to severe nausea associated with study drug administration.

Table 4 Open-Label Best Available Therapy (BAT) Dosing Details

Subjects assigned to BAT will receive one of the following treatment regimens at the discretion of the Principal Investigator:

- Continued IV echinocandin, or
- High-dose (800 mg QD) fluconazole, or
- Oral voriconazole 400 mg (6 mg/kg) twice daily for 2 doses, then 200 mg (3 mg/kg) twice daily (for subjects with *C. krusei* isolates only)[11]

Abbreviations: BAT = best available therapy; QD = once a day

Voriconazole Dosing Adjustments:

- For subjects weighing <40 kg: Decrease maintenance dose of 100 mg or 150 mg twice daily.
- For subjects with mild to moderate hepatic impairment (Child-Pugh Class A and B), use 50% of maintenance dose.

11.1.4.1 Dose Modification for Toxicity

In the event of moderate to severe nausea associated with the loading doses, the doses may be split into multiple doses spread over the dosing period, i.e., each 750 mg administered over a 12-hour period. A regimen adjustment to ibrexafungerp 375 mg (1½ tablet x 250 mg) BID (or matching placebo) will be allowed after loading dose for subjects with moderate to severe nausea associated with study drug administration.

Decisions to temporarily withhold therapy because of an AE must be reviewed on a case-by-case basis by the investigator. The Sponsor must be notified immediately of any event which requires interruption of a study drug, regardless of whether this event meets the definition of a serious adverse experience.

11.2 Dietary Requirements

Oral study drug should be administered preferably with or immediately after a meal. In addition, it is recommended that each subject identifies and keeps their optimal routine to facilitate compliance (for example, administering the study drug at breakfast and at dinner on treatment days).

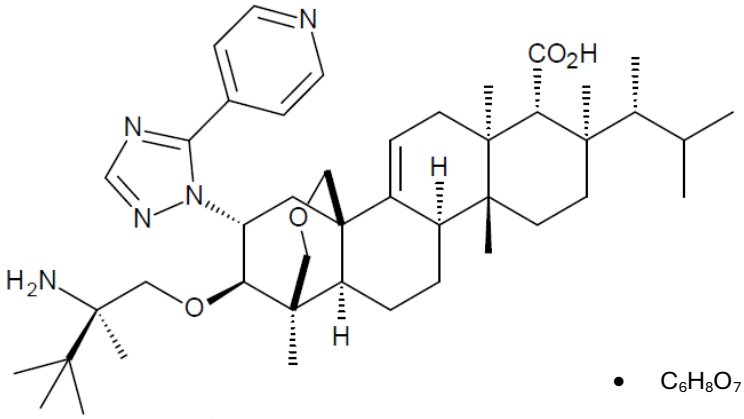
11.3 Study Drugs

The study drugs administered for the double-blind oral treatment component of the study will be provided by the Sponsor and will consist of oral ibrexafungerp (250 mg tablets and ibrexafungerp-matching placebo tablets) and oral fluconazole (200 mg tablets or capsules and fluconazole-matching placebo tablets or capsules). Ibrexafungerp (250 mg tablets) required for administration during the open-label oral treatment component will be provided by the sponsor.

11.3.1 Ibrexafungerp Description

Study Drug Identifier:	Ibrexafungerp
Formula:	$C_{50}H_{75}N_5O_{11}$ (citrate salt)
Molecular Weight:	922.18 (citrate salt)
Physical Description:	White to off-white solid
Chemical Name:	4H-1,4a-Propano-2H-phenanthro[1,2-c]pyran-7-carboxylic acid, 15-[(2R)-2-amino-2,3,3-trimethylbutoxy]-8-[(1R)-1,2-dimethylpropyl]-1,6 ,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-1,6a,8,10a-tetramethyl-14-[5-(4-pyridinyl)-1H-1,2,4-triazol-1-yl]-, (1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)

Figure 1: Chemical Structure of Ibrexafungerp Citrate



- $C_6H_8O_7$

11.3.2 Formulation, Packaging, and Labeling

Ibrexafungerp citrate drug product for oral administration will be supplied as a tablet containing 250 mg of ibrexafungerp active ingredient on a free-base basis. The placebo product matching ibrexafungerp will be supplied as a tablet matching the size and appearance of the active tablet. Ibrexafungerp and matching placebo tablets are packaged in induction sealed HDPE bottle with a polypropylene cap. In addition to the active ingredient, the tablet formulation also contains butylated hydroxy anisole, colloidal silicon dioxide, crospovidone, magnesium stearate (non-bovine), mannitol, and silicified microcrystalline cellulose.

Fluconazole capsules containing 200 mg of active ingredient will be sourced commercially and will be film-coated for blinding purposes. The placebo product matching fluconazole will be the identical film-coated capsule filled with inert excipient. Fluconazole and matching placebo capsules are packaged in induction sealed HDPE bottle with a polypropylene cap.

Additional supplies will be shipped upon request and approval by the Sponsor.

Labels on the bottles of ibrexafungerp and fluconazole will include the following information:

- Sponsor Name
- Study Protocol Number
- Place to write the subject number
- Product name and potency
- Number of tablets / capsules count per bottle (oral only)
- Dosing instructions
- Storage conditions
- Caution Statement: i.e. "Caution: New Drug – Limited by Federal (United States) Law to Investigational Use Only”

11.3.3 Storage and Stability

The pharmacist or appropriate designee at each clinical research site will be responsible for the study drug. For long-term storage at the site, oral study drug supplies (i.e., ibrexafungerp, fluconazole, and matching placebos) must be kept in a secure area (e.g., locked cabinet). Bottles of ibrexafungerp and fluconazole should be stored at room temperature.

The site will be required to keep a temperature log to establish a record of compliance with these storage conditions.

11.4 Drug Accountability

The investigator or designee will inventory and acknowledge receipt of all shipments of the study drug. An IWRS will be used to dispense study drugs to individual subjects. Drug accountability logs will be used to maintain accurate records of receipt, dispensing, administration to each subject and return of drug. A study monitor will periodically check the supplies of investigational products held by the site to verify accountability of all study drugs. After drug accountability has been completed by the monitor, all unused study drug and all medication containers will be returned to the Sponsor or destroyed on site if the site has procedures in place for study drug destruction.

Drug supplies will be maintained in a secure, limited-access storage area under the recommended storage conditions (see Section 11.3.3).

The study drug supplied for this study is only for use in subjects properly consented and enrolled under this protocol. This is a double-blind study. All site and sponsor personnel will be blinded to treatment assignment. A study site designee (e.g. pharmacist, study nurse/coordinator) will:

- Record the treatment in the appropriate drug accountability log
- Report and document any study medication issues such as crushed or broken tablets or capsules
  - All product quality complaints should be reported to the Sponsor
- Collect and count the number of oral tablets/capsules remaining at the EOT Visit
- Review tablet/capsule count, record any unused or remaining drug in the drug accountability log and eCRF, and note any discrepancies and reason for discrepancies

11.5 Subject Compliance with Study Drug Dosing

During the loading dose period (Days 1 and 2), subjects will take oral study medication in the morning upon arising and in the evening. From Day 3 onwards, subjects will take their medication once daily.

Subjects will be instructed to bring the study medication (including empty bottles) with them at each visit. Compliance will be assessed based on remaining study drug as compared to what should have been taken. Details of treatment, including any missing dose will be recorded in the eCRF.

Sites are encouraged to contact the medical monitor or Sponsor for concerns of compliance with the treatment regimen, especially for subjects who miss doses due to AEs related with tolerability.

12.0 Non-Study Treatments

12.1 Prior and Concomitant Medications

All systemic antifungal therapy, immunosuppressives, immunomodulators and chemotherapeutics administered within 28 days and all medications administered within 7 days before screening and through the EOT will be recorded on the eCRF. Only the use of other antifungal medications or medications to treat a study-drug related AE will be recorded after EOT through the 6-Week post-treatment follow-up visit. Start and stop times of concomitant medications taken during antifungal therapy will be recorded on the eCRF. Prior and concomitant medications will be reviewed and recorded at all visits.

Certain concomitant medications should be administered with caution or close monitoring as described in Section 20.1 (Appendix A).

12.2 Prohibited Medications:

A list of prohibited medications, applicable to ibrexafungerp and fluconazole is provided in Section 20.1 (Appendix A). The investigator should refer to the locally approved product labels of relevant medication (e.g., echinocandins, fluconazole, voriconazole) for other prohibited medications, as applicable.

12.3 Medications to be Administered with Caution and Monitored as Appropriate

A list of medications to be administered with caution and monitored as appropriate, applicable to ibrexafungerp and fluconazole is provided in Section 20.1 (Appendix A). The investigator should refer to the approved product labels of relevant medication (e.g., echinocandins, fluconazole, voriconazole) for medications to be administered with caution.

12.4 Contraception Requirements

Requirements are based on Guidelines from the Clinical Trials Facilitation and Coordination Group (CTFG[12]). Female subjects of childbearing potential < 2 years post-menopausal must agree to remain abstinent or agree to using (or have their partner use) one barrier method (e.g., female condom with spermicide) plus one other highly effective method of birth control from signing the consent form until at least 7 days after end of treatment.

Highly effective methods of birth control include:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

Male subjects must be vasectomized, abstain from sexual intercourse, or agree to use barrier contraception and also agree not to donate sperm from signing the consent form until at least 7 days after end of treatment.

12.5 Study Restrictions

There are no additional study restrictions other than those described in Section 10.2 (Exclusion Criteria) Section 11.2 (Dietary Requirements), and Section 12.2 (Prohibited Medications).

13.0 Study Procedures

The following sections provide a description of the individual study procedures to be performed during the conduct of the study. A detailed schedule of study assessments is provided in the Schedule of Visits and Procedures (Section 13.4.1).

Study days are counted relative to the first IV echinocandin dose, which is Study Day 1. For the purpose of PK sample collection, reference is made to “Oral Days”, i.e., Oral Day 1 is the first day of step-down therapy. For follow-up visits, weeks are counted relative to the EOT Visit. The Screening visit can occur before the start of IV echinocandin treatment, or whilst the subject is already receiving echinocandin treatment. Screening visit can be from Study Day -4 (4 days prior to start of IV echinocandin) to before EOIV. Screening and Randomization may occur on the same day. Study visits may be combined if they occur on the same day or within the protocol specified window period.

13.1 General Procedures

13.1.1 Informed Consent

Every study subject or legally authorized representative must provide written informed consent prior to any protocol specific procedures or any other study activities (see Section 18.3).

13.1.2 Enrollment and Assignment of Subject Identification

Subjects with a diagnosis of candidemia and/or invasive candidiasis will be invited to participate in the study. Subjects will be assigned a study number after having signed an informed consent

form and will be randomized if they meet all inclusion criteria and none of the exclusion criteria. This number will be unique to each subject and will be used to identify the subject throughout the study.

Subjects who are screen failures or who are not eligible for treatment will be recorded as such in the site's subject screening log. The subject numbers assigned to eligible subjects will be recorded on the electronic Case Report Form (eCRF). Only one subject number will be assigned to each eligible subject.

13.1.3 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed at Screening and randomization will occur as soon as a subject's eligibility is confirmed.

13.1.4 Medical History and Demographics

During the Screening visit, a complete medical history for the prior year will be recorded for each subject. The medical history will include previous and current medical diagnoses, as well as major surgical procedures and drug monitoring, if applicable. Subject demographics such as age, sex, race, ethnicity, and risk factors for mortality associated with invasive candidiasis will also be collected.

13.1.5 Prior and Concomitant Medications

Prior and concomitant medications will be reviewed at all visits from Screening through the 6-Week FU visit. Refer to Section 12.0 and Section 20.1 for details.

13.1.6 Complete Physical Examination

A complete physical examination (done either by the treating physician or by qualified study personnel, with appropriate source documentation), will be performed at Screening, EOIV, Day 14 and EOT and at other timepoints as clinically indicated by adverse event screening and underlying diseases. Complete physical examinations will include an assessment of general appearance, skin, eyes, heart, chest, abdomen, and the body site that corresponds to the site of *Candida* infection, if the patient is enrolled with an infection other than candidemia.

13.1.7 Retinal Examination

A retinal examination (bedside fundoscopy or other acceptable examinations) to rule out the presence of *Candida* endophthalmitis must be performed in subjects with candidemia during the Screening period. If a subject becomes symptomatic, the retinal examination should be repeated as needed. Subjects with evidence of endophthalmitis, including retinitis or vitritis diagnosed post

baseline, should be discontinued from study treatment, but will remain in the study until last follow-up visit.

13.1.8 APACHE II Score

The APACHE II score (Appendix 20.2) will be determined for each subject at Day 1 (1st dose of IV echinocandin) or closest day prior to Day 1, using local laboratory results. APACHE II score is repeated at EOIV, Day 14, and EOT.

13.1.9 qSOFA Score

The Quick Sequential (sepsis related) Organ Failure Assessment (qSOFA) score will be determined for each subject at Day 1 (1st dose of IV echinocandin) or closest day prior to Day 1, EOIV, and EOT.

13.1.10 Pregnancy Test

A urine or serum pregnancy test will be performed by the local laboratory for all female subjects of childbearing potential at Screening and will be repeated at EOT (based on CTFG guidelines[12]). Pregnancy tests may be conducted more often (e.g., on a monthly basis), depending on the risk of the subject to become pregnant per investigator's assessment, and per local regulations.

13.1.11 Management of IV Catheters

It is strongly recommended that IV catheters be removed or changed and replaced at a different site for all subjects with positive blood cultures for *Candida* within 48 hours of diagnosis.

13.1.12 Randomization

As soon as eligibility is confirmed, subjects will be randomized at a 1:1 ratio to one of the two treatment regimens.

13.1.13 IV Treatment Dosing

All subjects will receive treatment with an IV echinocandin (anidulafungin, caspofungin or micafungin) given in an open-label fashion as per local label instructions. Subjects may already be on echinocandin treatment at the time of screening/randomization and will receive IV echinocandin treatment until the criteria for switching to oral antifungal are met. The first day of IV echinocandin is Study Day 1.

13.1.14 Oral Treatment Dosing

Once the subject meets the criteria for step-down therapy, the subject will receive antifungal treatment depending on the treatment regimen that they were randomized to and the *Candida* species.

Further details of the study treatment and dietary requirements are provided in Section 11.1 and Section 11.2

13.1.15 End of Study

Subjects are followed until 42 days (± 3 days) after EOT. The 6-Week FU visit is the subject's end of study. The global End of Study coincides with the last visit of the last subject randomized.

13.1.16 Healthcare Economic Data

Healthcare economic data (subject days of hospital stay, subject days in ICU, days from discharge to readmittance to hospital for treatment of invasive candidiasis) will be collected at EOIV, EOT, and at the 2-Week and 6-Week FU visits. For these analyses, Day 1 will be the first day of IV echinocandin treatment.

13.2 Efficacy Procedures

13.2.1 Targeted Physical Examination to Evaluate the Signs and Symptoms of Infection

A targeted physical examination of the fungal disease site, including the clinical signs and symptoms of the fungal disease (done either by the treating physician or by qualified study personnel, with appropriate source documentation), will be conducted for all subjects at screening, EOIV, Day 14, EOT and Day 30 and at other timepoints as clinically indicated by adverse event screening, assessment of persistent or new signs and symptoms of invasive fungal disease, or to follow up on the course of the underlying disease.

The signs and symptoms of *Candida* infection include, but are not limited to, the following:

- Fever defined as oral temperature equivalent to ≥ 38.3°C (≥ 101°F) on one occasion or > 37.8°C (> 100°F) on two measurements at least 4 hours apart
- Clinically significant hypothermia < 36°C (< 96.8°F)
- Hypotension (systolic blood pressure of < 90 mmHg or > 30 mmHg decrease below normal baseline)
- Signs of inflammation at the *Candida* infected site
- Other evaluations such as echocardiography and ophthalmoscopy when performed per standard of care will be collected.

13.2.2 Mycological Testing

Subjects must have a diagnosis of invasive candidiasis (including candidemia) defined as evidence of *Candida* in either a bloodstream or tissue/fluid culture from a normally sterile site (excluding eye, cardiac and bone tissue, central nervous system or prosthetic device) collected within +/- 96 hours of the first dose of IV echinocandin (i.e. Day 1 ± 96 hours).

Local Reference laboratories will be used for identification and susceptibility testing of all fungal isolates collected during the study. **Samples should be sent to the local microbiology laboratory for speciation and susceptibility as early as possible**. The isolate from the initial and subsequent positive culture for *Candida* should be retained for confirmation of identification and susceptibility testing at the central reference microbiology laboratory.

13.2.2.1 Blood Cultures

Blood cultures will be collected at Screening, EOIV, Day 14 and at EOT. Cultures will be collected at Day 30, and at the 2-Week and 6-Week FU only if deemed necessary by the PI. Additional cultures may be performed as clinically indicated. As per guideline for subjects with candidemia, it is recommended to collect cultures every other day during IV echinocandin treatment until the demonstration of clearance of *Candida* from the bloodstream.

Generally, blood culture should involve samples from 2 separate draws, with at least one set of blood culture bottles drawn peripherally (directly from a vein) and the other set from any existing central IV catheter. The results of these studies should be documented in the eCRF. For subjects with suspected recurrent candidemia during oral therapy, a sample for blood culture should be drawn for susceptibility testing and determination of drug resistance.

The results from all blood cultures collected during the study will be entered in the EDC, regardless of if they were collected as part of study procedures or SOC (including results from initial positive culture to determine eligibility).

13.2.2.2 Culture of non-Blood Sites of *Candida* Infection

Cultures (tissue or fluid) from subjects who have non-blood sites of *Candida* infection will be collected at Screening, and if feasible at EOIV, Day 14 and at EOT. Cultures will be collected if deemed necessary and feasible at Day 30 and at the 2-Week and 6-Week FU visits. Additional cultures from subjects who have non-blood sites of *Candida* infection may be performed as clinically indicated.

NOTE: cultures of urine, sputum, bronchoalveolar lavage, oropharynx, or esophagus are to be EXCLUDED unless accompanied by a positive blood culture for *Candida*. Cultures of samples from indwelling drains are to be EXCLUDED unless the drain has been in place for < 24 hours.

13.2.3 Radiological Assessments of non-Blood Sites of *Candida* Infection

For subjects with fungal diseases where diagnosis and assessment of outcome are based on imaging, imaging scans (e.g., X-ray, ultrasound, computed tomography [CT], magnetic resonance imaging [MRI]) will be obtained for the assessment of infection.

Imaging scans will be obtained at Screening, Day 14 and EOT as applicable. Images collected as SOC up to 5 days before screening may be used as baseline scan. In addition to the scheduled time points, imaging scans will be collected anytime during therapy, as clinically indicated. The results of these imaging studies should be documented on the eCRF.

Radiographs and/or imaging scans may be assessed by a central reader.

13.2.4 Survival

Survival status (collected as ACM) will be recorded at Day 30 and at the 6-Week FU Visit. If the subject has died, the date and cause of death along with the reporting of SAE details will be recorded in the eCRF. If an in-person visit is not possible, Day 30 ACM may be assessed remotely.

13.2.5 Assessment of Clinical Response, Mycological Response and Global Response

Clinical Response, Mycological Response and Global Response (primary for EU only) will be assessed as secondary endpoints.

Clinical and Mycological Response will be assessed, and Global Response determined at EOIV, Day 14, EOT, Day 30, 2-week FU, and 6-week FU visits.

The following study procedures will be performed to assess treatment outcome for all subjects:

- Clinical signs and symptoms of fungal disease (Section 13.2.1)
- Mycological assessments (Section 13.2.2)
- Radiological assessments (e.g., X-ray, ultrasound, CT and MRI) (Section 13.2.3)

Assessment of response can be assessed remotely for Follow up visits when appropriate (e.g., subject was asymptomatic at EOT, and no additional cultures were needed during the follow up period).

See Section 17.7.1.3 for treatment outcome definitions.

13.2.6 Assessment of Recurrence or Emergent Infections

Recurrence will be assessed at the 2-Week and 6-Week FU Visits as a secondary efficacy endpoint. Assessment of recurrences can be done remotely when appropriate (e.g., subject was asymptomatic at EOT, and no additional cultures were needed during the follow up period). Other non-*Candida*

emergent fungal infections will be identified through 6 weeks after EOT. See Section 17.7.1.2 for recurrence definition.

13.3 Pharmacokinetic Procedures

Blood samples for PK analysis of ibrexafungerp in plasma will be collected from subjects who provide consent to participate in the PK sampling. Up to 7 blood samples may be collected at the following visits and sampling windows: Oral Days 1 and 2 (one sample collected between 3-6 hours after either the 1st or 2nd dose), Oral Day 7 (one sample collected before dosing and one sample 3-6 hours after dosing) and one sample collected 36 to 60 hours after the last dose, when feasible. Additional blood PK samples will be collected on Study Day 14 and Study Day 30 before dosing for subjects still receiving study treatment or when clinically indicated. Efforts will be made to record the exact time of drug intake and proximity of the last meal to dose on PK collection days. Home visits are allowed for the collection of PK samples in consenting subjects in accordance with local regulations and practicalities.

Procedures for collecting, storing, and shipping plasma samples for PK are described in the Central Lab Manual.

13.4 Safety Procedures

13.4.1 Vital Signs and Temperature

Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate, weight and body temperature, will be measured at screening, EOIV, Day 14 and EOT and at other timepoints as clinically indicated by adverse event screening and underlying diseases.

13.4.2 Clinical Safety Laboratory Assessments

Clinical safety laboratory tests will include biochemistry and hematology and will be collected at selected scheduled visits as indicated in Table 5. These tests will be performed by the central laboratory.

Safety laboratory tests are only required to be performed by the local laboratory at Screening so that timely results are available for study eligibility determination and for calculation of the APACHE II score at screening. If safety laboratory results are already available within the 48 hours prior to Screening from standard-of-care/routine testing, these results may be used to support eligibility determination. However, samples must still be obtained and sent to the central laboratory, as described below.

Additional clinical safety laboratory testing should be performed by the local laboratory per the site's standard of care for routine clinical management of the patient.

13.4.2.1 Biochemistry

Clinical chemistry testing performed by the central safety laboratory includes the following assessments:

▪ Sodium	▪ Bicarbonate
▪ Potassium	▪ Total protein
▪ Chloride	▪ Glucose
▪ Blood urea nitrogen (BUN)	▪ Albumin
▪ Creatinine	▪ Calcium
▪ Total creatine phosphokinase (CPK)	▪ Phosphate
▪ Aspartate aminotransferase (AST/SGOT)	▪ Alkaline phosphatase (AP)
▪ Alanine aminotransferase (ALT/SGPT)	▪ Bilirubin (total, direct, and indirect)
▪ Gamma glutamyl transferase (GGT)	▪ Triglycerides
▪ Lactic dehydrogenase (LDH)	▪ Amylase
▪ Lipase[a]	▪ Globulin
▪ Lipid profile (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL], and total cholesterol:HDL ratio)[a]	▪ Uric acid

[a] Only at screening

13.4.2.2 Hematology

Hematology testing performed by the central safety laboratory includes the following assessments:

▪ White blood cell (WBC) count	▪ Hemoglobin
▪ Red blood cell (RBC) count	▪ Hematocrit
▪ Platelet count	
▪ Differential white blood cell count will include percentages for segmented neutrophils, lymphocytes, monocytes, eosinophils, and basophils and absolute counts for neutrophils, lymphocytes, atypical lymphocytes, monocytes, eosinophils, and basophils.	

13.4.3 Adverse Events

For all randomized subjects, AEs will be collected and evaluated from the time the informed consent is signed throughout EOT. After EOT, and up to the 6-week FU, new AEs will be collected only if deemed related to the study drug, if it is a serious adverse event (SAE), or if it is related to a fungal infection. AEs and SAEs will be reviewed at all visits from the time the

informed consent is signed. See Section 15.0 for details regarding safety assessment and monitoring.

14.0 Study Schedule

A detailed schedule of all study visits and procedures is presented in Table 5.

Table 5 Schedule of Visits and Procedures (SCY-078-302)

Visit	Treatment Period								Post-Treatment Period	
	*IV Treatment		Oral Treatment/ Step-Down Treatment			Total Treatment (IV + Oral)			***2-Week FU (14 days after Last Dose [±3 days])	***6-Week FU (42 days after Last Dose [±3 days])
	Screening (Days -4 to before EOIV)	**EOIV	**Oral Day 1	Oral Day 2[b] (PK only)	Oral Day 7[b] (PK only)	Study Day 14 -2/+3 days	Study Day 30 ±3days	EOT +3 days		
GENERAL PROCEDURES										
Informed consent	X									
Assignment of subject Identification	X									
Inclusion/exclusion criteria[c]	X									
Randomization[a]	X									
Medical history and demographics	X									
Prior & concomitant medications	X----------									----------X
Complete physical examination[n]	X	X				X	X[n]	X	X[n]	X[n]
Retinal examination (candidemia pts)[d]	X					[d]				
Echocardiography (if per SOC)[e]	X									
EKG[j]	X									
APACHE II score	X	X				X		X		
qSOFA score	X	X						X		
Urine or serum pregnancy (β-hCG)[k]	X						X[k]	X		
Removal or change of IV catheter[f]	X									
IV treatment dosing*	X	X								
Oral treatment dosing			X----------					X		
Collect Healthcare Economic Data	X	X						X	X	X
EFFICACY PROCEDURES										
Targeted physical examination,	X	X				X	X	X	X[m]	X

Visit	Treatment Period								Post-Treatment Period	
	***IV Treatment**		**Oral Treatment/ Step-Down Treatment**			**Total Treatment** (IV + Oral)			*****2-Week FU (14 days after Last Dose** [±3 days]**)**	*****6-Week FU (42 days after Last Dose** [±3 days]**)**
	Screening (Days -4 to before EOIV)	****EOIV**	****Oral Day 1**	**Oral Day 2[b] (PK only)**	**Oral Day 7[b] (PK only)**	**Study Day 14** -2/+3 days	**Study Day 30** ±3days	**EOT** +3 days		
including clinical evaluation of signs and symptoms of infection[m]										
Blood cultures[g, l]	X	X				X	X[g]	X	X[g]	X[g]
Cultures of non-blood sites of *Candida* infection (if applicable)[h]	X	X[h]				X[h]	X[h]	X[h]	X[h]	X[h]
Imaging at non-blood sites of *Candida* infection (if applicable)[i]	X[i]					X[i]		X[i]		
Survival (ACM)[p]							X[p]			X
Assessment of Clinical, Mycological and Global Response[o]		X				X	X	X	X[o]	X[o]
Assessment of Recurrence									X[o]	X[o]
PK sample collection[b, l]			X----------X[b]							
Vital signs and temperature[n]	X	X				X	X[n]	X	X[n]	X[n]
Safety labs[j, l]	X	X				X	X[j]	X	X[j]	X[j]
AE monitoring	X----------X									

Abbreviations: ACM=all-cause mortality; β-hCG =beta human chorionic gonadotropin; EOT=end of treatment; ID=identification; IV=intravenous; PK=pharmacokinetics

- * The first day of study (Study Day 1) is the 1st day of treatment with IV echinocandin. Day 1 may be before or after screening/randomization. While on IV echinocandin, subjects should be assessed daily to determine if they meet the criteria for step-down therapy.
- ** EOIV and Oral Treatment Day 1 should ideally occur on the same day. Procedures should be performed after last IV echinocandin dose and prior to 1st Oral IP administration. Minimum period between completion of last IV infusion and first oral dose is 6 hours and maximum period is 24 hours.
- *** The 2-Week and 6-Week follow-up visits should be scheduled from the date of the last study drug antifungal dose administered (not the date of the EOT visit). These visits may be done telephonically, remotely or via home visits in accordance with local regulations and practicalities, except if an in person visit to the center is clinically indicated by adverse event screening, assessment of persistent or new signs and symptoms of invasive fungal disease, or to follow up on the course of the underlying disease.

a. Randomization should occur as soon as eligibility is confirmed.

b. These visits are for PK consenting subjects only. Blood samples for the pharmacokinetic analysis of ibrexafungerp in plasma will be collected from all subjects who provide their consent to participate in the PK sampling. PK samples will be obtained at the following visits and sampling windows: Oral Days 1 and 2 (one sample collected between 3-6 hours after either the morning or evening dose), Oral Day 7 (one sample collected before dosing and one sample 3-6 hours after dosing) and one sample collected 36 to

60 hours after last dose when feasible. Additional blood PK samples will be collected on Day 14 and Day 30 before drug dosing for subjects still receiving study treatment or when clinically indicated. Efforts will be made to record the exact time of dosing and proximity of the last meal on PK collection days Home visits are allowed for the collection of PK samples in consenting subjects in accordance with local regulations and practicalities.

c. Data available to support inclusion exclusion criteria collected as SOC prior to signature of IC will be collected as appropriate in the EDC.
d. If the subject becomes symptomatic, retinal examination should be performed as clinically indicated.
e. All standard of care echocardiography results, including those collected 30 days prior to randomization, will be documented, if applicable, in the eCRFs.
f. Removal of IV catheter for subjects with positive blood culture for *Candida* within 48 hours of diagnosis is strongly recommended. Data on catheter management will be recorded in the eCRFs.
g. Generally, two sets of blood cultures (at least one from a peripheral draw) will be collected for species identification and susceptibility at Screening, EOIV, Day 14 and EOT. Blood cultures will only be collected at Day 30 and follow-up visits if deemed necessary and at any other timepoints as clinically indicated. As per guideline for subjects with candidemia, it is recommended to collect cultures every other day during IV echinocandin treatment until the demonstration of clearance of Candida from the bloodstream.
h. Cultures of non-blood sites will be collected at Screening, and when feasible at subsequent visits including EOIV, Treatment Day 14 and EOT visit; if deemed necessary and feasible, at Day 30 and at the FU visits. Additional cultures from subjects who have non-blood sites of *Candida* infection may be performed as clinically indicated.
i. Imaging will be collected at Screening, Day 14 and EOT ±3 days when clinically relevant. Images collected as SOC within 72 hours prior to consent may be used as baseline scan. Additional images may be performed as clinically indicated.
j. Additional tests and evaluations should be performed per the site's standard of care for routine clinical management of the patient and follow-up of adverse events.
k. Pregnancy tests may be conducted more often (e.g., on a monthly basis), depending on the risk of the subject becoming pregnant per investigator's assessment, and per local regulations.
l. The total blood volume that will be collected over the course of the study (safety bloods, blood cultures for candidemia patients, PK samples when applicable), will be approximately 250-400mL (approx. 8-14 oz), depending on whether blood is collected for additional testing. The total blood volume collected will not exceed the amount of blood collected during a typical blood donation (i.e., 480 mL or 16 oz).
m. A targeted physical examination of the fungal disease site, including the clinical signs and symptoms of the fungal disease (done either by the treating physician or by qualified study personnel, with appropriate source documentation), will be conducted for all subjects at screening, EOIV, Day 14, EOT and Day 30 and at other timepoints as clinically indicated by adverse event screening, assessment of persistent or new signs and symptoms of invasive fungal disease, or to follow up on the course of the underlying disease.
n. A complete physical examination (done either by the treating physician or by qualified study personnel, with appropriate source documentation) will be conducted for all subjects at screening, EOIV, Day 14 and EOT and at other timepoints as clinically indicated by adverse event screening and underlying diseases.
o. Assessment of response and assessment of recurrences can be assessed remotely for Follow up visits when appropriate (e.g., subject was asymptomatic at EOT, and no additional cultures were needed during the follow up period).
p. If it is not possible to conduct Day 30 in-person, survival can be assessed remotely.

15.0 Safety Assessments and Monitoring

15.1 Definition of an Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a study drug/study intervention, whether or not related to the study drug/study intervention.

Any laboratory abnormality that is deemed to be clinically significant in the opinion of the investigator (e.g., associated with clinical signs or symptoms, require medical intervention, require interruption of the study drug treatment, leads to study discontinuation) will be considered an AE and should be recorded in the eCRF, whether or not it is related to the study drug. 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.

Stable chronic conditions that are present prior to clinical trial enrollment and do not worsen are not considered AEs and will be accounted for in the subject's medical history.

The following can be considered AEs:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after the initiation of treatment with study medication, even though it may have been present prior to the start of the study
- Continuous persistent disease or symptoms present at baseline that worsen after signing the informed consent or following the initiation of treatment with study medication but are not associated with the infection being treated.

The following are not considered AEs:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an AE
- Pre-existing disease or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic surgery or elective surgery or social/convenience admissions)
- Events (or associated signs and symptoms), that are related to the disease being studied, candidemia or invasive candidiasis, should not be recorded as AEs, unless the event fits the definition for an SAE (Section 15.2), in which case the SAE reporting procedure should be followed (Section 15.11).

15.2 Definition of a Serious Adverse Event

A SAE is defined as an AE meeting one of the following outcomes:

- Death
- Life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Any other important medical event that may not result in one of the above outcomes may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

A life-threatening AE is any AE that places the subject, in the view of the investigator, at immediate risk of death from the AE as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.

15.3 Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information.

An overdose can occur if a subject has taken, accidentally or intentionally, a drug administered in a dose exceeding the protocol-specified dose. An overdose must be reported within 24 hours of the site becoming aware of the overdose if such overdose occurs with an associated SAE. If an overdose occurs without an associated SAE, the overdose must be reported within 5 working days and documented in the subject medical record.

15.4 Pregnancy

In the event of a female subject becoming pregnant, the study drug will be immediately discontinued, and the subject will be followed up to determine the outcome of the pregnancy. The pregnancy must be reported to the Sponsor within 24 hours of the site becoming aware of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

15.5 Unexpected Adverse Event

An AE is considered "unexpected" if it is not listed in the IB Section 6.3 Possible Anticipated Adverse Events and Clinical Monitoring or is of greater specificity or severity than those that have been observed with the particular study drug being tested. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents.

15.6 Grading of Adverse Events

The severity (or intensity) of an AE refers to the extent to which it affects the subject's daily activities and will be classified by the investigator as mild, moderate, or severe using the following criteria:

- Mild: Awareness of sign or symptom, but easily tolerated. Not likely to require medical attention.
- Moderate: Discomfort enough to cause some interference with daily activity. May require medical intervention.
- Severe: Intense enough to disrupt daily activities. Likely requires medical intervention.

Clarification of the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

15.7 Causality Assessment

The investigator will assess causality (i.e., whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Related: The temporal relationship of the AE with the study drug makes causality possible and as likely or more likely than due to another cause such as other drugs, a surgical intervention, or an underlying disease.
- Not related: The temporal relationship of the AE with the study drug makes causality improbable and can be due to another cause such as other drugs, a surgical intervention, or an underlying disease.

15.8 Adverse Event Collection Timeframe

For randomized subjects, AEs and SAEs will be recorded from the time the ICF is signed (Screening) through EOT. After EOT, and up to the 6-Week FU, new AEs will be collected only if deemed related to the study drug, if it is a SAE, or if it is related to a fungal infection. All AEs reported by the subject or observed by members of the clinical staff will be evaluated by the PI or qualified designee. The PI will attempt, if possible, to establish a diagnosis based on presenting signs and symptoms. The nature of the AE, time of onset relative to study drug administration, duration, severity, and relationship to treatment should be determined. Details of any corrective treatment must be recorded in the eCRF. The PI will determine whether any changes have occurred in baseline signs and symptoms. All AEs and SAEs will be collected in the eCRF.

15.9 Serious Adverse Event Reporting Requirements

All SAEs must be reported within 24 hours of the site becoming aware of the SAE. Any event that is serious, study drug related, and unexpected as assessed by the medical monitor or the Sponsor will be submitted to the regulatory authorities in accordance with national regulatory laws and regulations. The PI will be responsible for reporting all SAEs that require reporting to the local or central Institutional Review Board/Ethics Committee (IRB/EC) in accordance with its regulations and guidelines.

15.10 Adverse Event and Serious Adverse Event Follow-up

All AEs and SAEs will be followed up to resolution (the subject's health has returned to his or her baseline status or all variables have returned to normal) or until an outcome is reached, stabilization occurs (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained, regardless of whether the subject is still participating in the study. All appropriate therapeutic measures should be undertaken and recorded. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

15.11 Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports and Follow-Up SAE Reports: To report an SAE, the SAE eCRF form within the Electronic Data Capture (EDC) system must be completed. All SAEs, whether or not deemed drug-related or expected, must be reported by the investigator or qualified designee within 24 hours of first becoming aware of the event. The investigator/qualified designee will enter the required information regarding the SAE into the appropriate form, which will automatically result in distribution of the information to the appropriate sponsor contact.

If the EDC system is temporarily unavailable (> 24 hours), the event, including the) investigator-determined causality to study drug, should be reported via a paper back-up SAE form AWINSA (contact information, i.e., e-mail or fax will be available on the SAE form).

Upon return of the availability of EDC system, the SAE information must be entered into the EDC system as soon as possible. The SAE form within the EDC system must be updated within 24 hours of knowledge/receipt of SAE follow-up information.

15.12 Procedures for Emergency Unblinding

The Investigator should only be unblinded if it is necessary to determine treatment of an emergency. Emergency unblinding is performed via the study Interactive Web Response System (IWRS) and investigators are able to unblind any subjects randomized at their institution. The independent pharmacovigilance group (PVG) can also unblind study subjects should emergency unblinding be deemed necessary during ongoing safety review. If for whatever reason the Investigator and PVG safety reviewer are unable to unblind a subject, select sponsor personnel can unblind subjects if needed. No sponsor personnel directly involved in managing the study or making treatment recommendations have unblinded access to treatment arm. If the evaluator is unblinded, the reason for unblinding should be documented in the comment page of the eCRF.

16.0 Data Collection, Study Monitoring, and Record Management

16.1 Data Collection and Reporting

Data for this study will be collected using eCRFs. The investigator and study site staff will receive training regarding the completion of the eCRF. Visit-specific data should be entered into the eCRF and be ready for review as soon as possible.

All protocol-required information collected during the study must be entered by the investigator or designated representative in the source documents and eCRF. All data entry, modification, or deletion will be recorded indicating the individual subject, original value, the new value, the reason for change, who made the change, and when the change was made. All data changes will be clearly indicated with a means to locate prior values. The investigator will maintain a list of individuals who are authorized to enter or correct data on the eCRFs.

The investigator or designated sub-investigator, following review of the data in the eCRF, will confirm the validity of each subject's data by signing the eCRF.

16.2 Study Monitoring

Study progress will be monitored by the sponsor or its representative as frequently as necessary to ensure adequate and accurate data collection, protocol compliance, and study conduct in accordance with accepted regulatory requirements. The principal investigator must make all the patient data available to the monitor for review during the planned site monitoring visits. Arrangements for monitoring visits will be made in advance, except in emergency cases.

16.3 Investigator Study Files

The PI is responsible for maintaining all study-related documents in study files. The Sponsor will notify the PI when retention of study files is no longer necessary. The following documents will be kept in the study files or be readily accessible:

- original protocol and all amendments
- signed agreement or protocol
- signed and dated study staff roles and responsibilities log
- copy of the current *curriculum vitae* of the PI and of all sub-investigators
- FDA Form 1572 for US Investigators and ICH E#6 Compliance Statement for Non-US Investigators
- IRB/EC membership list and all IRB/EC approvals for the protocol and amendments, informed consent documentation and all updates, advertisements, and written information provided to subjects; all IRB/EC correspondence; documentation that the IB and subsequent revisions have been submitted to the IRB/EC; documentation that all SAEs and any periodic safety reports have been submitted to the IRB/EC; and annual IRB/EC renewals (as required)
- updated laboratory certification and the laboratory's normal values (covering the entire time interval of the study for all laboratory tests conducted during the study);
- all confirmations of investigational drug receipt, drug accountability logs, and drug return records
- an electronic copy of all final subject eCRF data
- all correspondence to or from the Sponsor or its designees
- blank informed consent form
- Investigator's Brochure
- subject screening log
- subject list (contains subject initials and/or protocol-specific subject number)
- all subjects' original signed informed consents
- monitoring visit log

16.4 Retention of Records

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Sponsor will inform the PI/institution in writing of the need for record retention and will notify the PI/institution in writing when the trial-related records are no longer needed.

An investigator who withdraws from the responsibility of maintaining study records or wishes to move them to a new location has the obligation to place them in safekeeping and to inform the Sponsor of their location.

16.5 Data Protection

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data, SCYNEXIS has implemented and maintains the following measures:

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- SCYNEXIS will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The [participant/participants' parent(s)/LAR(s)] must be informed that [their personal/their child's] study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the [participant/participants' parent(s)/LAR(s)], that [their/their child's] data will be used as described in the informed consent.
- The [participant/participants' parent(s)/LAR(s)] must be informed that [their/their child's] medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between SCYNEXIS and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. Third parties working on behalf of SCYNEXIS are contractually bound to protect participant coded data. SCYNEXIS will protect participant coded data and will only share it as described in the ICF.
- SCYNEXIS has a global, internal policy that requires all staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

17.0 Statistical Analysis Plan

All statistical analysis will be performed using SAS® version 9.3 or later, unless otherwise stated. All statistical tests will be two-sided and interpreted at a 5% significance level.

Descriptive statistics (i.e., mean, standard deviation, median, minimum, maximum, etc.) will be provided for all continuous variables; frequencies and percentages will be tabulated for incidence

and categorical variables. For parameters measured over time, observed values and changes from baseline will be described for each time point.

A Statistical Analysis Plan (SAP) describing all final statistical analyses in detail will be provided as a separate document. The SAP will be finalized prior to the unblinding of the study treatments for analysis.

17.1 Sample Size Determination

This trial will randomize approximately 220 subjects into one of two treatment regimens at a 1:1 ratio. A sample size of 110 subjects per treatment group will provide > 90% power (two-sided α = 0.05) to declare non-inferiority (within a 20% non-inferiority margin [NIM]) of IV echinocandin followed by oral ibrexafungerp compared to IV echinocandin followed by oral fluconazole assuming a true 30-day ACM rate of 27% in both treatment groups. IV echinocandin followed by ibrexafungerp will be considered non-inferior to IV echinocandin followed by oral fluconazole if the upper limit of the 2-sided 95% CI for the difference in response rates between ibrexafungerp and fluconazole is less than 20%. In addition, a trial including 110 evaluable patients per arm would have 90% power to show non-inferiority for a global response endpoint, assuming a -20% NI margin, a true global response rate of 70% for each treatment group and one-sided alpha=0.025.

A blinded sample size reassessment will take place after 70% of the subjects have primary endpoint data available. The blinded sample size re-estimation will either confirm the initial sample size estimate or increase the sample size to ensure the study has adequate power for the primary outcome measure, up to a maximum of 308 subjects. No sample size adjustment downwards will be performed. The sample size re-estimation will be based on a blinded review of the ACM data for the ITT population, pooled across treatment groups. The sponsor will remain blinded to treatment group for both the FS-MITT and FN-ITT populations when performing this review.

17.2 Analysis Populations

The populations for the study are:

- Intent-to-Treat (ITT) Population: The ITT Population will include all randomized subjects.
- Modified Intention-to-Treat (MITT) Population: The MITT Population will include all subjects from the ITT population who received oral step-down therapy.
- Fluconazole susceptible (FS-MITT) Population: The FS-MITT population will include all subjects in the MITT population who are treated under the double-blinded portion of the study.
- Fluconazole non-susceptible (FN-MITT) Population: The FN-MITT population will include all subjects in the MITT population who received open-label step-down therapy.
- Per-protocol (PP) Population: The PP population will include all subjects in the ITT population who meet key inclusion and exclusion criteria and do not have major protocol deviations.

- PK Population: The PK population will include all enrolled subjects who provide at least one PK sample and no deviations significant enough to affect the interpretability of PK data.
- Safety Population: The Safety Population will include all subjects who receive at least one dose of on-study antifungal treatment (either IV or oral).

17.3 Patient Disposition, Discontinuation, and Baseline Data

Patient disposition in terms of the number and percentage of patients enrolled by site will be tabulated. The number of patients randomized, number completing the study, and reasons for discontinuation will be summarized by treatment group. Patient demographics and baseline characteristics such as age, race, sex, weight, height, body mass index, region, and other relevant parameters will be tabulated and compared across treatment groups. The stratification factors of APACHE II score (≤ 20 or > 20), absolute neutrophil count (≤500 or > 500 per cubic millimeter), and geographic region (North America-Europe, China and Other) will also be summarized by treatment group.

17.4 Independent Data Monitoring Committee (IDMC)

An external IDMC will be established to review safety data. The IDMC will review available, unblinded, safety data at least once a year during the conduct of the study i.e., from the first subject's enrollment in this study until the last subject has completed the safety follow-up visit and when approximately 70% of subjects have completed the safety follow-up visit. Other IDMC reviews may be conducted for safety reasons as required. The IDMC will be comprised of clinicians and a statistician who are experienced in studies of fungal infections. The roles and responsibilities of the IDMC, timing of meetings as well as the data to be provided for review will be described in a detailed charter, in compliance with guidelines of the FDA and ICH.

17.5 Handling of Missing Data, Dose Adjustments, and Early Withdrawals

Every effort will be made to collect all-cause mortality data to Day 30, and as such no missing data are expected. For subjects who withdraw from the study early, every effort will be made to collect end of treatment information at the point of withdrawal. Sensitivity analyses may be performed using multiple imputations to further assess the robustness of study results.

17.6 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary terminology. The number and percentage of subjects taking each medication before and after randomization will be tabulated by treatment group for each stage of the study.

17.7 Efficacy

17.7.1 Efficacy Analyses

Efficacy will be assessed primarily in terms of ACM. In addition, Global Response (primary for EU only), Clinical Response, Mycological Response, absence of recurrence, and survival with no recurrence will also be assessed (see Section 8.0 for primary and secondary study endpoints).

The addendum to ICH E9 introduces the concept of an estimand. The estimand framework is a systematic approach to ensure alignment among clinical trial objectives, trial execution/conduct, statistical analyses, and interpretation of results. The details of the primary and secondary estimands are described in Appendix 20.3 and the handling of estimands will be further detailed in the SAP.

The primary analysis will be conducted in the ITT population, so will include patients who receive double-blind step-down therapy and also those patients who receive open-label step-down therapy of ibrexafungerp or BAT.

17.7.1.1 All-Cause Mortality

All-cause mortality will be defined as death during the prespecified period of evaluation, regardless of attribution. Subject status (alive or deceased) as well as date of death will be documented. If the subject is deceased, the investigator's assessed relationship to the fungal infection will also be recorded. If an autopsy is conducted, key findings should be collected in the eCRF. Subjects whose vital status is not known at Day 30 will be considered as having died in the calculation of the all-cause mortality rate for the primary analysis.

17.7.1.2 Recurrence

Recurrence is defined as a diagnosis of invasive candidiasis and/or candidemia in subjects who previously achieved Global Success. Recurrence of the *Candida* infection is required to be with the same species and involving the same site that was initially identified at Screening. The DRC will be responsible for determining recurrence.

17.7.1.3 Treatment Outcome (Clinical Response, Mycological Response, Radiological Response, and Global Response)

Treatment outcome (Clinical Response, Mycological Response and Global Response) will be assessed as follows:

Clinical Response

Success:

- Resolution of all attributable clinical symptoms and physical findings
- Partial resolution of attributable clinical symptoms and physical findings

Failure:

- No resolution of any attributable clinical symptoms and physical findings and/or worsening, including subjects requiring any other systemic antifungal agent due to worsening after stepping down to the assigned oral antifungal.
- Not done or missing

Alternative approaches to handling missing data and intercurrent events will be specified in the SAP.

Mycological Response (by the DRC)

Success: Mycological response as defined by Eradication or Presumed Eradication

- Eradication: clearance of *Candida* from the bloodstream or invasive candidiasis source (clearance for candidemia is defined as 2 negative blood cultures drawn at least 24 hours apart)
- Presumed Eradication: subjects who have no follow-up cultures available but who have a clinical outcome of Success (i.e., improved based on objective, non-culture related parameters [e.g., clinical signs and symptoms or radiological findings])

Failure: Mycological response as defined by Persistence or Presumed Persistence

- Persistence: Persistent isolation of *Candida* species from blood specimens or specimens from other sterile sites
- Presumed Persistence: subjects who have no follow-up cultures available but who have a clinical outcome of failure

Radiological Response for qualified infections (by the DRC)

Success:

- Complete resolution of attributable radiological findings
- Partial resolution of attributable radiological findings (e.g., remaining findings not indicative of progressive or active infection)

Failure:

- No resolution of any attributable radiological findings and/or worsening

Note: Missing radiological outcomes will not be considered failures if the clinical and mycological outcomes are successful.

Global Response (by DRC)

Success: Defined as clinical success plus mycological success plus radiological success (when applicable) and did not receive alternative (rescue) antifungal therapy for invasive candidiasis or candidemia treatment initiated within 48 hours of Day 30 or EOT visits

or any time prior to FU timepoints.

Failure: All subjects that did not meet criteria for success.

17.7.2 Primary Efficacy Analysis

Based on feedback from different regulatory agencies, different primary efficacy variables will be used for the study. For non-EU, the primary efficacy variable for the study is the percentage of subjects with 30-day ACM, and for the EU, the primary efficacy variable is Global Response. Detailed analyses will be outlined in the SAP.

The primary efficacy assessment will be performed for the ITT population. Supplementary analyses will also be conducted for the MITT, FS-MITT, FN-MITT, and PP Populations. To assess non-inferiority, an estimate of the difference in mortality rates will be calculated along with a 95% confidence using the method of Mietinnen and Nurminen. Intravenous echinocandin followed by ibrexafungerp will be considered noninferior to IV echinocandin followed by oral fluconazole if the upper limit of the 2-sided 95% CI for the difference in response rates between the ibrexafungerp group and the fluconazole group is less than 20%. If non-inferiority is concluded, an assessment of superiority will also be performed. Superiority will be concluded if the entire 95% confidence interval is below zero. Additional supplemental and sensitivity analyses may be included in the SAP. A logistic regression analysis may be performed to identify predictors of mortality. Point estimates and the corresponding 95% confidence intervals for the odds ratios for the identified risk factors may also be calculated.

Survival will also be summarized by treatment group using Kaplan-Meier plots.

17.7.3 Secondary Efficacy Analysis

All categorical secondary efficacy variables will be analyzed using the same approach as for the primary efficacy variable where appropriate. The secondary efficacy assessment will be performed for the ITT, MITT, FS-MITT, FN-MITT, and PP Populations. Additional sensitivity /supplementary analyses will be specified in the SAP.

17.8 Pharmacokinetics

The PK analyses will be performed for the PK population. For the subset of subjects undergoing PK analysis, sparse PK samples collected during treatment (1, 2, and 7 days after the start of oral dosing and between 36 and 60 hours after the last dose) will be analyzed by Population PK (Pop PK) analysis using NONMEM to estimate PK parameters (e.g., C_{max} and AUC). Additional PK samples will be collected on Days 14 and 30 for subjects still receiving study treatment. A stand-alone Pop PK report will be prepared to describe the PK analyses from this part of the study. Efforts will be made to record the proximity of the last meal to dose on PK collection days. If sufficient subjects volunteer for PK sampling, an analysis of efficacy outcomes by attained exposure will be conducted.

17.9 Disease Severity and Healthcare Data Analysis

APACHE II Score, qSOFA Score and Healthcare Economic Data will be summarized using descriptive statistics.

17.10 Safety Analyses

The safety analysis will be performed for the Safety Population (all randomized subjects).

Additional safety analyses in subjects who receive oral step-down therapy and in subjects with adverse events occurring after oral step-down will be conducted.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class, preferred term and treatment group, and ordered by decreasing frequency for all subjects. Separate tabulations will list events according to seriousness, severity, and possible association with investigational therapy, if applicable. Subjects who discontinued treatment because of AEs and those who had a serious AE will be summarized.

Clinical laboratory data will be summarized using descriptive statistics and shifts from baseline (with categories for below, within, and above the normal range). Vital signs and body weight will also be summarized. Results will be summarized for each timepoint and for changes in each variable from baseline.

18.0 Ethics and Protection of Human Patients

18.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, the ethical principles established by the Declaration of Helsinki (as amended in Fortaleza, Brazil, October 2013), the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, the United States Code of Federal Regulations (CFR) sections that address clinical research studies, applicable European Union regulations, including the European Union Clinical Trial Regulation 536/2014 (EU-CTR) and/or other national and local ethical and legal requirements, as applicable.

18.2 Institutional Review Board/Ethics Committee Review

The PI or Contract Research Organization (CRO) must provide the IRB/EC with all appropriate materials, including a copy of the subject ICF. The study will not be initiated until the PI or CRO obtains written approval of the protocol and the subject ICF from the appropriate IRB/EC, and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the PI to the IRB/EC, medical monitor, and Sponsor in accordance with applicable government regulations and in agreement with policy established by the Sponsor.

18.3 Informed Consent

The ICH issued guidelines to provide protection for human subjects in clinical investigations. The ICH Tripartite Guideline for GCP establishes the general requirements for informed consent. Each subject will be provided with oral and written information in a language they can understand that describes the nature and duration of the study. Before undergoing screening, each subject must consent in writing to study participation. The subject (or the subject's legal representative) will sign and personally date the subject ICF. The person rendering consent will also sign and personally date the subject ICF as the person who obtained the consent of the subject. The original signed subject ICF will be retained with the study center's records. Each subject will receive a copy of his or her signed subject ICF. In addition, the PI, or his or her designee, must document in the case history that informed consent was obtained before study participation.

18.4 Future Use of Samples

Candida isolates collected during the study (see Section 13.2.2) may be maintained in repositories for potential future use. Future research of *Candida* isolates may include *in vitro* susceptibility testing of new or existing antifungals or analysis of mechanisms of resistance. Future research of *Candida* isolates may also include studies that are unknown at this time. The samples will be retained as long as deemed useful for research purposes. All samples will be identified only by a coded number to maintain patient confidentiality. Researchers requesting samples or information from the repository must have a research protocol approved by an Institutional Review Board/Ethics Committee. Samples will only be retained for patients that provided consent for future use.

18.5 Subject Privacy and Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number to maintain subject privacy and confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be performed with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the medical monitor, IRB/EC, the Food and Drug Administration (FDA), the Sponsor or where required by law. All local privacy laws must be followed.

18.6 Study Termination

The PI, the sponsor, the FDA, and the IRB/EC each reserve the right to terminate the study in the interest of subjects' safety and welfare. The sponsor reserves the right to terminate the study at any time for administrative reasons.

18.7 Financial Disclosure

The financial interests of all investigators from all participating clinical centers must be collected prior to study initiation and 1 year following the completion of the clinical trial.

19.0 References

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20.0 Appendices

20.1 Prohibited Medications and Medications to be Administered with Caution

20.1.1 Ibrexafungerp

Prohibited Medications:

No antifungal treatment other than the study treatment (blinded and open-label) is allowed during the study.

No investigational drugs (i.e., new chemical entities) other than the study drug are allowed within at least 30 days or five and a half half-lives of the investigational product before Screening and throughout the study.

Subjects exposed to prohibited medications may be allowed in the study when treatment options are limited, in discussion with the Sponsor based on a risk-benefit analysis.

Strong CYP3A4/5 inhibitors and CYP3A4/5 inducers

CYP	Strong/Moderate Inhibitors	Inducer[a]
3A4/5	Reversible inhibitors:[b] • boceprevir • conivaptan • indinavir • ketoconazole[c] • lopinavir/ritonavir • mibefradil • nefazodone • nelfinavir • telaprevir • telithromycin • itraconazole[c] • posaconazole[c] • voriconazole[c]	• avasimibe • carbamazepine • phenytoin • rifampin • St. John's wort
	Time-dependent inhibitors:[a] • clarithromycin • ritonavir • saquinavir	

a. The CYP3A4/5 inducers and strong time-dependent CYP3A4/5 inhibitors listed in this table are not permitted during the 72 hours prior to initiation of oral study drug and during study treatment with oral study drug.
b. The reversible CYP3A4/5 inhibitors listed in this table are not permitted during 48 hours prior to the administration of oral study drug, and during the study treatment.
c. No systemic antifungal treatment other than the study drug is allowed during the study, unless administered as BAT

Medications to be administered with Caution and Monitored as Appropriate

CYP3A4 Substrates	*In vitro*, ibrexafungerp was an inhibitor of CYP3A mediated metabolism of midazolam, but was only a weak inhibitor of metabolism of testosterone. The clinical significance of this inhibition is unknown; caution should be exercised when administering ibrexafungerp with drugs known to be CYP3A sensitive substrates with narrow therapeutic index. Subjects receiving sirolimus, tacrolimus or warfarin are permitted for enrollment in the study and these medications may be administered concomitantly with ibrexafungerp with close monitoring. The administration of either sirolimus or tacrolimus should be offset by no less than 2 hours with the administration of ibrexafungerp. At a minimum, blood levels of sirolimus and tacrolimus or prothrombin time/partial thromboplastin time/international normalized ratio for subjects on warfarin should be measured after the first dose of ibrexafungerp and when the subject has received between 3 and 7 days of ibrexafungerp (at which time, ibrexafungerp concentrations will have reached steady state). Dosing adjustments and subsequent monitoring of sirolimus, tacrolimus and warfarin should be undertaken in accordance with product prescribing information for the respective agents.
P-gp Substrates	Ibrexafungerp resulted in a 1.4-fold increase in the systemic exposure of the sensitive P-gp substrate dabigatran. Therefore, ibrexafungerp is a mild inhibitor of P-gp. Subject receiving drugs that are P-gp substrates with narrow therapeutic index (e.g. digoxin, colchicine, vinblastine, talinolol) may be enrolled in the study with close monitoring.
OATP1B3 Substrates	Ibrexafungerp resulted in a 2.8-fold increase in the systemic exposure of the sensitive OATP1B3 transporter substrate pravastatin. Subjects receiving drugs that are OATP1B3 substrates such as statins, repaglinide, olmesartan, enalapril, valsartan, paclitaxel and docetaxel, cisplatin, and methotrexate may be enrolled in the study with close monitoring.
Proton Pump Inhibitors (PPIs)	Proton pump inhibitors (PPIs) may interfere with ibrexafungerp absorption. Pantoprazole, a PPI, decreased ibrexafungerp exposure by approximately 25%. Use PPIs with caution.

20.1.2 Fluconazole

Fluconazole Label (LAB-0380-13.0, 06/2022)[13]

Prohibited medications:

Coadministration of other medicinal products known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as erythromycin, pimozide and quinidine

Medications to be administered with caution and monitored as appropriate

Potential effect of the drug on fluconazole, or potential effect of fluconazole on the drug. Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor and a strong inhibitor of CYP2C19. Concomitant administration of drugs with a narrow therapeutic window metabolized through CYP2C9 and CYP3A4 should be monitored for adverse reactions:

alfentanil, amiodarone, amitriptyline, nortriptyline, amphotericin B, calcium channel blockers, carbamazepine, celecoxib, coumarine-type anticoagulants, cyclophosphamide, cyclosporin, fentanyl, HMG CoA reductase inhibitors, ibrutinib, ivacaftor and fixed dose ivacaftor combinations, Lemborexant, losartan, lurasidone, methadone, NSAIDs, olaparib, oral hypoglycemics, phenytoin, prednisone, rifabutin, rifampin, saquinavir, short acting benzodiazepines, sirolimus, tacrolimus, theophylline, tofacitinib, tolvaptan, triazolam, vinca alkaloids, vitamin A, voriconazole, zidovudine

In addition to the drugs listed, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 co-administered with fluconazole and caution should be exercised when using these combinations and patients should be carefully monitored.

20.2 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 (°C)	≥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	
Respiratory 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	350-499	200-349		<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]	x2 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 post elective 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 1985[14]

a. Mean arterial pressure = (systolic blood pressure + [2 x 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 the hospital admission and conform to the following criteria:

Liver	Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper gastrointestinal bleeding attributable to portal hypertension; pr 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 (i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respiratory dependency.
Renal	Receiving chronic dialysis.
Immunocompromised	The patient has received therapy that suppresses reistance to infection (e.g., immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS).

20.3 Estimands

20.3.1 Primary Estimand

20.3.1.1 Primary Estimand (non-EU)

The primary (non-EU) clinical question of interest is: What is the treatment effect on all-cause mortality at Day 30 when treated with IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) relative to IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) in fluconazole susceptible participants or best available treatment (BAT) in fluconazole resistant participants, with a diagnosis of candidemia and/or invasive candidiasis, regardless of treatment discontinuation?

The primary estimand for non-EU is described by the following attributes:

- Population: Adult (≥ 18 years of age) male and female participants with a diagnosis of candidemia and/or invasive candidiasis, defined as evidence of *Candida* spp. in either bloodstream or tissue/fluid culture prior to initiation of IV echinocandin, accompanied by any related clinical sign and/or symptom. Participants can be fluconazole susceptible or fluconazole resistant.
- Treatment conditions: IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) versus IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) or BAT, regardless of adherence. IV plus oral treatment duration will be a minimum of two weeks, to a maximum of six weeks.
- Variable: Vital status (dead/alive) at Day 30.
- Summary measure: Difference in the proportion of deaths in the IV + ibrexafungerp [p1] and IV + fluconazole (or BAT) [p2] treatment groups [p1-p2].
- Intercurrent events (ICE):
    - Study treatment discontinuation (due to any reason) – treatment policy strategy (interest is in the treatment effect regardless of study treatment discontinuation).
    - Use of concomitant potentially effective systemic antifungal agents – treatment policy strategy (interest is in the treatment effect regardless of use of systemic antifungal agents).

Rationale for estimand:

Interest lies in the treatment effect regardless of whether the full course of randomized treatment was taken or not, and the use of other systemic antifungal agents which reflects how patients may be treated in clinical practice. Hence a treatment policy strategy is appropriate.

20.3.1.2 Primary Estimand (EU)

The primary (EU) clinical question of interest is: What is the treatment effect on successful Global Response rate at EOT when treated with IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) relative to IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) in fluconazole susceptible participants or BAT in fluconazole resistant participants, without the use of systemic antifungal agents as rescue medication and with a diagnosis of candidemia and/or invasive candidiasis regardless of treatment discontinuation treating death as a failure?

The primary estimand for EU is described by the following attributes:

- Population: Adult (≥ 18 years of age) male and female participants with a diagnosis of candidemia and/or invasive candidiasis, defined as evidence of *Candida* spp. in either bloodstream or tissue/fluid culture prior to initiation of IV echinocandin, accompanied by any related clinical sign and/or symptom. Participants can be fluconazole susceptible or fluconazole resistant.
- Treatment conditions: IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) versus IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) or best available treatment (BAT), regardless of adherence. IV plus oral treatment duration will be a minimum of two weeks, to a maximum of six weeks.
- Variable: Successful global response, as determined by the blinded data review committee (DRC) is based on clinical response as determined by the PI, mycological, and radiological response (when applicable) at EOT. It is defined as clinical success plus mycological success plus radiological success (when applicable), without the participant receiving concomitant potentially effective systemic antifungal agent prior to EOT.
    - Successful clinical response is defined as resolution of all, or partial resolution of attributable clinical symptoms and physical findings present at baseline.
    - Successful mycological response is defined as eradication (clearance for candidemia i.e., two negative blood cultures drawn at least 24 hours apart) or presumed eradication (participants who have no follow-up cultures available, but who have a successful clinical outcome) by EOT.
    - Successful radiological response for qualified infections, as determined by the DRC is defined as complete resolution or partial resolution (e.g., remaining findings not indicative of progressive or active infection) of attributable radiological findings.
- Summary measure: Difference in the proportion of participants with successful global response in the IV + ibrexafungerp [p1] and IV + fluconazole (or BAT) [p2] treatment groups [p1-p2].
- Intercurrent events (ICE):
    - Study treatment discontinuation – treatment policy strategy (interest is in the treatment effect regardless of study treatment discontinuation).

- Use of concomitant potentially effective systemic antifungal agents– composite strategy. This intercurrent event is captured through the definition of clinical response and will be counted as global response failure. (Note: Use of systemic antifungal agents as secondary prophylaxis after EOT is allowed in the study).
- Death – composite strategy. This intercurrent event is captured through the definition of clinical response and will be counted as global response failure.

Rationale for estimand:

Interest lies in the treatment effect without the use of other systemic antifungal agents regardless of whether the full course of randomized treatment was taken or not which reflects how patients may be treated in clinical practice. Hence a treatment policy strategy is appropriate for not completing the full course of randomized treatment. Use of other systemic antifungal agents will affect the clinical response and the mycological response and hence the global response will be considered as failure. Death will affect the clinical response, and the global response will be considered as failure.

20.3.2 Secondary Estimands

For each of the secondary endpoints, the estimands will follow a similar approach to the estimand for the primary endpoint and the same general strategies for determination of ICEs will be used.

The summary measures for the secondary endpoints are based on the difference between treatment groups and these endpoints will be summarized.

Efficacy:

The secondary clinical efficacy questions of interest are: What is the effect on global response/clinical/mycological/recurrent/fungal-free survival outcomes when treated with IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) relative to IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) in fluconazole susceptible participants or BAT in fluconazole resistant participants, without the use of systemic antifungal agents as rescue medication and with a diagnosis of candidemia and/or invasive candidiasis regardless of treatment discontinuation treating death as a failure?

Safety:

Safety endpoints will use a treatment policy strategy for the ICE of withdrawal from treatment as the safety will be assessed at all post-Baseline assessments irrespective of whether the participant completed the treatment or received non-study concomitant therapy.

PK:

The plasma concentration endpoints will use a while-on-treatment policy strategy for the ICEs of withdrawal from treatment.

Estimand for the Secondary Endpoints

Secondary Endpoint	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
Global Response at Day 14	Participants with Invasive Candidiasis/ Candidemia	IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) versus IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) or best available treatment (BAT), regardless of adherence	See Table 10	Difference in the proportion of participants with successful global response in the IV + ibrexafungerp [p1] and IV + fluconazole (or BAT) [p2] treatment groups [p1-p2]	Study treatment discontinuation – treatment policy strategy Use of systemic antifungal agents – composite strategy Death – composite strategy
Global Response at Day 30 and EOT	Participants with Invasive Candidiasis/ Candidemia	IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) versus IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400	See Table C	Difference in the proportion of participants with successful global response in the IV + ibrexafungerp [p1] and IV + fluconazole (or BAT) [p2] treatment groups [p1-p2]	Study treatment discontinuation – treatment policy strategy Use of systemic antifungal agents – composite strategy Death – composite strategy

Secondary Endpoint	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
		mg QD) or best available treatment (BAT), regardless of adherence			
Clinical Response at Day 14, Day 30 and EOT	Participants with Invasive Candidiasis/ Candidemia	IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) versus IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) or best available treatment (BAT), regardless of adherence	See Table A	Difference in the proportion of participants with successful clinical response in the IV + ibrexafungerp [p1] and IV + fluconazole (or BAT) [p2] treatment groups [p1-p2]	Study treatment discontinuation – treatment policy strategy Use of systemic antifungal agents – composite strategy Death – composite strategy
Mycological Response at Day 14, Day 30 and EOT	Participants with Invasive Candidiasis/ Candidemia	IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) versus IV echinocandin followed	See Table B	Difference in the proportion of participants with successful mycological response in the IV + ibrexafungerp [p1] and IV +	Study treatment discontinuation – treatment policy strategy Use of systemic antifungal agents – composite strategy

Secondary Endpoint	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
		by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) or best available treatment (BAT), regardless of adherence		fluconazole (or BAT) [p2] treatment groups [p1-p2]	Death – composite strategy
No recurrence of *Candida* infection at 2 weeks and 6 weeks after EOT	Participants with Invasive Candidiasis/ Candidemia	IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) versus IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) or best available treatment (BAT), regardless of adherence, in participants who previously achieved successful Global response prior to EOT	See Protocol section 17.6.1.2	Difference in the proportion of participants with no recurrence of *Candida* infection in the IV + ibrexafungerp [p1] and IV + fluconazole (or BAT) [p2] treatment groups [p1-p2]	Study treatment discontinuation – treatment policy strategy Use of systemic antifungal agents – composite strategy Death – composite strategy

Secondary Endpoint	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
Fungal-free survival at 6 weeks after EOT	Participants with Invasive Candidiasis/ Candidemia	IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) versus IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) or best available treatment (BAT), regardless of adherence	Mycological success and alive at 6 weeks after EOT	Difference in the proportion of patients who are mycological success and alive.	Study treatment discontinuation – treatment policy strategy Use of systemic antifungal agents – composite strategy Death – composite strategy
Safety	Participants with Invasive Candidiasis/ Candidemia	IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD) versus IV echinocandin followed by oral fluconazole (800 mg QD for one day, followed by 400 mg QD) or best	TEAEs, drug-related AEs, discontinuations due to AEs, SAEs, and safety laboratory assessments	Summary statistics (appropriate for each type of endpoint) in the IV + ibrexafungerp and IV + fluconazole (or BAT) groups separately	Study treatment discontinuation – treatment policy strategy Use of systemic antifungal agents – treatment policy

Secondary Endpoint	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
		available treatment (BAT), regardless of adherence			
Pharmacokinetic	Participants with Invasive Candidiasis/ Candidemia	IV echinocandin followed by oral ibrexafungerp (750 mg BID for two days, followed by 750 mg QD)	Population PK analysis	Summary statistics (appropriate for each type of endpoint) in the IV + ibrexafungerp group	Study treatment discontinuation – while on treatment strategy

Table A: Clinical Outcome and Response at post Baseline visit – Day 14, Day 30 and EOT

Defining Criteria	Outcome	Response
Resolution of all attributable clinical symptoms and physical findings of IC/Candidemia present at Baseline (and no new symptoms or findings), without the participant receiving other systemic antifungal agents as rescue medications before the Visit	Clinical resolution	Clinical success
Partial resolution of attributable clinical symptoms and physical findings of IC/Candidemia present at Baseline (and no new symptoms or findings), without the participant receiving other systemic antifungal agents as rescue medications before the Visit	Partial clinical resolution	Clinical success
No resolution of any attributable clinical symptoms and physical findings of IC/Candidemia present at Baseline, after stepping down to the assigned oral antifungal prior to or on the date of the Visit	No clinical resolution	Clinical failure
Worsening of any attributable clinical symptoms and physical findings of IC/Candidemia present at Baseline, including the participant receiving any other potentially effective systemic antifungal agents to	Clinical worsening	Clinical failure

treat IC/candidemia after stepping down to the assigned oral antifungal prior to or on the date of the Visit		
The Baseline clinical assessment is missing	Unable to determine	Clinical failure at all visits
Clinical Assessment (Day 14/30/EOT) is missing	Unable to determine	Clinical failure at visit

Table B: Mycological Outcome and Response (by DRC) at post Baseline visit – Day 14, Day 30 and EOT

Defining Criteria	**Outcome**	**Response**
Clearance of *Candida* from the bloodstream or invasive candidiasis source (defined as 2 negative blood cultures drawn at least 24 hours apart) prior to Visit, without the participant receiving other systemic antifungal agents as rescue medications before the Visit	Mycological eradication	Mycological success
Participants with IC who have no follow-up cultures available but who have a clinical response of Success (i.e. improvement based on objective, non-culture related parameters (e.g. clinical signs and symptoms or radiological findings)) at visit, without the participant receiving other systemic antifungal agents as rescue medications before the Visit	Presumed mycological eradication	Mycological success

Participants with persistent isolation of *Candida* species from blood specimens or specimens from other sterile sites at visit.	Mycological persistence	Mycological failure
Participants with IC who have no follow up cultures available (missing) but who have a clinical response of failure at visit.	Presumed mycological persistence	Mycological failure

Table C: Global Response at each visit – Day 14, Day 30, and EOT

Defining Criteria	**Response**
Successful clinical response and successful mycological response and successful radiological response and did not receive systemic antifungals as rescue medication for IC/candidemia prior to visit	Success
Participants that did not meet criteria for success	Failure

20.4 Protocol Revision History

20.4.1 Protocol Amendment 4

20.4.1.1 Protocol Amendment 4: Revisions to Protocol Amendment 2

Revisions to Protocol dated 24 November 2022. **Current Version and Date: Protocol Amendment 4 (Protocol Version 4.0) dated 12 August 2024.** Amended to delete the ~~strikethrough~~ text and include the **bolded** text.	
Protocol Section	*Rationale and modification* **Overall Rationale for Amendment 4 (Updates to Amendment 2)** ➢ Valuable feedback was collected from PI's during Investigator Meetings and updates were made to reduce the trial participation burden on the patients, without compromising on patient safety and scientific integrity of the study. In addition, based on feedback from operational teams, information was added or text amended to provide clarification to different protocol sections. ➢ Safety reviews by an Independent Data Monitoring Committee (IDMC) were added following recommendation from some participating institutions. ➢ The MARIO study was transitioned to the European Union Clinical Trial Regulation (CTR), and text related to Data Protection was added as required under CTR. ➢ Estimand definitions were added in line with recommendations in the Addendum to ICH E9. ➢ Background information was updated to be aligned with the latest updates to the Investigator's Brochure (IB) Version 19.0, Apr 15, 2024, and the updated Brexafemme® Prescriber's Information.
	Reduced the number of in-clinic mandatory visits, expanded the visit window periods and simplified mandatory procedures and data collection to reduce the burden on patients, without compromising on patient safety and scientific integrity of the study.
9.1 Overall description of the study 13.0 Study procedures	The study will consist of a Screening visit which includes randomization, **[from 4 days prior to start of IV echinocandin, i.e.** Day -4 to before **end of IV echinocandin (**EOIV**)]**, an end of IV treatment (EOIV) visit, Oral Treatment Day~~s~~ 1 ~~and 2~~ visit~~s~~, Oral Treatment Day**s** 2 **and** 7 visit**s** (PK subset only), an end of antifungal treatment (EOT) visit, Day 14 and Day 30 visits (IV + Oral), a 2-Week FU visit (14 days after EOT) and a 6-Week FU visit (42 days after EOT). The EOIV and Oral Treatment Day 1 should ideally occur on the same day. The Day 14 and Day 30 visits may occur before, on, or after EOT. Other study visits may also be combined if they occur on the same day, **or within the protocol specified window period**. **The 2-Week and 6-Week follow-up visits may be done telephonically, remotely or via home visits, except if an in person visit to the center is clinically indicated by adverse event screening, assessment of persistent or new signs and symptoms of invasive fungal disease, or to follow up on the course of the underlying disease. EOT is end of all protocol specified treatments, including IV and oral.** **For subjects enrolled with candidemia, at least one post-baseline culture should be collected during IV echinocandin treatment.**
13.1.6 Complete physical examination	**A** complete physical examination **(done either by the treating physician or by qualified study personnel, with appropriate source documentation),** will be performed at Screening ~~and from the EOIV visit through the 6-Week FU visit.~~, **EOIV, Day 14 and EOT and at other timepoints as clinically indicated by adverse event screening and underlying diseases.**
13.1.7 Retinal examination	A retinal examination **(bedside fundoscopy or other acceptable examinations)** to rule out the presence of Candida endophthalmitis must be performed ~~at~~ **in subjects with candidemia during the** Screening **period.** ~~(within 72 hours of randomization) and on the Day 14 visit.~~ If a subject ~~is~~**becomes** symptomatic, the retinal examination ~~may be~~

	~~conducted at other time points,~~**should be repeated** as needed. Subjects with evidence of endophthalmitis, including retinitis or vitritis **diagnosed post baseline**, should be discontinued from study treatment, **but will remain in the study until last follow-up visit**.
13.2.1 Targeted physical examination to evaluate the signs and symptoms of infection	A targeted physical examination of the fungal disease site, including the clinical signs and symptoms of the fungal ~~infection, will be conducted for all subjects at all study visits~~ **disease (done either by the treating physician or by qualified study personnel, with appropriate source documentation), will be conducted for all subjects at screening, EOIV, Day 14, EOT and Day 30 and at other timepoints as clinically indicated by adverse event screening, assessment of persistent or new signs and symptoms of invasive fungal disease, or to follow up on the course of the underlying disease.**
13.2.3 Radiological assessment of non-blood sites of *Candida* infection	Images collected as SOC ~~within 72 hours prior to consent~~ **up to 5 days before screening** may be used as baseline scan**.**
13.2.4 Survival	**If an in-person visit is not possible, Day 30 ACM may be assessed remotely.**
13.2.5 Assessment of clinical response, mycological response and global response	**Assessment of response can be assessed remotely for Follow up visits when appropriate (e.g., subject was asymptomatic at EOT and no additional cultures were needed during the follow up period).**
13.2.6 Assessment of recurrence of emergent infections	**Assessment of recurrences can be assessed remotely for Follow up visits when appropriate (e.g., subject was asymptomatic at EOT and no additional cultures were needed during the follow up period).**
13.3 Pharmacokinetic procedures	**Home visits are allowed for the collection of PK samples in consenting subjects in accordance with local regulations and practicalities.**
13.4.1 Vital signs and temperature	Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate, weight and body temperature, will be measured ~~from Screening through EOT, and will also be determined at the 2-Week and 6-Week FU visits~~ **at screening, EOIV, Day 14 and EOT and at other timepoints as clinically indicated by adverse event screening and underlying diseases.**
14.0 Study Schedule	*Expanded certain window periods:* Day 14 - ~~±2~~ **-2/+3** days; Day 30 ~~±~~ ~~2~~ ~~±~~**3** days
12.1 Prior and concomitant medications	~~All medications (including prescription and over-the-counter medications, supplements, and herbal products)~~ **All systemic antifungal therapy, immunosuppressives, immunomodulators and chemotherapeutics administered** within 28 days **and all medications administered within 7 days** before screening and through the EOT will be recorded on the eCRF.
	Added clarifying text to address recurrent questions from sites and CRAs.
10.1 Inclusion criteria	2.Subject has a diagnosis of candidemia and/or invasive candidiasis, defined as evidence of Candida spp. in either a bloodstream or tissue/**fluid** culture from a normally sterile site.
10.2 Exclusion criteria	3.Subject has severe hepatic impairment ~~and~~ **due to** a history of chronic cirrhosis (Child-Pugh score > 9).
11.1.2 Randomization and switch to oral therapy	**Drug administration via naso-gastric (NG), percutaneous endoscopic gastrostomy (PEG) and Jejunostomy (J) tubes is allowed. Administration instructions are provided in the study specific product manual.**

13.1.8 APACHE II Score	The APACHE II score **(Appendix 20.2)** will be determined for each subject at Day 1 (1st dose of IV echinocandin) or closest day prior to Day 1, **using local laboratory results. APACHE II score is repeated** at EOIV, Day 14, and EOT.
13.2.2 Mycological testing AND 13.2.2.2 Culture of non-blood sites of *Candida* infection	Subjects must have a diagnosis of invasive candidiasis (including candidemia) defined as evidence of Candida in either a bloodstream or tissue/**fluid** culture from a normally sterile site Culture (**tissue or fluid)….**
13.2.2.1 Blood cultures	~~Two sets of~~ Blood cultures will be collected… **Generally, blood culture should involve samples from 2 separate draws, with at least** one set of blood culture ~~should be~~ **bottles** drawn peripherally (directly from a vein) and the other set from any existing central IV catheter. The results from all blood cultures collected during the study **will be entered in the EDC**, regardless of if they were collected as part of study procedures or SOC **(including results from initial positive culture to determine eligibility)**.
13.3 Pharmacokinetic procedures	**….**and **one sample collected** 36 to 60 hours after the last dose, when feasible.
13.4.2 Clinical safety laboratory assessments	Clinical safety laboratory tests will include biochemistry and hematology **and will be collected at selected scheduled visits as indicated in Table 5. These tests will be performed by the central laboratory.** Safety laboratory tests ~~will~~ **are only required** to be performed by the local laboratory at Screening so that timely results are available for study eligibility determination **and for calculation of the APACHE II score at screening**.
15.1 Definition of an Adverse event	Any laboratory abnormality that is deemed to be clinically significant in the opinion of the investigator **(e.g., associated with clinical signs or symptoms, require medical intervention, require interruption of the study drug treatment, leads to study discontinuation)** will be considered an AE and should be recorded in the eCRF, whether or not it is related to the study drug. **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.** ~~The disease being studied or signs or symptoms associated with the disease, unless more severe than expected for the subject's condition or a worsening of the disease being studied~~ **Events (or associated signs and symptoms), that are related to the disease being studied, candidemia or invasive candidiasis, should not be recorded as AEs, unless the event fits the definition for an SAE (Section 15.2), in which case the SAE reporting procedure should be followed (Section 15.11).**
	Clarification – statistical section
17.1 Sample size determination	The sample size re-estimation will be based on a blinded review of the ACM data **for the ITT population**, pooled across treatment groups. **The sponsor will remain blinded to treatment group for both the FS-MITT and FN-ITT populations when performing this review.**
17.7.2 Primary efficacy analysis	**Additional supplemental and sensitivity analyses may be included in the SAP.**
17.9 Disease severity and Healthcare Data Analysis	*Added text for analysis of data on "Disease Severity" and "Healthcare Data"* **APACHE II Score, qSOFA Score and Healthcare Economic Data will be summarized using descriptive statistics.**

	Corrections
8.3 Secondary endpoints	•The percentage of subjects with Successful Clinical Response at Day 14, **Day30** and EOT as determined by the PI and the DRC. •The percentage of subjects with Successful Mycological Response at Day 14, **Day30** and EOT as determined by the DRC. • The percentage of subjects with no recurrence ~~before EOT and~~ at 2 weeks and 6 weeks after EOT as determined by the DRC.
11.3.1 Ibrexafungerp description – Chemical Name	~~(1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-~~ 4H-1,4a-Propano-2H-phenanthro[1,2-c]pyran-7-carboxylic acid, 15- [(2R)-2-amino-2,3,3-~~trimethylbutyl]oxy-~~**trimethylbutoxy**]-8-[(1R)-1,2-dimethylpropyl]~~-14-[5-(4-pyridinyl)-1H-1,2,4-triazol-1-yl]-~~1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-1,6a,8,10a-tetramethyl-~~4H-1,4a-propano-2H-phenanthro[1,2-c]pyran-7-carboxylic acid, citrate salt]~~**14-[5-(4-pyridinyl)-1H-1,2,4-triazol-1-yl]-, (1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)**
13.1.11 Management of IV catheters	It is strongly recommended that IV catheters be removed or changed and replaced at a different site for all subjects with positive blood cultures for Candida within 48 hours of ~~randomization~~ **diagnosis**.
17.7.1.3 Treatment outcome – Mycological response by the DRC	Presumed Eradication: subjects ~~with invasive candidiasis~~ who have no follow-up cultures available but who have a clinical outcome of Success Presumed Persistence: subjects ~~with invasive candidiasis~~ who have no follow-up cultures available but who have a clinical outcome of failure
17.7.2 Primary efficacy analysis	The primary efficacy assessment will be performed for the ITT population. ~~Sensitivity~~ **Supplementary** analyses will also be conducted for the MITT, FS-MITT, FN-MITT, and PP Populations.
	Following recommendations from some participating institutions, safety reviews by an Independent Data Monitoring Committee (IDMC) was added.
9.1 Overall Description of the Study	**The IDMC will review available, unblinded, safety data at least once a year during the conduct of the study i.e., from the first subject's enrollment in this study until the last subject has completed the safety follow-up visit, and when approximately 70% of subjects have completed the safety follow-up visit. Additional IDMC meetings may be held as required for safety data reviews. Details will be provided in the IDMC Charter.**
17.4 Independent Data Monitoring Committee (IDMC)	**An external IDMC will be established to review safety data. The IDMC will review available, unblinded, safety data at least once a year during the conduct of the study i.e., from the first subject's enrollment in this study until the last subject has completed the safety follow-up visit and when approximately 70% of subjects have completed the safety follow-up visit. Other IDMC reviews may be conducted for safety reasons as required. The IDMC will be comprised of clinicians and a statistician who are experienced in studies of fungal infections. The roles and responsibilities of the IDMC, timing of meetings as well as the data to be provided for review will be described in a detailed charter, in compliance with guidelines of the FDA and ICH.**
	Text added per the requirement of EU Clinical Trial Regulations
Section 16.5 Data Protection	**Data Protection** **To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of**

	information and processed personal data, SCYNEXIS has implemented and maintains the following measures: • **Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.** • **SCYNEXIS will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.** • **The [participant/participants' parent(s)/LAR(s)] must be informed that [their personal/their child's] study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the [participant/participants' parent(s)/LAR(s)], that [their/their child's] data will be used as described in the informed consent.** • **The [participant/participants' parent(s)/LAR(s)] must be informed that [their/their child's] medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.** • **The contract between SCYNEXIS and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.** • **Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. Third parties working on behalf of SCYNEXIS are contractually bound to protect participant coded data. SCYNEXIS will protect participant coded data and will only share it as described in the ICF.** **SCYNEXIS has a global, internal policy that requires all staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.**
18.1 Ethical Conduct of the Study	The study will be conducted …**including the European Union Clinical Trial Regulation 536/2014 (EU-CTR)**….
	Estimand definitions were added in line with recommendations in the Addendum to ICH E9.
17.7.1 Efficacy Analysis	**The addendum to ICH E9 introduces the concept of an estimand. The estimand framework is a systematic approach to ensure alignment among clinical trial objectives, trial execution/conduct, statistical analyses, and interpretation of results. The details of the primary and secondary estimands are described in Appendix 20.3 and the handling of estimands will be further detailed in the SAP.**
Appendix 20.3 Estimands	**Appendix 20.3 Estimands** *is an additional Appendix that was added to describe the Estimand Framework in detail.*
6.1 Background Information	*Deleted text duplication and redundant text related to non-candida infection; added safety information from latest draft of the IB; added preclinical safety information from the IB to align with the updated Brexafemme® label.* ~~In addition, invasive aspergillosis has emerged worldwide as an important cause of nosocomial and community-acquired infection in a wide spectrum of immunocompromised patients. These include patients receiving cancer chemotherapy, hematopoietic stem cell transplantation and solid organ transplantation, and patients with advanced human immunodeficiency virus (HIV) infection. The overall mortality rate of invasive aspergillosis remains high, particularly the most profoundly immunocompromised patient populations.~~

	~~*Candida* is among the most common cause of healthcare-associated bloodstream infections in the United States (US), with an estimate of 25,000 healthcare-associated *Candida* infections occurring among hospitalized patients in the US each year.~~ **Preclinical safety** **In pregnant rabbits, oral ibrexafungerp administered during pregnancy was associated with fetal malformations at exposures generally greater than the estimated human exposure at the intended doses in this study. Oral ibrexafungerp administered to pregnant rats during pregnancy was not associated with fetal harm. The potential significance of these observations in rabbits to humans is not known. However, as a precaution, ibrexafungerp should not be used in pregnancy because it may cause fetal harm.** Long-term toxicology studies have been conducted in rats and dogs. In the six-month study in rats, no new toxicities or target organs of toxicity were identified (compared to the results of the shorter-term studies~~), and~~). **Daily administration of oral ibrexafungerp for 26 weeks in rats, at the highest dose was associated with marked, but reversible, lung, stomach lining, and peripheral nerve abnormalities. The potential significance of these observations in rats to humans is not known.** **Available data on ibrexafungerp use in pregnant women are insufficient to draw conclusions about any drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Women of childbearing potential are required to use two approved contraceptive methods as described in the protocol and informed consent document.** **Two cases with significant elevation of hepatic enzymes [one was a serious adverse reaction SAR)] have been reported in the clinical development program, both events resolved without intervention. Similarly, two SARs of acute kidney injury (AKI) have been reported. The association of hepatic dysfunction and AKI with ibrexafungerp is however not proven and there is no preclinical data to indicate an association either. Hepatic and renal function are being monitored in the study. Two SAEs of hallucinations and two SAEs of pneumonitis have been reported from clinical trial programs. Hallucinations and Pneumonitis were considered as potential risks requiring monitoring.**
Appendix 20.2	***Added Modified Acute Physiology and Chronic Health Evaluation (APACHE) II Score***
Appendix 20.3	***Added: Estimands***
Appendix 20.4.1	***Added Protocol Amendment 4 under Revision History***
Throughout the document	***Updated****: Synopsis; Table of Content; Section numbers; List of Abbreviations* *Updated Protocol Version and Date* *Added Trial Numbers* *Updated information for Study Medical Monitor* *Typographical and grammatical edits and minor rephrasing of language to simplify or clarity* *Updated list of abbreviations and abbreviations used in text* *Updated Table 5 – Schedule of Visits and Procedures* *Updated and added Table footnotes in line with applicable protocol sections*

20.4.1.2 Protocol Amendment 4: Revisions to Protocol Amendment 3

Revisions to Protocol Amendment 3 dated 04 August 2023.
Current Version and Date: Protocol Amendment 4 (Protocol Version 4.0) dated 12 Aug 2024.

Amended to delete the ~~strikethrough~~ text and include the **bolded** text.

Protocol Section	*Rationale and modification*
	Overall Rationale for Amendment 4 ➢ The MARIO study was transitioned to the European Union Clinical Trial Regulation (CTR), and text related to Data Protection was added as required under CTR. ➢ Safety information was added based on the latest updates to the Investigator's Brochure Version 19.0, Apr 15, 2024. ➢ Clarifying text was added based on feedback from CRAs and site staff.
6.1 Background Information	*Deleted text duplication and redundant text related to non-candida infection and added information from latest draft of the IB.* ~~In addition, invasive aspergillosis has emerged worldwide as an important cause of nosocomial and community-acquired infection in a wide spectrum of immunocompromised patients. These include patients receiving cancer chemotherapy, hematopoietic stem cell transplantation and solid organ transplantation, and patients with advanced human immunodeficiency virus (HIV) infection. The overall mortality rate of invasive aspergillosis remains high, particularly the most profoundly immunocompromised patient populations. *Candida* is among the most common cause of healthcare-associated bloodstream infections in the United States (US), with an estimate of 25,000 healthcare-associated *Candida* infections occurring among hospitalized patients in the US each year.~~ **Two cases with significant elevation of hepatic enzymes [one was a serious adverse reaction SAR)] have been reported in the clinical development program, both events resolved without intervention. Similarly, two SARs of acute kidney injury (AKI) have been reported. The association of hepatic dysfunction and AKI with ibrexafungerp is however not proven and there is no preclinical data to indicate an association either. Hepatic and renal function are being monitored in the study. Two SAEs of hallucinations and two SAEs of pneumonitis have been reported from clinical trial programs. Hallucinations and Pneumonitis were considered as potential risks requiring monitoring.**
9.0 Overall Description of the study **17.4 Independent Data Monitoring Committee (IDMC)**	*Clarifications related to IDMC* The IDMC will review **available, unblinded**, safety data ~~approximately 1 year after study initiation,~~ at least once a year ~~while~~**during** the **conduct of the study i.e., from the first subject's enrollment in this** study ~~is ongoing~~**until the last subject has completed the safety follow-up visit,** and when approximately 70% of subjects ~~are randomized. Other~~ **have completed the safety follow-up visit. Additional** IDMC ~~reviews~~ **meetings** may be ~~conducted~~ **held** as required **for safety data reviews**.
8.3 Secondary Endpoints **11.3.1 Ibrexafungerp description**	*Corrections* • The percentage of subjects with no recurrence ~~before EOT and~~ at 2 weeks and 6weeks after EOT as determined by the DRC. *Correction to ibrexafungerp chemical name* ~~(1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-~~ 4H-1,4a-Propano-2H-phenanthro[1,2-c]pyran-7-carboxylic acid, 15- [(2R)-2-amino-2,3,3-~~trimethylbutyl]oxy-~~**trimethylbutoxy**]-8-[(1R)-1,2-dimethylpropyl]-~~14-[5-(4-pyridinyl)-1H-1,2,4-triazol-1-yl]-~~1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-1,6a,8,10a-tetramethyl-~~4H-1,4a-propano-2H-phenanthro[1,2-c]pyran-7-carboxylic acid, citrate salt]~~**14-[5-(4-pyridinyl)-1H-1,2,4-triazol-1-yl]-, (1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)**
17.9 Disease severity and Healthcare Data Analysis	*Added text for analysis of data on "Disease Severity" and "Healthcare Data"* **APACHE II Score, qSOFA Score and Healthcare Economic Data will be summarized using descriptive statistics.**

Section 16.5 Data Protection	*Text added per CTR requirement* **Data Protection** **To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data, SCYNEXIS has implemented and maintains the following measures:** • **Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.** • **SCYNEXIS will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.** • **The [participant/participants' parent(s)/LAR(s)] must be informed that [their personal/their child's] study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the [participant/participants' parent(s)/LAR(s)], that [their/their child's] data will be used as described in the informed consent.** • **The [participant/participants' parent(s)/LAR(s)] must be informed that [their/their child's] medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.** • **The contract between SCYNEXIS and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.** • **Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. Third parties working on behalf of SCYNEXIS are contractually bound to protect participant coded data. SCYNEXIS will protect participant coded data and will only share it as described in the ICF.** • **SCYNEXIS has a global, internal policy that requires all staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.**
18.1 Ethical Conduct of the Study	***Text added related to EU-CTR*** The study will be conducted …**including the European Union Clinical Trial Regulation 536/2014 (EU-CTR)**….
Throughout the document	*Added Trial numbers* *Updated Protocol version and date, Table of Content,Synopsis* *Updated information for Study Medical Monitor* *Added Protocol Amendment 4 under Revision History* *Minor rephrasing to simplify or clarify – no changes to study conduct*

20.4.2 Protocol Amendment 3

Revisions to Protocol dated 24 November 2022.
Current Version and Date: Protocol Amendment 3 (Protocol Version 3.0) dated 04 August 2023.

Amended to delete the ~~strikethrough~~ text and include the **bolded** text.

Protocol Section	*Rationale and modification*
	Overall Rationale for Amendment 3 Valuable feedback was collected from PI's during Investigator Meetings and updates were made to reduce the trial participation burden on the patients, without compromising on patient safety and scientific integrity of the study. In addition, based on feedback from operational teams, information was added or text amended to provide clarification to different protocol sections. Estimand definitions were added in line with recommendations in the Addendum to ICH E9. Safety reviews by an Independent Data Monitoring Committee (IDMC) were added following recommendation from some participating institutions. Preclinical data was added to align with the updated Brexafemme® Prescriber's Information, which was updated following approval of ibrexafungerp for the indication "Reduction in the incidence of recurrent vulvovaginal candidiasis".
	Reduced the number of in-clinic mandatory visits, expanded the visit window periods and simplified mandatory procedures and data collection to reduce the burden on patients, without compromising on patient safety and scientific integrity of the study.
9.1 Overall description of the study 13.0 Study procedures	The study will consist of a Screening visit which includes randomization, **(from 4 days prior to start of IV echinocandin, i.e.** Day -4 to before EOIV**)**, an end of IV treatment (EOIV) visit, Oral Treatment Day~~s~~ 1 ~~and 2~~ visit~~s~~, Oral Treatment Day**s** 2 **and** 7 visit**s** (PK subset only), an end of antifungal treatment (EOT) visit, Day 14 and Day 30 visits (IV + Oral), a 2-Week FU visit (14 days after EOT) and a 6-Week FU visit (42 days after EOT). The EOIV and Oral Treatment Day 1 should ideally occur on the same day. The Day 14 and Day 30 visits may occur before, on, or after EOT. Other study visits may also be combined if they occur on the same day, **or within the protocol specified window period**. **The 2-Week and 6-Week follow-up visits may be done telephonically, remotely or via home visits in accordance with local regulations and practicalities, except if an in person visit to the center is clinically indicated by adverse event screening, assessment of persistent or new signs and symptoms of invasive fungal disease, or to follow up on the course of the underlying disease.**
13.1.6 Complete physical examination 13.1.7 Retinal examination	**A** complete physical examination **(done either by the treating physician or by qualified study personnel, with appropriate source documentation),** will be performed at Screening ~~and from the EOIV visit through the 6-Week FU visit.~~, **EOIV, Day 14 and EOT and at other timepoints as clinically indicated by adverse event screening and underlying diseases.** A retinal examination **(bedside fundoscopy)** to rule out the presence of Candida endophthalmitis must be performed ~~at~~ **in subjects with candidemia during the** Screening **period**. ~~(within 72 hours of randomization) and on the Day 14 visit.~~ If a subject ~~is~~**becomes** symptomatic, the retinal examination ~~may be conducted at other time points,~~**should be repeated** as needed. Subjects with evidence of endophthalmitis, including retinitis or vitritis **post baseline**, should be discontinued from study treatment.
13.2.1 Targeted physical examination to evaluate the signs	A targeted physical examination of the fungal disease site, including the clinical signs and symptoms of the fungal ~~infection, will be conducted for all subjects at all study visits~~

and symptoms of infection	**disease (done either by the treating physician or by qualified study personnel, with appropriate source documentation), will be conducted for all subjects at screening, EOIV, Day 14, EOT and Day 30 and at other timepoints as clinically indicated by adverse event screening, assessment of persistent or new signs and symptoms of invasive fungal disease, or to follow up on the course of the underlying disease.**
13.2.3 Radiological assessment of non-blood sites of *Candida* infection	Images collected as SOC within ~~72 hours prior to consent~~ **the screening period** may be used as baseline scan**.**
13.2.5 Assessment of clinical response, mycological response and global response	**Assessment of response can be assessed remotely for Follow up visits when appropriate (e.g., subject was asymptomatic at EOT, and no additional cultures were needed during the follow up period).**
13.2.6 Assessment of recurrence of emergent infections	**Assessment of recurrences can be assessed remotely for Follow up visits when appropriate (e.g., subject was asymptomatic at EOT, and no additional cultures were needed during the follow up period).**
13.3 Pharmacokinetic procedures	**Home visits are allowed for the collection of PK samples in consenting subjects in accordance with local regulations and practicalities.**
13.4.1 Vital signs and temperature	Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate, weight and body temperature, will be measured ~~from Screening through EOT, and will also be determined at the 2-Week and 6-Week FU visits~~ **at screening, EOIV, Day 14 and EOT and at other timepoints as clinically indicated by adverse event screening and underlying diseases.**
14.0 Study Schedule	*Expanded certain window periods:* Day 14 - ~~±2~~ **-2/+3** days; Day 30 ~~± 2~~ ±**3** days
12.1 Prior and concomitant medications	~~All medications (including prescription and over-the-counter medications, supplements, and herbal products)~~ **All systemic antifungal therapy, immunosuppressives, immunomodulators and chemotherapeutics administered** within 28 days **and all medications administered within 7 days** before screening and through the EOT will be recorded on the eCRF.
	Added clarifying text to address recurrent questions from sites and CRAs.
9.1 Overall description of the study; 11.1.4 Subjects with isolates Non-Susceptible to fluconazole	Subjects with infections due to Candida species that are frequently not susceptible to fluconazole (i.e., C. auris, C. krusei, C. glabrata, **are considered presumed resistant for this protocol**)…
10.1 Inclusion criteria	2.Subject has a diagnosis of candidemia and/or invasive candidiasis, defined as evidence of Candida spp. in either a bloodstream or tissue/**fluid** culture from a normally sterile site.
10.2 Exclusion criteria	3.Subject has severe hepatic impairment ~~and~~ **due to** a history of chronic cirrhosis (Child-Pugh score > 9).
11.1.2 Randomization and switch to oral therapy	**Drug administration via naso-gastric (NG), percutaneous endoscopic gastrostomy (PEG) and Jejunostomy (J) tubes is allowed. Administration instructions are provided in the study specific product manual.**

13.1.8 APACHE II Score	The APACHE II score **(Appendix 20.2)** will be determined for each subject at Day 1 (1st dose of IV echinocandin) or closest day prior to Day 1, **using local laboratory results. APACHE II score is repeated** at EOIV, Day 14, and EOT.
13.2.2 Mycological testing AND 13.2.2.2 Culture of non-blood sites of *Candida* infection	Subjects must have a diagnosis of invasive candidiasis (including candidemia) defined as evidence of Candida in either a bloodstream or tissue/**fluid** culture from a normally sterile site Culture (**tissue or fluid)….**
13.2.2.1 Blood cultures	~~Two sets of~~ Blood cultures will be collected… **Generally, blood culture should involve samples from 2 separate draws, with at least** one set of blood culture ~~should be~~ drawn peripherally (directly from a vein) and the other set from any existing central IV catheter. The results from all blood cultures collected during the study will be entered in the EDC, regardless of if they were collected as part of study procedures or SOC **(including results from initial positive culture to determine eligibility)**.
13.3 Pharmacokinetic procedures	**….**and **one sample collected approximately** 36 to 60 hours after the last dose, when feasible.
13.4.2 Clinical safety laboratory assessments	Clinical safety laboratory tests will include biochemistry and hematology **and will be collected at selected scheduled visits as indicated in Table 5. These tests will be performed by the central laboratory.** Safety laboratory tests ~~will~~ **are only required** to be performed by the local laboratory at Screening so that timely results are available for study eligibility determination **and for calculation of the APACHE II score at screening**.
15.1 Definition of an Adverse event	Any laboratory abnormality that is deemed to be clinically significant in the opinion of the investigator **(e.g., associated with clinical signs or symptoms, require medical intervention, require interruption of the study drug treatment, leads to study discontinuation)** will be considered an AE and should be recorded in the eCRF, whether or not it is related to the study drug. **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.** ~~The disease being studied or signs or symptoms associated with the disease, unless more severe than expected for the subject's condition or a worsening of the disease being studied~~ **Events (or associated signs and symptoms), that are related to the disease being studied, candidemia or invasive candidiasis, should not be recorded as AEs, unless the event fits the definition for an SAE (Section 15.2), in which case the SAE reporting procedure should be followed (Section 15.11).**
	Clarification – statistical section
17.1 Sample size determination	The sample size re-estimation will be based on a blinded review of the ACM data **for the ITT population**, pooled across treatment groups. **The sponsor will remain blinded to treatment group for both the FS-MITT and FN-ITT populations when performing this review.**

17.7.2 Primary efficacy analysis	**Additional supplemental and sensitivity analyses may be included in the SAP.**
8.3 Secondary endpoints 13.1.11 Management of IV catheters 17.7.1.3 Treatment outcome – Mycological response by the DRC 17.7.2 Primary efficacy analysis	*Corrections* •The percentage of subjects with Successful Clinical Response at Day 14, **Day30** and EOT as determined by the PI and the DRC. •The percentage of subjects with Successful Mycological Response at Day 14, **Day30** and EOT as determined by the DRC. It is strongly recommended that IV catheters be removed or changed and replaced at a different site for all subjects with positive blood cultures for Candida within 48 hours of ~~randomization~~ **diagnosis**. Presumed Eradication: subjects ~~with invasive candidiasis~~ who have no follow-up cultures available but who have a clinical outcome of Success Presumed Persistence: subjects ~~with invasive candidiasis~~ who have no follow-up cultures available but who have a clinical outcome of failure The primary efficacy assessment will be performed for the ITT population. ~~Sensitivity~~ **Supplementary** analyses will also be conducted for the MITT, FS-MITT, FN-MITT, and PP Populations.
9.1 Overall Description of the Study 17.4 Independent Data Monitoring Committee (IDMC)	*Following recommendations from some participating institutions, safety reviews by an Independent Data Monitoring Committee (IDMC) was added.* **The IDMC will review safety data approximately 1 year after study initiation, at least once a year while the study is ongoing and when approximately 70% of subjects are randomized. Other IDMC reviews may be conducted as required. Details will be provided in the IDMC Charter.** **An external IDMC will be established to review safety data. The IDMC will review safety data approximately 1 year after study initiation, at least once a year while the study is ongoing and when approximately 70% of subjects are randomized. Other IDMC reviews may be conducted as required. The IDMC will be comprised of clinicians and a statistician who are experienced in studies of fungal infections. The roles and responsibilities of the IDMC, timing of meetings as well as the data to be provided for review will be described in a detailed charter, in compliance with guidelines of the FDA and ICH.**
17.7.1 Efficacy Analysis Appendix 20.3 Estimands	*Estimand definitions were added in line with recommendations in the Addendum to ICH E9.* **The addendum to ICH E9 introduces the concept of an estimand. The estimand framework is a systematic approach to ensure alignment among clinical trial objectives, trial execution/conduct, statistical analyses, and interpretation of results. The details of the primary and secondary estimands are described in Appendix 20.3 and the handling of estimands will be further detailed in the SAP.** **Appendix 20.3 Estimands** *is an additional Appendix that was added to describe the Estimand Framework in detail.*
	Preclinical Safety information from the Investigator Brochure was added, to align with the updated Brexafemme® label.

6.1 Background Information	**Preclinical safety** **In pregnant rabbits, oral ibrexafungerp administered during pregnancy was associated with fetal malformations at exposures generally greater than the estimated human exposure at the intended doses in this study. Oral ibrexafungerp administered to pregnant rats during pregnancy was not associated with fetal harm. The potential significance of these observations in rabbits to humans is not known. However, as a precaution, ibrexafungerp should not be used in pregnancy because it may cause fetal harm.** Long-term toxicology studies have been conducted in rats and dogs. In the six-month study in rats, no new toxicities or target organs of toxicity were identified (compared to the results of the shorter-term studies~~), and~~). **Daily administration of oral ibrexafungerp for 26 weeks in rats, at the highest dose was associated with marked, but reversible, lung, stomach lining, and peripheral nerve abnormalities. The potential significance of these observations in rats to humans is not known.** **Available data on ibrexafungerp use in pregnant women are insufficient to draw conclusions about any drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Women of childbearing potential are required to use two approved contraceptive methods as described in the protocol and informed consent document.**
Appendix 20.2	***Added Modified Acute Physiology and Chronic Health Evaluation (APACHE) II Score***
Appendix 20.3	***Added: Estimands***
Appendix 20.4.1 Protocol Revision History Protocol Amendment 3	***Added Protocol Amendment 3 under Revision History***
Throughout the document	*Updated Synopsis.* *Updated Table of Content.* *Updated Section numbers (17.5 through 17.9).* *Typographical and grammatical edits and minor rewording of language as needed for clarity.* *Updated Protocol Version and Date.* *Updated list of abbreviations and abbreviations used in text.* *Updated Table 5 – Schedule of Visits and Procedures.* *Updated and added Table footnotes in line with applicable protocol sections.*

20.4.3 Protocol Amendment 2

Revisions to Protocol dated 16 December 2021.
Current Version and Date: Protocol Amendment 2 (Protocol Version 2.1) dated 24 November 2022.

Amended to delete the ~~strikethrough~~ text and include the **bolded** text

Protocol Section	*Change and Rationale*
6.2 Rationale for study endpoints	*Per EMA Scientific Advice - Added Primary Endpoint for EU. Rephrased Primary Objective to accommodate the addition. Added (and BAT) throughout the document, where treatment regimens are referenced to accommodate open-label arm.*
7.1 Primary Objective	To demonstrate that treatment of Invasive Candidiasis/ Candidemia with IV echinocandin followed by oral ibrexafungerp is non-inferior to IV echinocandin followed by oral fluconazole **(or BAT)**. ~~based on 30-day all-cause mortality (ACM).~~
8.1 Primary Endpoint	**The percentage of subjects with Successful Global Response, as determined by the DRC at EOT (EU only)**
17.6 Efficacy 17.6.2 Primary efficacy analysis	**Based on feedback from different regulatory agencies, different primary efficacy variables will be used for the study. For non-EU, the primary efficacy variable for the study is the percentage of subjects with 30-day ACM, and for the EU, the primary efficacy variable is Global Response. Detailed analyses will be outlined in the SAP.**
9.1 Overall description of the study 13.0 Study Procedures 14.0 Study Schedule	*Clarification of the Study Visits throughout the document* **Study Day 1 is the first day of IV echinocandin treatment and may occur before the Screening visit.** The study will consist of a Screening visit (Day -4 to ~~Day 1~~ **before EOIV) which includes randomization**, ~~a Randomization visit, Day 1/ Baseline (first dose of IV echinocandin)~~ an end of IV treatment (EOIV) visit, ~~an~~ Oral Treatment Day**s** 1 and 2 visit**s**, Oral Treatment Day ~~2 and Day~~ 7 ~~visit s~~ (PK subset only), an end of antifungal treatment (EOT) visit, Day 14 and Day 30 visits **(IV + Oral)**, a 2-Week FU visit (14 days after EOT) and a 6-Week FU visit (42 days after EOT). ~~The Screening and Randomization visits may occur on the same day.~~ Study days are counted relative to the first IV echinocandin dose**, which is Study Day 1**. **For the purpose of PK sample collection, reference is made to "Oral Days", i.e., Oral Day 1 is the first day of step-down therapy.** For follow-up visits, weeks are counted relative to the EOT Visit. The Screening visit **can occur before the start of IV echinocandin treatment, or whilst the subject is already receiving echinocandin treatment. Screening visit can be from Study Day -4 to before EOIV**. ~~and Study Day 1 Visit (first dose of on-study treatment) may occur on the same day. Other s~~ **Screening and Randomization may occur on the same day.** Study visits may also be combined if they occur on the same day.
9.1 Overall description of the study 13.1.2 Enrollment and assignment of Subject Identification	*Clarification of subject enrollment/randomization process, enrollment/randomization terminology and procedures linked to enrollment/randomization, throughout the document* Subjects with a diagnosis of candidemia and/or invasive candidiasis will be invited to participate in the study, ~~. Subjects will be invited to participate in the study~~ either prior to or while they are receiving an IV echinocandin. **After having signed an informed consent form, s~~S~~ubjects will be assigned a study number**. **Following screening,** subjects who meet all inclusion criteria and none of the exclusion criteria will be **randomized**. ~~asked to sign an informed consent form and be enrolled in the study if they~~

13.1.3 Inclusion and Exclusion criteria Section 13.0 General Procedures Section 14 Study Schedule	~~meet all inclusion criteria and none of the exclusion criteria.~~ **Screening and randomization** ~~Enrollment in the study~~ should occur as soon as possible after the diagnosis of candidemia and/or invasive candidiasis has been made. It is anticipated that most subjects may be on IV echinocandin at the time of randomization. **However, randomization may occur before or after the initiation of IV echinocandin which is Study Day 1.** Deletion of outdated text related to Assignment of Subject Identification ~~At Screening, all eligible subjects will receive an 8-digit subject identification (ID) number that will be composed of a 3-digit study number (302) and a 2-digit site number followed by a 3-digit sequentially assigned subject number starting at 001. Subject numbers will be sequentially assigned by the database upon entry by the site. For instance, if site 01 enters the first subject in the database, the subject ID will be 302-01-001. The second subject entered in the database will get the subject number 002 as entered by any site, so that if site 02 enters the second subject, the subject ID will be 302-02-002.~~
9.1 Overall description of the study 11.1.4 Subjects with isolates non-susceptible to fluconazole – open-label arm (Group 2)	*Added that Subjects with breakthrough infections whilst receiving azole prophylaxis treatment will receive open label treatment.* The oral component of the regimen (ibrexafungerp or fluconazole) will be administered as double-blind, double-dummy treatment, unless the Candida spp. isolate is identified as suspected or confirmed non-susceptible to fluconazole (i.e., *C.glabrata, C.krusei or C.auris*, **or subjects with breakthrough infections whilst receiving azole prophylaxis treatment**). These s~~S~~ubjects with isolates non-susceptible to fluconazole will receive open label ibrexafungerp (if originally randomized to receive oral ibrexafungerp as step-down) or BAT (if originally randomized to receive oral fluconazole as step-down).
Throughout the document where Step-down criteria / criteria for switching to oral, is listed: Synopsis, 6.2 Rationale for the study, 9.1 Overall study description; 11.1.2 Randomization and switch to oral therapy;	*Rephrase of the step-down criterion related to negative blood cultures for candidemia patients:* From "~~have no post baseline positive blood culture in the previous 48 hours~~" to "**blood cultures negative for at least 48 hours"**
9.2 Study blinding, randomization, and stratification	*Updated geographical regions for stratification, and clarified timepoint for stratification* Subjects will be stratified according to geographic region (~~US~~ **North America**-Europe, **China** and Other), scores on the Acute Physiology and Chronic Health Evaluation (APACHE II) instrument (≤ 20 or > 20) and absolute neutrophil count (≤ 500 or > 500 per cubic millimeter) **at Day 1 (1st dose of IV echinocandin) or closest day prior to Day 1** ~~enrollment.~~
10.1 Inclusion criteria	*Correction of the window period for collection of baseline culture* 2.Subject has a diagnosis of candidemia and/or invasive candidiasis, defined as evidence of *Candida* spp. in <u>either</u> a bloodstream or tissue culture from a normally sterile site (excluding eye, cardiac and bone tissue, central nervous system or prosthetic device) collected **within** ± ~~≤~~4 days (96 hours) ~~prior to~~ **of** initiation of IV echinocandin…

	Changed contraception requirement in compliance with CTFG Guidelines, based on 5 times the half-life of all drugs (ibrexafungerp, fluconazole and BAT): 4. Female subjects of childbearing potential < 2 years post-menopausal must agree to and comply with using one barrier method (e.g., female condom with spermicide) plus one other highly effective method of birth control **(Section 12.4)**, or sexual abstinence **from signing the consent form until at least 7 days after end of treatment.** ~~while participating in this study~~. Male subjects must be vasectomized, abstain from sexual intercourse, or agree to use barrier contraception **(Section 12.4)**, and also agree not to donate sperm **from signing the consent form until at least 7 days after end of treatment**. ~~while participating in the study and for 90 days thereafter.~~ *Addition of German specific requirement not to allow legal representatives to provide consent:* 5. Subject and/or legal representative is able to understand and sign a written informed consent form (ICF), which must be obtained prior to treatment and any study-related procedures. Informed consent via electronic signature will be allowed **(Exception for Germany - no subject who requires a legal representative, will be eligible for participation).**
10.2 Exclusion criteria	*Broaden the exclusion criteria as follows:* 5.Patients with baseline QTcF ≥ 500 msec, **history or family history of Torsades de Pointes or other conditions that would put the subject at undue risk of development of ventricular arrhythmias (including Torsades de Pointes).** 7.Subject has a **known history of allergy**, hypersensitivity **or serious reaction to** ibrexafungerp, **any of the azole or echinocandin class of antifungal** ~~and/or fluconazole~~ or to any of the components of the formulations. **14. Subject is pregnant or breastfeeding or plans to become pregnant**
11.1.3 Subjects with isolates assumed or known susceptible to fluconazole – switch to double-blind arm (Group 1) Tables 1 and 2	*Corrections made to Tables 1 and 2 – number of ibrexafungerp tablets and fluconazole capsules. Text in corresponding section (11.1.3) is correct.* *Added text to clarify:* **The maximum dose of fluconazole is 800 mg QD.** *Clarification that, for subjects with renal impairment on dialysis, the fluconazole dose on non-dialysis days should be **50%.***
11.1.4 Subjects with isolates non-susceptible to fluconazole – open-label arm (Group 2)	*Added text for clarification with respect to administration of BAT during open-label treatment:* **Administration of BAT should be according to the locally approved label for the applicable drug**
11.1.4.1 Dose modification for toxicity	*Added guidance for managing severe nausea during loading doses of ibrexafungerp:* **In the event of moderate to severe nausea associated with the loading doses, the doses may be split into multiple doses spread over the dosing period, i.e., each 750 mg administered over a 12-hour period.**
12.2 Prohibited medications	*Added text related to prohibited medications and medications to be administered with caution:*

12.3 Medications to be administered with caution and monitored as appropriate	A ~~full~~ list of prohibited medications, **applicable to ibrexafungerp and fluconazole** is provided in Section 20.1 (Appendix A). **The investigator should refer to the locally approved product labels of relevant medication (e.g., echinocandins, fluconazole, voriconazole) for other prohibited medications, as applicable.**
12.4 Contraception Requirements	*Added section on Contraception Requirements* **12.4 Contraception Requirements** **Requirements are based on Guidelines from the Clinical Trials Facilitation and Coordination Group (CTFG). Female subjects of childbearing potential < 2 years post-menopausal must agree to remain abstinent or agree to using (or have their partner use) one barrier method (e.g., female condom with spermicide) plus one other highly effective method of birth control from signing the consent form until at least 7 days after end of treatment.** **Highly effective methods of birth control include:** • **Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal)** • **Progestogen-only hormonal contraception (oral, injectable, implantable)** • **Intrauterine device (IUD)** • **Intrauterine hormone-releasing system (IUS)** • **Bilateral tubal occlusion** • **Vasectomized partner** **Male subjects must be vasectomized, abstain from sexual intercourse, or agree to use barrier contraception and also agree not to donate sperm from signing the consent form until at least 7 days after end of treatment.**
13.1.10 Pregnancy test AND 14.0 Schedule of Events	*Added guideline for Pregnancy Tests (CTFG)* A urine or serum pregnancy test will be performed by the local laboratory for all female subjects of childbearing potential at Screening and will be repeated at EOT **(based on CTFG guidelines[12])**. Pregnancy tests may be conducted more often (e.g., on a monthly basis), **depending on the risk of the subject to become pregnant per investigator's assessment, and** per local regulations.
13.1.15 End of Study	*Added a section to clarify "End of Study"* **13.1.15 End of Study** **Subjects are followed until 42 days (± 3 days) after EOT. The 6-Week FU visit is the subject's end of study. The global End of Study coincides with the last visit of the last subject randomized.**
13.2.2 Mycology Testing	*Clarification and Correction:* Subjects must have a diagnosis of invasive candidiasis (including candidemia) defined as evidence of Candida in either a bloodstream or tissue culture from a normally sterile site (excluding eye, cardiac and bone tissue, central nervous system or prosthetic device) collected within 96 hours ~~prior to enrollment~~ **of the first dose of IV echinocandin (i.e. Day 1 ± 96 hours).** *Added statement re Reference Laboratory:* **Reference laboratories will be used for identification and susceptibility testing of all isolates collected during the study.**
	Added and Refined

13.2.2.1 Blood Cultures	**As per guideline for subjects with candidemia, it is recommended to collect cultures every other day during IV echinocandin treatment until the demonstration of clearance of *Candida* from the bloodstream.** **One set of b**~~B~~lood culture should be drawn peripherally (directly from a vein) **and the other set from any existing** ~~; however, if this is not possible, a~~ central IV catheter ~~may be used~~.
13.2.2.2 Culture of non-Blood Sites of *Candida* infection	*Correction:* Cultures of samples from indwelling drains are to be EXCLUDED unless the drain has been in place for **< 24** ~~<48~~ hours.
13.3 Pharmacokinetic procedure 17.7 Pharmacokinetics	*Additional sample added at end of treatment and clarification for samples on Days 1 and 2* Up to **7**~~6~~ blood samples may be collected at the following visits and sampling windows: **Oral** Days 1 and 2 ~~of step-down therapy~~ (one sample collected between 3-6 hours **after either the 1st or 2nd** ~~post~~ **dose**), **Oral** Day 7 ~~of step-down therapy~~ (one sample collected before dosing and one sample 3-6 hours after dosing) **and 36 to 60 hours after the last dose, when feasible**. Additional blood PK samples will be collected on **Study** Day 14 and **Study** Day 30 before dosing for subjects still receiving study treatment or when clinically indicated. Efforts will be made to record the **exact time of drug intake and** proximity of the last meal to dose on PK collection days. Procedures for collecting, storing, and shipping plasma samples for PK are described in the study PK Manual.
14.0 Schedule of Events	*Blood volume added as footnote:* **l. The total blood volume that will be collected over the course of the study (safety bloods, blood cultures for candidemia patients, PK samples when applicable), will be approximately 250-400mL (approx. 8-14 oz), depending on whether blood is collected for additional testing. The total blood volume collected will not exceed the amount of blood collected during a typical blood donation (i.e., 480 mL or 16 oz)**
15.4 Pregnancy	*Rephrase and clarify:* **In the event of a** f~~F~~emale subject~~s~~ ~~who~~ becom**ing** pregnant, ~~should~~ **the study drug** will be immediately discontinued ~~from the study~~ and the subject will be followed up to determine the outcome of the pregnancy.
15.12 Procedure for emergency unblinding	*Detailed description of emergency unblinding procedure* **The Investigator should only be unblinded if it is necessary to determine treatment of an emergency. Emergency unblinding is performed via the study Interactive Web Response System (IWRS) and investigators are able to unblind any subjects randomized at their institution. The independent pharmacovigilance group (PVG) can also unblind study subjects should emergency unblinding be deemed necessary during ongoing safety review. If for whatever reason the Investigator and PVG safety reviewer are unable to unblind a subject, select sponsor personnel can unblind subjects if needed. No sponsor personnel directly involved in managing the study or making treatment recommendations have unblinded access to treatment arm.** ~~The study personnel responsible for the treatment assignment can provide the information necessary to unblind the investigator (evaluator), in case of an emergency.~~ If the evaluator is unblinded, the reason for unblinding should be documented in the comment page of the eCRF.

17.6.1.3 Treatment Outcome	*Text added for handling of missing data:* **Alternative approaches to handling missing data and intercurrent events will be specified in the SAP**
17.6.3 Secondary efficacy analysis	*Text added for sensitivity analysis:* **Additional sensitivity analyses will be specified in the SAP.**
20.1.2 Fluconazole Label Information: Prohibited medication and Medication to be administered with caution	*Text Added for fluconazole:* **Prohibited medications:** **Coadministration of other medicinal products known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as erythromycin, pimozide and quinidine** **Medications to be administered with caution and monitored as appropriate:** **Potential effect of the drug on fluconazole, or potential effect of fluconazole on the drug. Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor and a strong inhibitor of CYP2C19. Concomitant administration of drugs with a narrow therapeutic window metabolized through CYP2C9 and CYP3A4 should be monitored for adverse reactions:** **alfentanil, amiodarone, amitriptyline, nortriptyline, amphotericin B, calcium channel blockers, carbamazepine, celecoxib, coumarine-type anticoagulants, cyclophosphamide, cyclosporin, fentanyl, HMG CoA reductase inhibitors, ibrutinib, ivacaftor and fixed dose ivacaftor combinations, Lemborexant, losartan, lurasidone, methadone, NSAIDs, olaparib, oral hypoglycemics, phenytoin, prednisone, rifabutin, rifampin, saquinavir, short acting benzodiazepines, sirolimus, tacrolimus, theophylline, tofacitinib, tolvaptan, triazolam, vinca alkaloids, vitamin A, voriconazole, zidovudine** **In addition to the drugs listed, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 co-administered with fluconazole and caution should be exercised when using these combinations and patients should be carefully monitored.**
20.2.1	*Added Protocol Amendment 2 under Revision History and renumbered appendices accordingly*
Throughout the document	*Synopsis Updated* *Introduced typographical and grammatical edits and reworded language slightly as needed for clarity* *Protocol version and date updated* *Updated list of abbreviations and abbreviations used in text*

20.4.4 Protocol Amendment 1

Revisions to Protocol dated 28 June 2021 (Protocol Version 0.6)
Current Version and Date: Protocol Amendment 1 (Protocol Version 1.0) dated 16 December 2021.

Amended to delete the ~~strikethrough~~ text and include the **bolded** text

Protocol Section	Change and Rationale
Cover Page and throughout document	Added the project name "**MARIO**" to the study title
Synopsis: Treatment duration and switch from IV to Oral Therapy AND Section 9.1 Overall Description of Study: Treatment duration and switch from IV to Oral Therapy	**Clarification of IV treatment duration** ~~IV echinocandin treatment should be administered for a minimum of 1 day and, ideally, a maximum of 5 days (including both off- and on-study treatment). It is expected that the subjects be switched to the randomly assigned study drug (oral antifungal therapy) as soon as they are able to tolerate oral medication and are hemodynamically stable (i.e., do not require use of vasopressors), and Candida species is known. If a subject requires greater than 5 days of IV echinocandin because of inability to tolerate oral medications and/or requires vasopressor medications due to hemodynamic instability, the switch to oral study drug should occur as soon as possible (i.e., as soon as they are able to tolerate oral medication and are hemodynamically stable). Subjects will receive systemic antifungal treatment (including both the IV and oral components of the treatment) for a minimum of 14 days and a maximum of 6 weeks.~~ **In line with current treatment guidelines, the antifungal treatment duration will depend on subjects' invasive candidiasis condition and response to therapy (e.g., for candidemia antifungal treatment should continue for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia) with an anticipated treatment duration ranging from 14 days to 6 weeks.** **Subjects will receive IV echinocandin treatment until the criteria for switching to oral antifungal treatment are met. The switch from IV echinocandin to oral antifungal should occur as soon as the criteria for switching is met (they are clinically stable, able to tolerate oral medication, are hemodynamically stable, have no post-baseline positive blood culture in the previous 48 hours, the *Candida* species is known, and no mucositis of GvHD affecting the gut with severity > Grade 3) and ideally within 5 days of start of the IV echinocandin. While on IV echinocandin, subjects should be assessed daily to determine if they meet the criteria for step-down therapy.**
Synopsis: Key Inclusion Criteria AND Section 10.1 Inclusion Criteria	**Refinement of Inclusion criteria** 2. Subject has a diagnosis of candidemia and/or invasive candidiasis, defined as evidence of *Candida* spp. in **either** a bloodstream or tissue culture from a normally sterile site (excluding eye, cardiac and bone tissue, central nervous system or prosthetic device) collected ≤ 4 days (within 96 hours) prior to initiation of IV echinocandin accompanied by **any** related clinical sign~~s~~ and/or symptom~~s~~ (e.g., fever [on one occasion > 38°C], hypotension, or local signs of inflammation) ~~within 48 hours prior to initiation of IV echinocandin~~. ~~3. Subject is anticipated to be able to take oral tablets and capsules within 5 days~~. 6. Subject and/or legal representative is able to understand and sign a written informed consent form (ICF), which must be obtained prior to treatment and any study-related procedures. **Informed consent via electronic signature will be allowed.**
Synopsis: Key Exclusion Criteria	**Refinement of Exclusion criteria**

AND Section 10.2: Exclusion Criteria	1. Subject has any of the following forms of invasive candidiasis at Screening: d. Meningitis, endophthalmitis, ~~chorioretinitis,~~ or any central nervous system infection. f. Urinary tract candidiasis due to ascending *Candida* infection secondary to **unresolved** obstruction or ~~surgical instrumentation of~~ **non-removeable device** in the urinary tract. g. Patients with a sole diagnosis of mucocutaneous candidiasis, i.e., oropharyngeal, esophageal or genital candidiasis; or *Candida* **lower urinary tract infection** or *Candida* isolated solely from respiratory tract specimens. h. Patients with **concurrent** invasive fungal infection other than *Candida* spp., e.g., cryptococcosis, mold infection or endemic fungal infection. ~~i. Patients with polymicrobial intra-abdominal infection or intra-abdominal abscess that includes bacterial pathogens,~~ ~~k.~~j.Subject has an ~~inappropriately controlled~~ **uncontrolled** fungal disease source (e.g., indwelling vascular catheter or device that cannot be removed or an abscess that cannot be drained) that is likely to be the source of the candidemia or invasive candidiasis ~~4. Subject has severe renal impairment during Screening (creatinine clearance <30 mL/min by Cockroft Gault) including subjects on hemodialysis or chronic renal replacement therapy.~~ ~~5.~~4.Subject has received more than 48 hours of non-echinocandin ~~therapy~~ **antifungal therapy for the treatment of invasive candidiasis (including candidemia)** within 96 hours preceding initiation of IV echinocandin. **a. Exception: Receipt of antifungal therapy to which any *Candida* spp. isolated in qualifying culture is not susceptible.** **5. Baseline QTcF ≥ 500 msec.**
Synopsis: Study Treatments – Open-Label IV Component AND Section 11.1.1: Open-Label IV Component	**<u>Clarification of IV treatment duration</u>** Subjects will receive ~~a minimum of 1 day and, ideally, a maximum of 5 days of~~ IV echinocandin treatment until the criteria for switching to oral antifungal treatment are met. **The switch from IV echinocandin to oral antifungal should occur as soon as the criteria for switching is met and ideally within 5 days of start of echinocandin. While on IV echinocandin**, subjects should be assessed daily to determine if they meet the criteria for step-down therapy.
Synopsis: Study Treatments – Switch to oral therapy AND Section 11.1.2: Randomization and Switch to Oral Therapy	**<u>Clarification of IV to oral step-down criteria</u>** Unless there is a documented reason why switching to oral therapy is not adequate for the subject, subjects should be switched to the randomly assigned oral study drug as soon as: • **They are clinically stable (e.g. no worsening of signs and symptoms associated with invasive candidiasis).** • They are able to tolerate oral medication. • They are hemodynamically stable (i.e., do not require use of vasopressors). • **They have no post-baseline positive blood cultures in the previous 48 hours.** • The *Candida* species causing the infection is known. • They have no mucositis or GvHD affecting the gut with severity > Grade 3.
Synopsis: Study Treatments – Subjects with Isolates assumed or known susceptible to fluconazole - Switch to double-blinded	**<u>Added Information on fluconazole loading dose and guidelines for dose adjustment for patients with impaired renal function</u>** • Fluconazole Group: **loading dose of 800 mg QD Day 1, followed y 400 mg QD from Day 2 onwards. This may be adjusted at 12mg/kg (loading dose) and** 6 mg/kg **(maintenance dose)** rounded to the closest 200 mg **for underweight or overweight**

<table>
<tr><td>oral therapy (Group 1)

AND

Section 11.1.3: Subjects with Isolates assumed or known susceptible to fluconazole - Switch to double-blinded oral therapy (Group 1)</td><td>subjects (e.g., for a 70 kg person, the daily dose will be ~ 400 mg QD) + placebo matching ibrexafungerp.

For subjects with renal impairment, the fluconazole dose adjustments in the table below are recommended per fluconazole label.

<table><tr><th>Creatine clearance (ml/min)</th><th>Percent of recommended dose</th></tr><tr><td>>50</td><td>100%</td></tr><tr><td>≤50 (no dialysis)</td><td>50%</td></tr><tr><td>Regular dialysis</td><td>100% after each dialysis</td></tr></table>
When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance in adults:

Males: <u>Weight (kg) x (140-age)</u>
72 x serum creatinine (mg/100 mg/100 mL)
Females: 0.85 x value obtained by above formula.</td></tr>
<tr><td>Section 11.2.4: Subjects with isolates non-susceptible to fluconazole – open-label arm (Group 2)</td><td><u>Added Voriconazole dosing adjustment</u>

Voriconazole Dosing Adjustments:
For subjects weighing <40 mg: Decrease maintenance dose of 100 mg or 150 mg twice daily.

For subjects with mild to moderate hepatic, impairment (Child-Pugh Class A and B), use 50% of maintenance dose.</td></tr>
<tr><td>Section 13.1: General Procedures</td><td>Added the qSOFA Score and Healthcare Economic Data collection

13.1.9: qSOFA Score

The qSOFA score will be determined for each subject at Screening, EOIV, and EOT.

13.1.15: Healthcare Economic Data
Healthcare economic data (subject days of hospital stay, subject days in ICU, days from discharge to readmittance to hospital for treatment of invasive candidiasis) will be collected at EOIV, EOT, and at the 2-Week and 6-Week FU visits. For these analyses, Day 1 will be the first day of IV echinocandin treatment.</td></tr>
<tr><td>Section 13.2.1: Targeted Physical Examination to evaluate the signs and symptoms of infection</td><td><u>Added</u>

Other evaluations such as echocardiography and ophthalmoscopy when performed per standard of care will be tracked.</td></tr>
<tr><td>Section 13.2.3: Radiological assessments of non-blood sites of Candida infections</td><td><u>Clarified the requirements</u>

<s>Radiographs or imaging</s> For subjects with fungal diseases where diagnosis and assessment of outcome are based on imaging, imaging scans (e.g., X-ray, ultrasound, computed tomography [CT,], magnetic resonance imaging [MRI)]) will be <s>performed</s> obtained for the assessment of infection.

Imaging scans will be obtained at Screening, Day 14 and EOT as applicable. Images collected as SOC within 72 hours prior to consent may be used as baseline scan. In</td></tr>
</table>

	addition to the scheduled time points, imaging scans will be collected anytime during therapy, as clinically indicated.
Section 17.1: Sample size determination	**Addition text** **In addition, a trial including 110 evaluable patients per arm would have 90% power to show non-inferiority for a global response endpoint, assuming a -20% NI margin, a true global response rate of 70% for each treatment group and one-sided alpha=0.025.** **A blinded sample size reassessment will take place after 70% of the subjects have primary endpoint data available. The blinded sample size re-estimation will either confirm the initial sample size estimate or increase the sample size to ensure the study has adequate power for the primary outcome measure, up to a maximum of 308 subjects. No sample size adjustment downwards will be performed. The sample size re-estimation will be based on a blinded review of the ACM data pooled across treatment groups.**
Section 17.6.1.1: All-Cause Mortality	**Additional text** **Subjects whose vital status is not known at Day 30 will be considered as having died in the calculation of the all-cause mortality rate for the primary analysis.**
Section 17.8: Safety Analyses	**Additional text** The safety analysis will be performed for the Safety Population **(all randomized subjects).** **Additional safety analyses in subjects who receive oral step-down therapy and in subjects with adverse events occurring after oral step-down will be conducted.**
Appendix 20.1.2: Medication to be administered with caution and monitored as appropriate	**Additional information added** **OATP1B3 Substrates: Ibrexafungerp resulted in a 2.8-fold increase in the systemic exposure of the sensitive OATP1B3 transporter substrate pravastatin. Subjects receiving drugs that are OATP1B3 substrates such as statins, repaglinide, olmesartan, enalapril, valsartan, paclitaxel and docetaxel, cisplatin, and methotrexate may be enrolled in the study with close monitoring.** **Proton Pump Inhibitors (PPIs): Proton pump inhibitors (PPIs) may interfere with ibrexafungerp absorption. Pantoprazole, a PPI, decreased ibrexafungerp exposure by approximately 25%. Use PPIs with caution.**