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Statistical Analysis Plan

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)

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STATISTICAL ANALYSIS PLAN

Protocol 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

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1. LIST OF ABBREVIATIONS

ACM	All-cause mortality
AE	Adverse event
ADaM	Analysis Data Model
APACHE II	Acute Physiology and Chronic Health Evaluation
ATC	Anatomical Therapeutic Chemical
BAT	Best Available Therapy
BDRM	Blinded Data Review Meeting
CI	Confidence interval
DRC	Data Review Committee
eCRF	Electronic case report form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EKG	Electrocardiogram
EOIV	End of IV treatment
EOT	End of antifungal treatment
FN-MITT	Fluconazole Non-Susceptible MITT
FU	Follow-up
FS-MITT	Fluconazole Susceptible MITT
GvHD	Graft Versus Host Disease
IC	Informed Consent
ICE	Intercurrent events
ITT	Intent-to-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MITT	Modified Intent-to-Treat
NIM	Non-inferiority margin
PD	Pharmacodynamic(s)

PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Preferred term
qSOFA	Quick Sequential Organ Failure Assessment
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
USA	United States of America
WHODD	WHO Drug Dictionary

2. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analysis and reporting for the SCY-078-302 Protocol Amendment 4 dated 12 August 2024. This is a Phase 3, multicenter, prospective, randomized, double-blind study of two treatment regimens for candidemia and/or invasive candidiasis: intravenous (IV) echinocandin followed by oral ibrexafungerp versus IV echinocandin followed by oral fluconazole.

This SAP does not include the description of the population PK/PD analyses, which are described in a separate stand-alone PK/PD analysis plan.

3. STUDY OBJECTIVES

3.1 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 Best Available Therapy [BAT]) based on All-cause Mortality (ACM) at Day 30 (non-EU) and Global Response (clinical, radiological and mycological response as confirmed by the Data Review Committee [DRC] at End of Treatment [EOT]) for the EU only.

3.2 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 DRC at Day 14.

3.3 Other Secondary Objectives

- To compare the efficacy of the treatment regimens, based on:
    - Global Response at Day 30 and EOT as determined by the Principal Investigator (PI) and 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 of ibrexafungerp.

3.4 Estimands

The primary, key secondary and safety estimands are described in Table 1 below. The analyses will be performed on the Intent-to-Treat (ITT) Population as defined in Section 7. Other secondary efficacy endpoints will generally be subject to the population, intercurrent event (ICE) handling strategy, and population-level summary measures similar to the primary estimand. Supplementary analyses for the primary and key secondary estimands will be performed using the MITT, FS-MITT, FN-MITT, and PP Populations.

Intercurrent events include study treatment discontinuation (due to any reason) and use of concomitant potentially effective systemic antifungal agents (as collected in electronic case report form [eCRF]). Additional intercurrent event for key secondary estimand is death due to any cause.

Table 1. List of Primary and Key Secondary Estimands

Estimand	Definition	Attributes			
		Population	Variable / Endpoint	Primary Intercurrent Event Handling Strategy	Population-Level Summary Measure
Primary Estimand (non-EU)	Treatment effect on all-cause mortality (ACM) at Day 30	ITT	Vital status (dead/alive) at Day 30	Any occurrence of ICE is ignored	Difference between IV + ibrexafungerp and IV + fluconazole (or BAT) with respect to the proportion of patients in the ITT population experiencing ACM at Day 30
Primary Estimand (EU)	Treatment effect on successful global response at EOT, as determined by the DRC	ITT	Successful global response at EOT, as determined by the blinded DRC	Study treatment discontinuation: participants will be treated as non-responders. Use of concomitant potentially effective systemic antifungal agents or death: participants will be treated as non-responders according to the endpoint definition.	Difference between IV + ibrexafungerp and IV + fluconazole (or BAT) with respect to the proportion of patients in the ITT population achieving a successful global response at EOT, as determined by the blinded DRC
Key Secondary Estimand	Treatment effect on successful global response at Day 14, as determined by the DRC	ITT	Successful global response at Day 14, as determined by the blinded DRC	Study treatment discontinuation: participants will be treated as non-responders. Use of concomitant potentially effective systemic antifungal agents or death: participants will be treated as non-responders according to the endpoint definition.	Difference between IV + ibrexafungerp and IV + fluconazole (or BAT) with respect to the proportion of patients in the ITT population achieving a successful global response at Day 14, as determined by the blinded DRC

4. STUDY DESCRIPTION

4.1 Overall Design

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 (or BAT) 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.

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.

4.2 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 (Day -4 to before end of IV) which includes randomization, an end of IV treatment (EOIV) visit, an Oral Treatment Day 1, 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 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. EOT is the end of all protocol specified treatments, including IV and oral.

4.3 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.

4.4 Study Schema

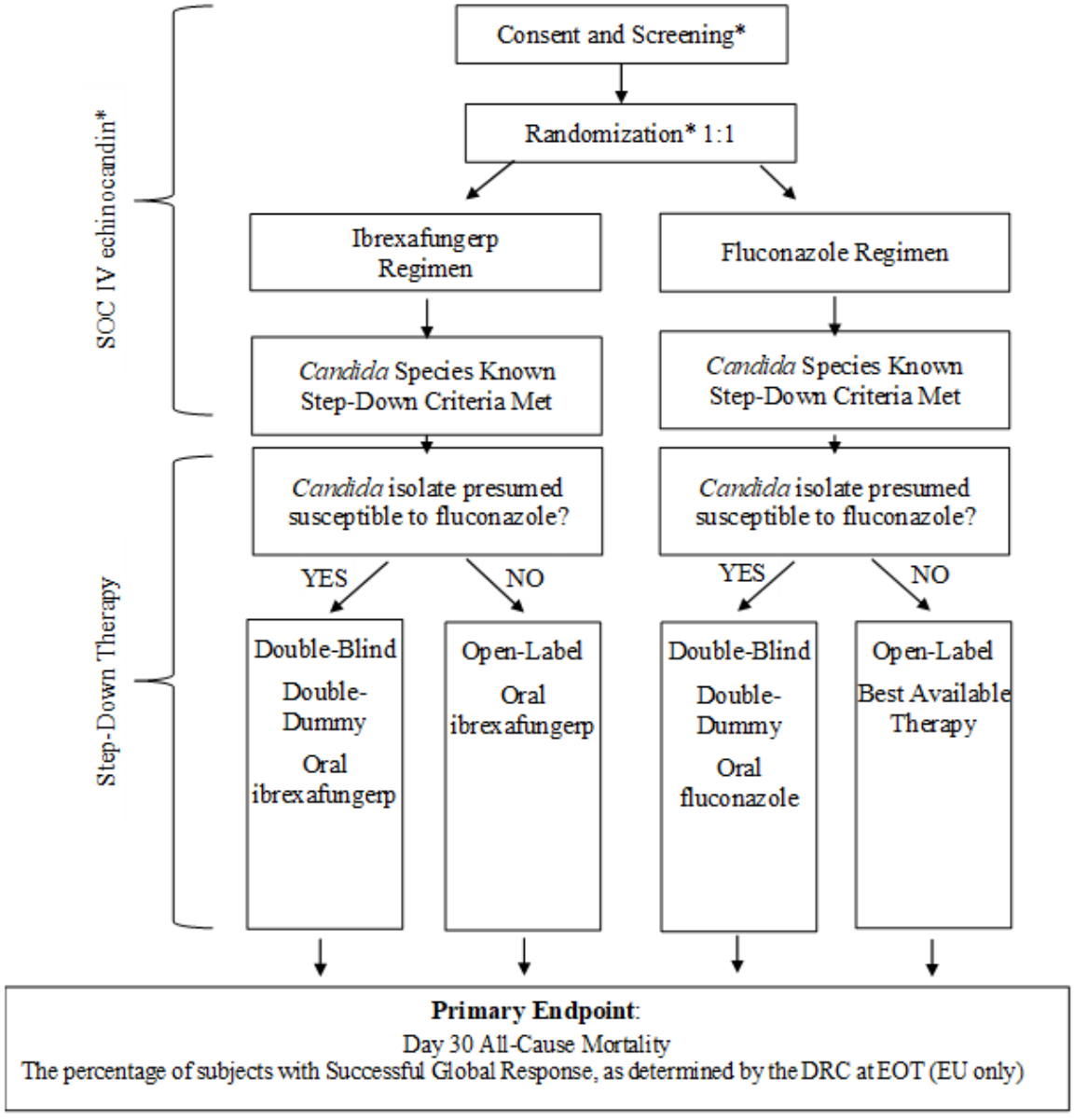


Figure 1. Study Schema

4.5 Study Treatment

All randomized subjects will receive IV echinocandin therapy followed by step-down oral treatment or other BAT as described below. Eligible subjects (Group 1) 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. 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 oral ibrexafungerp (if originally randomized to receive oral ibrexafungerp as step-down) or BAT (if originally randomized to receive oral fluconazole as step-down).

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 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 $\geq$ 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.

4.6 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).

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. For subjects enrolled with candidemia, at least one post-baseline culture should be collected during IV echinocandin treatment.

5. SAMPLE SIZE AND POWER CALCULATION

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% NIM, 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 and global response at EOT (as determined by the DRC) for the ITT population, pooled across treatment groups. The sponsor and DRC will remain blinded to treatment group for both the FS-MITT and FN-ITT populations when performing this review.

6. ANALYSIS ENDPOINTS

6.1 Primary Endpoint

Non-EU primary endpoint: ACM at Day 30 in the ITT population.

EU primary endpoint: Percentage of subjects with Successful Global Response, as determined by the DRC at EOT in the ITT population.

6.2 Key Secondary Endpoint

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

6.3 Other Secondary 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 and no recurrence at 6 weeks after EOT as determined by the DRC.

6.4 Safety Endpoints

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

6.5 PK Endpoint

Description of ibrexafungerp plasma concentrations.

6.6 Efficacy Endpoint Definitions

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. Subjects whose

vital status is not known at Day 30 will be considered as having died in the calculation of the ACM rate for the primary analysis.

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.

Clinical Response (by the PI and DRC)

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

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 with invasive candidiasis 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 with invasive candidiasis 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 the DRC)

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.

7. ANALYSIS POPULATIONS

The populations for the study are:

ITT Population: The ITT Population will include all randomized subjects. This will be the population for the primary endpoint. Subjects will be analyzed according to the treatment to which they were randomized.

Modified Intent-to-Treat (MITT) Population: The MITT Population will include all subjects from the ITT population who received either double-blind or open-label 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 do not have major protocol deviations preventing contribution to the primary analysis of the primary efficacy endpoint as assessed at the blinded data review meeting (BDRM). Subjects will be analyzed according to the treatment to which they were randomized.

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. Significant deviations will be assessed at the BDRM.

Safety Population: The Safety Population will include all subjects who receive at least one dose of on-study antifungal treatment (either IV or oral). Subjects will be analyzed according to their actual treatment arm.

8. ANALYTICAL PLAN AND STATISTICAL METHODS

8.1 General Conventions and Statistical Considerations

All analyses will be performed, and data appendices will be created using SAS® statistical analysis software (SAS, SAS/GRAPH and SAS/STAT; version 9.4 or higher of SAS for Windows [SAS Institute Inc.; Cary, NC, USA]). Analysis Datasets produced for analysis will follow CDISC ADaM standard IG 1.3. ADaM specifications will follow conformance rules for Define.xml v.2.1. CDISC compliance of datasets will be checked by Pinnacle Enterprise software version 5.2.0 or higher and Pinnacle reports will be produced.

In general, continuous variables will be summarized using the following standard descriptive summary statistics: number of observations, mean, standard deviation (SD), median, minimum, maximum and number of observations missing. Use of decimal places in descriptive statistics will be as follows:

- Min, Max: same as the actual data
- Mean, Geometric Mean and Median: actual data + 1 decimal
- SD: actual data + 2 decimals

Categorical data will be described using frequency counts and percentage. Percentage will be based on the number of patients in the selected analysis population unless otherwise stated. Percentages will be rounded to one decimal place except for one hundred percent, which will be presented as 100%. Tests will use a two-sided alpha=0.05 unless otherwise specified.

In general, summaries will include three columns: ibrexafungerp regimen, fluconazole regimen and Overall. For ITT, MITT, PP, PK and Safety populations pooled treatment groups (IV echinocandin followed by oral ibrexafungerp or IV echinocandin followed by oral fluconazole/BAT) will be presented. For FS-MITT population the following columns will be presented: IV echinocandin followed by double-blind oral ibrexafungerp, IV echinocandin followed by double-blind oral fluconazole and Overall, which will include all patients from fluconazole susceptible population. For FN-MITT population the following columns will be presented: IV echinocandin followed by open-label oral ibrexafungerp, IV echinocandin followed by open-label BAT and Overall, which will include all patients from fluconazole non-susceptible population.

8.2 Definition of Baseline, Study Visits, and Visit Windows

It is anticipated that most subjects may be on IV echinocandin at the time of randomization. The last non-missing assessment made prior randomization will be used as baseline.

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 (from 4 days prior to start of IV echinocandin, i.e. Day -4 to before EOIV) which includes randomization, an EOIV visit, an Oral Treatment Day 1,

Oral Treatment Days 2 and 7 visit (PK subset only), an EOT, 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. EOT is end of all treatment, including IV and oral. See study schedule for details.

Other than baseline observations, data will be summarized by scheduled visit. No re-mapping of analysis visits will be performed based on the actual timing of assessments. Unscheduled post-baseline observations will only be reported in listings.

As there will be no visit reassignment, visit windows are not necessary.

8.3 Handling of Missing Data

8.3.1 Incomplete/Missing Dates

The following rules will be applied for AEs, prior medications and concomitant medications with incomplete start dates:

- If day is missing for start date and month and year are the same as month and year for the first IV administration, then start date is set to the first IV administration date
- If day is missing for start date and month and year are not the same as month and year for the first IV administration, then impute Day 1 of the month
- If day and month are missing for start date and the year is the same as the year for the first IV administration, then start date is set to the first IV administration
- If day and month are missing for start date and the year is less than year for the first IV administration then impute July 15th of the year.
- If day and month are missing for start date and the year is greater than year for the first IV administration, then impute January 1st of the year.
- If the imputed start date is greater than or equal to the corresponding non-missing end date, then start date equals the end date.

The following rules will be applied for AEs, prior medications and concomitant medications with incomplete end dates:

- If day is missing for end date and month and year are non-missing, then day will be imputed as last day of the month.
- If day and month are missing for end date and year is non-missing, then day and month will be imputed as December 31st.

The completely missing start and end dates of AEs and CMs will not be imputed.

8.3.2 Missing Efficacy data

Every effort will be made to collect all-cause mortality data to Day 30, and as such no missing data are expected. For primary endpoint ACM analysis subjects whose status (alive or deceased) is unknown will be considered as having died. For primary endpoint Successful Global Response, as determined by the DRC at EOT, missing outcomes are not possible by definition.

For secondary efficacy endpoints subjects whose response is unknown will be treated as non-responders (i.e. subject with missing clinical response will be treated as non-responder and included in the denominator when calculating the percentage for outcome).

8.3.3 Missing Safety Data

Missing AE severity will be imputed as 'Moderate'.

Missing AE relationship to any study drug will be imputed as 'Related'.

8.4 Patient Disposition

The screen failure and reason for screen failure will be summarized by number and percentage for all screened patients. Summary of inclusion not met/exclusion criteria met will be provided. Number of patients dosed but not randomized will also be presented.

The number and percentage of patients enrolled by site will be tabulated.

The number of patients randomized, completed open-label IV treatment, completed oral treatment, completed and discontinued from the study, will be summarized by number and percentage by treatment group. Summaries will be provided for ITT, MITT, FS-MITT, FN-MITT, PP and Safety populations.

The number and percentage of patients in each analysis population will also be provided. Subjects who discontinued from the double-blinded period due to non-susceptible pathogen and transferred to the unblinded period will be included in FN-MITT population and also summarized by number and percentage separately.

Listings will be provided for patients' study disposition, including reasons for discontinuation from the study, and date/cause of death.

8.5 Protocol Deviations

Protocol deviations will be classified as major and minor deviations as described in Protocol Deviation Management Plan.

Major protocol deviations will be summarized by treatment arm and all deviations will be listed. Summaries will be provided for ITT, MITT, FS-MITT, FN-MITT, PP and Safety populations.

8.6 Patient Characteristics

8.6.1 Baseline and Demographic Characteristics

Patient demographics and baseline characteristics such as age, race, ethnicity, sex, childbearing potential, weight, height, body mass index, region, qSOFA score, EKG parameters and overall EKG interpretation, LVEF (%) and overall interpretation of Echocardiogram/MUGA and risk factors for mortality associated with invasive candidiasis will be summarized by treatment group.

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 and compared.

Summaries will be presented for ITT, MITT, FS-MITT, FN-MITT, PP and Safety populations.

Listings will be provided for all demographic and baseline variables.

8.6.2 Diagnosis at Baseline

Summary of the diagnosis including location of infection and signs and symptoms prior to initiation of IV therapy will be summarized by treatment groups and listed. Summaries will be provided for ITT, MITT, FS-MITT, FN-MITT, PP and Safety populations.

8.6.3 Blood and Non-blood Cultures at Baseline

Fungal and bacterial pathogens identified from the baseline blood and non-blood cultures will be presented. Pathogen identification will be done by local reference laboratories and confirmed by the central reference microbiology laboratory. List of baseline pathogens will be delivered to PSI in a form of the excel spreadsheet. The number and percentage of patients with isolated pathogens will be presented by genus and species. In addition, the number and percentage of patients with mono-microbial and poly-microbial infections will be presented.

Several tables providing the frequency distribution of the minimum inhibitory concentrations (MIC) by treatment group will be provided:

- The distribution of MIC to fluconazole for the baseline pathogens
- Summary of susceptibility result interpretation.

All summaries will be provided for the ITT, MITT, FS-MITT, FN-MITT and PP populations.

8.6.4 Medical History and Current Medical Conditions

Medical history (both prior and concurrent conditions) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later and summarized by System Organ Class (SOC) and preferred term [PT]). Summaries will be presented for ITT, MITT, FS-MITT, FN-MITT, PP and Safety populations and sorted by decreasing frequency in Total group.

Listings will be provided for all medical history findings.

8.6.5 Prior and Concomitant Medication

All prior and concomitant medications will be coded using WHODD Global B3 version and summarized by the Anatomical Therapeutic Chemical (ATC) level 2 and ATC level 4. Separate summaries will be provided for concomitant antifungal medication.

A medication is considered prior if the end date of the medication is prior to Day 1 (start of IV echinocandin). If end date of the medication coincide with date of Day 1 and start time of IV echinocandin administration or start time of IV echinocandin is unavailable then medication will be considered concomitant. A medication is considered concomitant if it started or was ongoing on or after Day 1 and before EOT.

Imputation rules specified in Section 8.3.1 will be applied to partial/missing dates.

Surgeries and concomitant procedures will also be summarized by treatment group. Summaries will be presented for ITT, MITT, FS-MITT, FN-MITT, PP and Safety populations and sorted by decreasing frequency in Total group.

Listings will be provided for all prior and concomitant medications and separately for antifungal medications. Prior and concomitant procedures and surgeries will be listed separately.

8.7 Efficacy Endpoints and Analysis

8.7.1 Analysis of Primary Efficacy Endpoints

Based on feedback from different regulatory agencies, different primary efficacy variables are used for the study. For non-EU, the primary efficacy variable is the percentage of subjects with 30-day ACM and for the EU, the primary efficacy variable is the percentage of subjects with Successful Global Response, as determined by the DRC at EOT. The primary efficacy assessments will be performed for 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.

Two independent analyses will be performed for two primary endpoints separately. No multiplicity adjustment will be made.

8.7.1.1 ACM (non-EU)

To assess non-inferiority, an estimate of the difference in mortality rates will be calculated along with a 95% confidence interval (CI) using the stratified method of Miettinen and Nurminen [1] with randomization stratification factors (see Section 4.1). IV 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 mortality 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.

Sensitivity analyses will also be conducted for the MITT, FS-MITT, FN-MITT, and PP Populations.

8.7.1.2 Successful Global Response, as determined by the DRC at EOT (EU only)

Global Response will be analyzed similar to the ACM endpoint. This endpoint is considered primary only for the EU authorities.

8.7.2 Additional Analyses of the Primary Efficacy Endpoints

Covariate analysis

As secondary analyses of the primary efficacy endpoints two independent logistic regression analyses with the stepwise selection method may be performed to identify predictors of mortality and global response. The alpha level for both entering and removing a covariate will be 0.10. Point estimates and the corresponding 95% confidence intervals for the odds ratios will be calculated for the following risk factors:

- Acute Kidney Injury
- Broad Spectrum Antibiotics
- Burns
- Central Venous Catheter not removed
- Diabetes mellitus
- Dialysis
- End Stage renal disease
- Gastrointestinal perforation
- Hepatic Dysfunction
- ICU admission
- Immunosuppressive therapy
- Major surgery
- Mechanical Ventilation
- Neutropenia
- Pancreatitis
- Presence of septic shock
- Source control within 24 Hours

- Thrombocytopenia
- Total Parenteral Nutrition

Analysis will be performed for the ITT, MITT, FS-MITT, FN-MITT, and PP Populations.

Survival analysis

Overall survival is defined as the time (in days) from Day 1 to death from any cause. Patients still alive at the end of study, or lost to follow-up, will be censored at last day known alive. Patients with no post-baseline information will be censored at the date of randomization plus 1 day.

The following statistics will be displayed:

- The proportion of patients who are alive at Day 14, Day 30, 2-Week FU and 6-Week FU visits with exact 95% CI estimated by Kaplan-Meier method
- The median time to death determined by Kaplan-Meier method. Its 95% CI will be performed using the Brookmeyer-Crowley method
- Survival curves will be displayed for both treatment groups and log-rank test p-value presented

Summaries and survival curves will be provided for the ITT, MITT, FS-MITT, FN-MITT, and PP Populations.

Subgroup Analyses

Analyses of the primary endpoints will be conducted by stratification factors: APACHE II score (≤ 20 or > 20), absolute neutrophil count (≤500 or > 500 per cubic millimeter) and geographic region.

8.7.3 Analysis of Key Secondary Efficacy Endpoint

Key secondary endpoint is the percentage of subjects with Successful Global Response, as determined by the DRC (based on PI-determined clinical response, mycological response and radiological response [when applicable]) at Day 14. Methodology similar to analysis of primary endpoints will be used, difference in response rates between treatment groups will be calculated along with a 95% CI using the method of Miettinen and Nurminen. Summaries will be provided for the ITT, MITT, FS-MITT, FN-MITT, and PP Populations.

8.7.4 Analysis of Other Secondary Efficacy Endpoints

The following analyses of secondary endpoints will be performed similar to the key secondary endpoint:

Table 2

Analysis	Visit
Global Response as determined by the PI	Day 14, Day 30, EOT

Analysis	Visit
Global Response as determined by the DRC	Day 14*, Day 30, EOT**
Clinical Response as determined by the PI	Day 14, Day 30, EOT
Clinical Response as determined by the DRC	Day 14, Day 30, EOT
Mycological Response as determined by the DRC	Day 14, Day 30, EOT
No recurrence as determined by the DRC	2-Week FU, 6-Week FU
Successful Global Response at EOT and no recurrence	6-Week FU

*Key secondary endpoint
**Primary endpoint (EU only)

For clinical response and radiological response full or partial resolution of all attributable clinical symptoms and physical findings will be considered a success. For mycological response eradication and presumed eradication will be considered a success.

Summaries will be provided for the ITT, MITT, FS-MITT, FN-MITT, and PP Populations.

8.7.5 Additional Efficacy Analyses

Categorical results of efficacy assessments, such as signs and symptoms of infection, radiological response, clinical response, type of response (ex. complete global response or partial global response), APACHE II score and qSOFA score will be summarized by number and percentage and listed.

Fungal and bacterial pathogens identified in post-baseline blood and non-blood cultures will be summarized by genus and species and listed.

Summaries will be provided for the ITT, MITT, FS-MITT, FN-MITT, and PP Populations.

8.7.6 Pharmacokinetics Analysis

Full details of PK analysis will be provided in a PK Analysis Plan.

PK samples will be collected from consenting subjects during treatment (1, 2, and 7 days after the start of oral dosing) and additionally on Days 14 and 30 for subjects still receiving study treatment. NONMEM software will be used to estimate PK parameters (e.g., Cmax, AUC, etc. …). A stand-alone PK report will be prepared to describe the PK analyses.

8.8 Exposure to Study Treatment

All 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 BAT. It is anticipated that most subjects may be on IV echinocandin at the time of randomization.

The IV component of these treatment regimens will be given as open-label therapy. 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). See study schema for details.

All summaries of exposure parameters will be provided for all study populations. All data on study drug exposure, including switch to oral therapy and unblinding due to non-susceptible isolate will be listed.

IV treatment

The following parameters of IV echinocandin administration will be calculated and summarized by means of descriptive statistics:

- IV treatment duration from randomization till EOIV (days)
- IV treatment duration from Day 1 till EOIV (days)
- Total dose administered from randomization (mg)
- Total dose administered from Day 1 till EOIV (mg)

IV echinocandin administered before randomization will be captured in the eCRF as concomitant medication and details of the administration will be listed.

Oral treatment

Following parameters will be calculated and summarized by means of descriptive statistics:

- Oral treatment duration (days)
- Number of tablets taken
- Number of missed doses
- Reasons for missed doses
- Total dose (mg) administered
- Compliance calculated as number of tablets/capsules taken*100/(number of tablets/capsules taken + number of missed doses).

For BAT only oral treatment duration parameter will be calculated.

8.9 Safety Analysis

All safety analyses will be performed for the Safety population and additionally for the subgroup of subjects who received oral step-down therapy and for the subgroup of subjects with adverse events occurring after oral step-down.

8.9.1 Adverse Events

AEs will be coded according to the MedDRA version 24.1 or higher.

A Treatment emergent adverse event (TEAE) is defined as an AE occurred after the first dose of IV treatment. Given that IV treatment may begin before Screening visit, TEAE may occur before Informed consent is signed. If AE date coincides with the date of first IV administration and either of AE onset time or IV administration time is missing, then AE will be considered as TEAE. AEs having date missing will be considered as TEAEs. AEs having missing onset date and not missing end date will be considered as TEAE unless end date is prior to the date of the first IV administration after IC.

An overall summary of AEs prior to treatment and TEAEs will be presented by treatment group and overall. It will include the number and percentage of patients with at least one event of specified category and total number of events. The following categories will be summarized:

- AE/TEAE
- Serious AE/TEAE
- Non-serious AE/TEAE
- AE/TEAE related to open label IV Echinocandin
- TEAE/serious TEAE with onset after oral step-down
- TEAE/serious TEAE related to blinded oral drug
- TEAE/serious TEAE related to unblinded oral drug
- TEAE/serious TEAE related to BAT
- TEAE leading to premature discontinuation of open label IV Echinocandin
- TEAE leading to premature discontinuation of blinded oral drug
- TEAE leading to premature discontinuation of unblinded oral drug
- TEAE leading to premature discontinuation of BAT
- AE/TEAE leading to death.

Similar summaries will be presented for TEAEs for IV open-label treatment period, oral blinded treatment period, oral unblinded treatment period, and post-treatment period.

The incidence of TEAEs will be summarized by SOC and PT and by SOC, PT and maximum severity and ordered by decreasing frequency in active treatment group. For incidences, if the same AE (based on SOC and PT) is reported for the same subject more than once, the AE is counted only once for that SOC and PT, and at the highest severity. For number of events, all events with specified severity will be counted.

In addition, the incidence of SAEs, TEAEs related to open label IV Echinocandin, TEAEs related to blinded oral drug, TEAEs related to unblinded oral drug, TEAEs related to BAT, TEAEs with onset after oral step-down, TEAEs leading to study drug interruption, TEAEs leading to premature

discontinuation of study drugs and TEAEs leading to death will be presented by SOC and PT and will be tabulated by treatment group.

Separate listings will be prepared for all AEs, SAEs, AEs leading to discontinuation of the study drug and AEs leading to death.

8.9.2 Vital Signs

Vital signs include data on pulse rate (bpm), systolic/diastolic blood pressure (mmHg), respiratory rate (breaths/min), temperature (C^o), weight (kg), height (cm) and body mass index (kg/m^2). Descriptive statistics will be provided for vital signs observed values and changes from baseline to post-baseline time points by treatment group and overall.

A listing of vital signs data will be presented.

8.9.3 Laboratory Assessments

Clinical laboratory tests will include biochemistry and hematology.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units on Study Data Tabulation Model (SDTM) level. Only central laboratory data will be used for the summaries, however both local and central results will be presented in the listings.

Hematology and chemistry parameters will be summarized descriptively and changes from baseline to post-baseline visits for each parameter will be presented. Summary tables will be presented by treatment group and overall.

Shift tables (number and percentage) classified by reference range indicator (Low, Normal, and High) and CTCAE toxicity grade from baseline to every post-baseline and worst post-baseline visit will be presented separately by laboratory test, where applicable. The number of patients in a particular treatment group having both baseline and post-baseline results available will be used as the denominator. Patients experienced both Low and High values outside of the reference range will be counted in both categories at worst post-baseline visit.

All laboratory data will be listed, including toxicity grades and normal ranges; values outside their normal range will be flagged as H (high, above normal) or L (low, below normal), where applicable.

Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) scatter plot will be produced for liver function tests (ALT, AST and Total bilirubin).

A listing will also be provided for the pregnancy test (Screening, EOT or Unscheduled visit).

8.9.4 Physical Examination

Number and percentage of patients with abnormal findings at physical examination will be summarized by number and percentage of patients by treatment group and overall and listed.

8.9.5 EKG

The following EKG parameters will be listed by visit: HR (beats/min), PR interval (msec), RR interval (msec), QRS interval (msec), QT interval (msec) and QTcF interval (msec). Overall EKG interpretation will also be listed.

8.9.6 Echocardiography/MUGA

LVEF (%) and overall interpretation of Echocardiogram/MUGA scans will be listed by visit.

8.9.7 Retinal Examination

Results of retinal examination will be summarized by number and percentage of patients by treatment group and overall and listed.

8.10 Healthcare Economic Data

The following healthcare economic parameters will be summarized by means of descriptive statistics and listed: subject days of hospital stay, subject days in intensive care unit, days from discharge to readmittance to hospital for treatment of invasive candidiasis/candidemia.

9. INTERIM ANALYSIS

No interim analysis (IA) planned.

A blinded sample size reassessment (see Section 5) will be performed by Scynexis or their designee.

10. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

The planned analyses as described in this SAP do not deviate from the description in the protocol.

11. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version. Detailed programming specifications are provided in the Mock Tables, Listings and Figures (TFLs) file.

12. LIST OF TABLES, FIGURES AND LISTINGS

See Mock TFLs file.

13. REFERENCES

1) Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4: 213–226

2) Flexible Method to Apply Multiple Imputation Using SAS/IML® Studio. Xue Yao, University of Manitoba, Winnipeg, MB, Canada; Lisa M. Lix, University of Manitoba, Winnipeg, MB, Canada. SAS Global Forum 2013, Paper 283-2013

14. APPENDIX I. STUDY SCHEDULE

	Treatment Period								**Post-Treatment Period**	
Visit	***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[b]** -2/+3 days	**Study Day 30[b]** ±3 days	**EOT[b]** +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							

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[b]** -2/+3 days	**Study Day 30[b]** ±3 days	**EOT[b]** +3 days		
Collect Healthcare Economic Data	X	X						X	X	X
EFFICACY PROCEDURES										
Targeted physical examination, including clinical evaluation of signs and symptoms of infection[m]	X	X				X	X	X	X[m]	X
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 to become 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.