SCYNEXIS, Inc.

Clinical Trial Protocol

Open-Label Study to Evaluate the Efficacy and Safety of SCY-078 (Ibrexafungerp) in Patients with Fungal Diseases that are Refractory to, Resistant to or Intolerant of Standard Antifungal Treatment (**FURI**)

SCYNEXIS Protocol Number SCY-078-301

Original Protocol Issue Date:	30 November 2016
Protocol Amendment 1 Issue Date:	23 March 2017
Protocol Amendment 2 Issue Date	13 August 2019
Protocol Amendment 3 Issue Date:	21 November 2022

US IND Number 107,521

EudraCT Number 2017-000381-29

1.0 Contact Information

Contract Research Organization	
Study Medical Monitor	
Clinical Project Manager	
Safety Contact	
Sponsor	SCYNEXIS, Inc.

2.0 Protocol Approvals

PROTOCOL ID: SCY-078-301

Open-Label Study to Evaluate the Efficacy and Safety of Ibrexafungerp in Patients with Fungal Diseases that are Refractory to, Resistant to or Intolerant of Standard Antifungal Treatment (**FURI**)

SCYNEXIS, Inc. Approval:

21 November 2022

VP Clinical Development and Medical Affairs 1 Evertrust Plaza, 13th Floor Jersey City, NJ 07302 Phone: +201 884 2243 Fax: +1 201 884 5490 E-mail: nkechi.azie@scynexis.com	Date

Investigator Agreement Statement

PROTOCOL ID: SCY-078-301

*Open-Label Study to Evaluate the Efficacy and Safety of Ibrexafungerp in Patients with Fungal Diseases that are Refractory to, Resistant to or Intolerant of Standard Antifungal Treatment (**FURI**)*

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 subject. 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)

3.0 Table of Contents

LIST OF FIGURES

LIST OF TABLES

4.0 Abbreviations

ABBREVIATION	DEFINITION
ABPA	allergic bronchopulmonary aspergillosis
ACM	all-cause mortality
AE	adverse event
ALT	alanine aminotransferase
AMB	amphotericin B
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
AUC_{last}	area under the concentration-time curve up to the last measurable concentration
Azole-R	azole-resistant
BAL	bronchoalveolar lavage
BDG	β-D-glucan
BID	twice daily
BL	baseline
BUN	blood urea nitrogen
C_{avg}	average concentration
CD	compact disk
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	clearance/fraction absorbed
CLSI	Clinical and Laboratory Standards Institute
C_{max}	maximum concentration
CMC	chronic mucocutaneous candidiasis
CPA	chronic pulmonary aspergillosis
CPK	creatine phosphokinase
CRO	contract research organization
CRP	c-reactive protein
CT	computerized tomography
CYP	cytochrome
D	day
D/I	disseminated/invasive
DF	dimorphic fungi
DRC	Data Review Committee
DVD	digital versatile disk

EC	Ethics Committee esophageal candidiasis
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data capture
EOT	End of Treatment
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
FEV1	Forced expiratory volume during the first second
FU	follow up
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GMI	galactomannan index
GSI	glucan synthesis inhibitors
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HRCT	high resolution computerized tomography
IC	invasive candidiasis
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IDSA	Infectious Disease Society of America
IgE	immunoglobulin E
IPA	invasive pulmonary aspergillosis
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
KOH	potassium hydroxide
LAM	lactation amenorrhea method
LDH	lactate dehydrogenase
MALDI-TOF	matrix-assisted laser desorption/ionization
MEC	minimum effective concentration
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MRC	Medical Research Council
MRI	magnetic resonance imaging

MSG-EORTC	Mycosis Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria
NG	nasogastric
NOAEL	no-observed-adverse-effect-level
OATP1B3	organic anion transporting polypeptide 1B3
OPC	oropharyngeal candidiasis
PCR	polymerase chain reaction
PE	physical exam
PEG	percutaneous endoscopic gastrostomy
PI	principal investigator
PK	pharmacokinetics
Pop PK	population pharmacokinetics
PP	per protocol
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SGRQ	St. George's Respiratory Questionnaire
SOC	standard of care
spp	species
TOC	test of cure
Tx	treatment
ULN	upper limit of normal
US	United States
VSS	vulvovaginal signs and symptoms
VVC	vulvovaginal candidiasis
WBC	white blood cell
WHO	World Health Organization
WK	week
β-hCG	β-human chorionic gonadotropin

5.0 Protocol Synopsis

Title: Open-Label Study to Evaluate the Efficacy and Safety of SCY-078 (Ibrexafungerp) in Patients with Fungal Diseases that are Refractory to, Resistant to or Intolerant of Standard Antifungal Treatment (**FURI**)

Primary Objectives:

The primary objectives listed below apply to all eligible fungal diseases:

- To evaluate the efficacy of ibrexafungerp in the treatment of severe fungal diseases as determined by a Data Review Committee (DRC) at the primary time point for the fungal disease
- To evaluate the safety of ibrexafungerp

Overall Secondary Objectives:

The overall secondary objectives listed below apply to all eligible fungal diseases:

- To evaluate the efficacy of ibrexafungerp as determined by the DRC at other time points
- To evaluate the efficacy of ibrexafungerp as determined by the Investigator
- To determine the efficacy of ibrexafungerp by pathogen
- To determine the efficacy of ibrexafungerp by fungal disease and disease category
- To evaluate the efficacy of ibrexafungerp by recurrence of the baseline fungal disease
- To evaluate the efficacy of ibrexafungerp by reason for enrollment (refractory, resistance, relapse, intolerance, toxicity, need for oral therapy)
- To determine All-Cause Mortality (ACM)
- To evaluate the pharmacokinetics (PK) of ibrexafungerp by population PK analysis

Disease-Specific Secondary Objectives:

- To evaluate the efficacy of ibrexafungerp as determined by other disease-specific endpoints (see below).

Primary Endpoints:

The primary endpoints listed below apply to all eligible fungal diseases:

- Efficacy as measured by the percentage of subjects with Global Response at:
  TOC for Vulvovaginal Candidiasis (VVC, Day 17), Chronic Mucocutaneous Candidiasis (CMC, EOT or Day 84), Chronic Pulmonary Aspergillosis (CPA, EOT or Day 90), Allergic Bronchopulmonary Aspergillosis (ABPA, EOT or Day 90) (whichever comes first) and at EOT for all other diseases as determined by a DRC
- Safety as measured by: physical examination, vital signs, AEs, and laboratory tests

Overall Secondary Endpoints:

The overall secondary endpoints listed below apply to all eligible fungal diseases:

- The percentage of subjects who achieve Global Response at additional time points as applicable for each disease, disease category and reason for enrollment (Table 16 in the full protocol), as determined by the DRC and by the Investigator
- The percentage of subjects who achieve Clinical Response by pathogen at time points applicable for each disease, disease category and reason for enrollment (Table 16 in the full protocol), as determined by the DRC and the Investigator
- The percentage of subjects who achieve Mycological Response by pathogen at time points applicable for each disease, disease category and reason for enrollment (Table 16 in the full protocol), as determined by the DRC and the Investigator

- The percentage of subjects who achieve Clinical Response by fungal disease, disease category and reason for enrollment at time points applicable for each disease (Table 16 in the full protocol), as determined by the DRC and the Investigator
- The percentage of subjects who achieve Mycological Response by fungal disease, disease category and reason for enrollment at time points applicable for each disease (Table 16 in the full protocol), as determined by the DRC and the Investigator
- The percentage of subjects with a recurrence of the baseline fungal disease at the 25-Day FU for VVC and at the 6-Week FU for all other diseases as determined by the DRC
- ACM at Day 30 for Invasive Candidiasis (IC) and candidemia and at Day 42 for all diseases
- Time to death from any cause
- Describe ibrexafungerp plasma concentrations

Disease-Specific Secondary Endpoints:
Disease-specific secondary endpoints, as assessed by the DRC

Acute IC / Candidemia disease-specific endpoints

- Completion of study drug antifungal treatment (i.e. no recurrence, no use of other antifungal treatment, no discontinuation for any reason)

Acute or Chronic Severe Mucocutaneous Candidiasis

- Percentage subjects with mycological cure by Day 84
- Percentage subjects with clinical response by Day 30 and Day 84
- Percentage of subjects with continued symptom relief at 6-week FU

Chronic Pulmonary Aspergillosis (CPA) disease-specific endpoints

- Six-Minute Walk test and MRC Dyspnea Score at Day 90 and Day 180
- Weight change at Day 90 and Day 180
- Improvement in inflammatory markers (CRP, plasma viscosity, albumin, platelet count, disease-specific immunoglobulin levels) at Day 90 and Day 180
- Change in total IgG and *Aspergillus* IgG at Day 90 and Day 180, if elevated at Baseline
- All-cause mortality at Day 90, Day 120 and Day 180
- Recurrence at Day 180

Allergic Bronchopulmonary Aspergillosis (ABPA) disease-specific endpoints:

- Percentage of subjects who exhibit a Global Response at Day 42
- Percentage of subjects with Clinical Improvement (as measured on a 4-point scale) at TOC, Day 90, Day 180, then every 3 months while on therapy, and 6-month follow-up (FU)
- Percent decline in total IgE (baseline IgE minus time point IgE/baseline IgE) at Day 42 and Day 90
- Number of subjects who experience an ABPA exacerbation at the 3-month and 6-month FUs
- Time to first ABPA exacerbation
- Change in lung function (FEV1 and FVC) at Day 42
- Number of Asthma exacerbations and ABPA exacerbations at the 3-month and 6-month FUs
- All-cause mortality at Day 90, Day 120 and Day 180

Invasive Pulmonary Aspergillosis (IPA) disease-specific endpoint

- The percentage of subjects who attain a galactomannan index (GMI) decrease including absolute and percent reduction from Baseline to Weeks 1, 2, 4 and 6, when feasible
- Time to achieve a clinically meaningful GMI absolute and percent decrease

- All-cause mortality at Day 84

Disseminated/invasive dimorphic fungal disease-specific endpoint

- All-cause mortality at Day 84

Other emerging fungi including yeasts and molds disease-specific endpoint

- All-cause mortality at Day 84

Study Phase: 3

Study Design: This is a multicenter, open-label, non-comparator, single-arm study to evaluate the efficacy, safety and PK of ibrexafungerp in male and female subjects ≥18 years of age with documented severe fungal diseases for whom standard of care (SOC) antifungal treatment is not appropriate due to refractoriness, resistance, relapse, intolerance, toxicities, need for oral therapy or other reasons.

Subjects must have a documented eligible fungal disease that has been refractory to, has relapsed after, or subject has intolerance to or demonstrated toxicities resulting from an approved SOC antifungal treatment as listed in the full protocol, or isolate is resistant to, or has a high MIC and is unlikely to respond to antifungal SOC. Subjects are also eligible if, in the judgement of the Investigator, continued IV antifungal therapy is not feasible or desirable due to clinical or logistical circumstances or if other oral antifungal alternatives are not appropriate. Subjects should meet these and other study criteria to be considered for enrollment. Inclusion of each subject in the study must be approved by the Sponsor (or Sponsor designee) prior to initiation of study drug.

The study will be conducted at approximately 40 sites globally and is planned to enroll and treat approximately 220 (+10%) subjects.

For all subjects except VVC subjects, there will be a Screening visit, a Baseline visit (also considered Day 1), several scheduled visits depending on the subject's fungal disease, an EOT visit and a follow-up visit 6 weeks after EOT. FOR ABPA subjects there will be additional follow-up visits 3 months and 6 months after EOT. For CMC, CPA and ABPA subjects, there will be a TOC visit on EOT or Day 84 for CMC or Day 90 for CPA and ABPA subjects, whichever comes first. Following Screening, eligible subjects will receive the study drug loading dose on Days 1 and 2 and the study drug maintenance dose from Day 3 up to EOT.

Subjects with VVC will have a Screening visit, a Baseline/Day 1 visit, and scheduled visits on [redacted] Day 17 (TOC), 25-day FU (Day 32) and 35-day FU (Day 42). VVC subjects will receive treatment every three days for a total of three dosing days (i.e., on Days 1, 4 and 7). The EOT and 35-Day FU visits may be a phone contact for asymptomatic subjects

All eligible subjects will receive ibrexafungerp monotherapy for up to 180 days at a dosing regimen that will depend on fungal disease. Ibrexafungerp will be available as combination therapy for selected subjects. The treatment duration may be extended beyond 180 days, if needed, for certain fungal diseases. Sponsor approval must be obtained for any extension of treatment beyond 180 days. Subjects with VVC will receive oral doses of [redacted]. Subjects who have a recurrence after TOC (VVC subjects) or EOT (other subjects), may be considered for re enrollment upon discussion with the sponsor.

Efficacy evaluations will consist of clinical evaluations of the signs and symptoms of infection, mycological testing, imaging and serological testing as applicable for each fungal disease. Additional procedures will be conducted for selected fungal diseases.

PK: The PK data obtained from this study will be part of the Population PK analyses that will be performed. For subjects who are willing to participate in the PK sampling, blood samples will be collected

on Day 2 (one sample collected anytime post dosing), Days 3 to 5 (one sample collected predose on any of these days) and Days 7 to 10 (one sample collected predose on any of these days). Additional blood PK samples will be collected when clinically indicated. Tissue samples collected as part of SOC procedures (e.g., biopsies) may be sent for drug concentration analysis, when available.

Subjects will be evaluated for safety throughout the study, including parameters such as physical exam, vital signs, adverse events (AEs) and concomitant medications, and safety laboratory tests (hematology, blood chemistry and urinalysis).

Results from the study will be analyzed against historical and concurrent SOC-treated subjects, who will be selected from literature reviews and other data resources.

Target Population: Male and female subjects ≥18 years of age with documented eligible severe fungal diseases for whom SOC antifungal treatment is not appropriate due to refractoriness, resistance, intolerance, relapse, toxicities, need for oral therapy or other reasons.

KEY Inclusion Criteria:

Subject must fulfill all of the following **KEY** criteria at Screening and/or Baseline to be eligible for study admission:

1. Subject is a male or female adult ≥18 years of age on the day the study informed consent form (ICF) is signed.
2. Subject has a documented eligible fungal disease that has been refractory or resistant to SOC, has relapsed after, or the subject has intolerance to or demonstrated toxicities resulting from an approved SOC antifungal treatment. The subject is also eligible if, in the judgement of the Investigator, long-term IV antifungal therapy is not feasible or desirable due to clinical (isolate is resistant to or has a high MIC and is unlikely to respond to antifungal SOC) or logistical circumstances or if other antifungal alternatives are not appropriate.

   A summary of eligible fungal diseases is listed below and a detailed description of diagnostic, refractoriness, intolerance, toxicity and relapse criteria is available in Table 5 in the full protocol:
   - Acute or chronic invasive candidiasis, including candidemia
   - Acute or chronic severe mucocutaneous candidiasis, including:
     - Esophageal candidiasis (EC)
     - Oropharyngeal candidiasis (OPC)
     - Chronic mucocutaneous candidiasis (CMC)
     - Vulvovaginal candidiasis (VVC)
   - Disseminated/invasive dimorphic fungi:
     - Coccidioidomycosis
     - Histoplasmosis
     - Blastomycosis
   - Chronic Pulmonary Aspergillosis (CPA)
   - Allergic Bronchopulmonary Aspergillosis (ABPA)
   - Invasive Pulmonary Aspergillosis (IPA)
   - Other emerging fungi including yeasts and molds (e.g., sachromycetes, scopulariopsis, mucorales)

KEY Exclusion Criteria:

Subject will be excluded from participation in the study if he/she meets any of the following **KEY** exclusion criteria at Screening and/or Baseline:

1. Subject has an invasive fungal disease with central nervous system involvement unless the subject is planned to receive combination therapy with ibrexafungerp and other antifungal.
2. Subject has an inappropriately controlled fungal disease source (e.g., persistent catheters, devices, identified undrained abscess) that is likely to be the source of the fungal disease.
3. Subject is hemodynamically unstable and/or requiring vasopressor medication for blood pressure support.
4. Subject has abnormal liver test parameters: AST or ALT >10 x ULN and/or total bilirubin >5 x ULN. **Note**: Subjects with unconjugated hyperbilirubinemia with a diagnosis of Gilbert's disease **are not excluded**.
5. Subject is unlikely to survive 30 days.

Study Drugs:

Ibrexafungerp citrate drug product for oral administration will be supplied as compressed oral tablets containing 250 mg of ibrexafungerp active ingredient on a free base basis. In addition to the active ingredient, the oral tablet formulation also contains silicified microcrystalline cellulose, crospovidone, mannitol, colloidal silicon dioxide, magnesium stearate (non-bovine), and butylated hydroxyanisole. Ibrexafungerp is packaged in bottles containing 30 tablets.

Ibrexafungerp tablets are to be stored at room temperature: between 15°C and 25°C with allowable limited excursions of up to 30°C.

Randomized Treatment Groups: This is an open-label, non-comparator, single-arm study. All subjects will receive ibrexafungerp monotherapy except subjects with refractory or relapsing invasive pulmonary aspergillosis (IPA), mucormycosis or other molds with unpredictable ibrexafungerp activity, who will receive combination therapy. Combination therapy may also be administered to other subjects based on Investigator's judgement and contingent on Sponsor approval. Subjects will receive ibrexafungerp on an inpatient or outpatient basis, as needed for each fungal disease.

Ibrexafungerp Monotherapy for All fungal Diseases, Excluding VVC

Subjects will receive ibrexafungerp monotherapy given as an initial loading dose of 750 mg (3 tablets of 250 mg each) given BID (total daily dose = 1500 mg) during the first 2 days of treatment and then subsequent oral doses of 750 mg (3 tablets of 250 mg each) QD for up to 180 days, depending on fungal disease. Treatment beyond 180 days may be permitted under certain circumstances to be agreed upon by the Investigator and the Sponsor on a per-subject basis. Subjects may be considered for re-enrollment upon discussion with the sponsor.

If subjects cannot swallow the whole tablet, the tablets may be split. In the event subjects experience gastrointestinal intolerance on the 750 mg QD dose, the tablets may be split and/or administered at 10 to 20-minute intervals. [redacted]

Ibrexafungerp Monotherapy for VVC

Subjects with VVC will receive ibrexafungerp monotherapy given as oral doses of [redacted] Subjects treated for VVC who have a recurrence may receive additional cycles of ibrexafungerp treatment similar to the initial regimen upon discussion with the Sponsor.

Ibrexafungerp Combination Therapy

Monotherapy with ibrexafungerp is not recommended for refractory or relapsing IPA or mucormycosis. All subjects enrolled for refractory or relapsing IPA or mucormycosis should receive ibrexafungerp given

as combination therapy. Subjects with IPA and intolerance to other SOC options can be considered for enrollment to receive ibrexafungerp monotherapy, upon discussion with the Sponsor.

For subjects who have infections due to other emerging fungi, including yeasts and molds, but have no culture isolate available (to confirm susceptibility to ibrexafungerp), combination therapy should be considered and discussed with the Sponsor. Combination therapy will also be allowed for other subjects based on Investigator's judgement and contingent on Sponsor approval.

Acceptable antifungal therapy includes voriconazole, isavuconazole, posaconazole, or amphotericin B (AMB) at the doses recommended per their label. When used in combination with the azoles, the dose of ibrexafungerp should be reduced from 750 mg to 500 mg.

The following combination options are allowed:

- addition of ibrexafungerp to any ongoing antifungal therapy
- replacement of one (toxic/ineffective) element of a two-antifungal combination therapy with ibrexafungerp
- replacement of current monotherapy with a new combination, generally:
    - replacement of AMB monotherapy with an azole plus ibrexafungerp combination, or
    - replacement of an azole monotherapy with an AMB plus ibrexafungerp combination
- continuation of an azole plus echinocandin combination where the subject could go home on an oral regimen by replacing the parenteral echinocandin with ibrexafungerp

Study Blinding, Randomization and Stratification: This is an open-label study

Study Evaluations

Efficacy Evaluations: Efficacy evaluations will consist of clinical evaluations of the signs and symptoms of infection, mycological testing (including, but not limited to, fungal culture, KOH and other fungal stains, and T2 testing), imaging (e.g., CT, MRI, X-Ray or ultrasound) and serological testing (including, among others, ß-D-glucan levels, GM and fungal antibody titers) as applicable for each fungal disease. Additional procedures (esophagoscopy, spirometry, St. George's Respiratory Questionnaire [SGRQ], 6-Minute Walk test and Medical Research Council [MRC] Dyspnea Scale) will be conducted for selected fungal diseases.

Efficacy will be assessed primarily in terms of Global Response at TOC for VVC (Day 17), EOT visit or Day 84 (CMC) or Day 90 (CPA and ABPA) whichever comes first, and at EOT for all other fungal diseases, as determined by an independent DRC. Global Response will be a composite global outcome composed of clinical (including radiological, when applicable) and mycological (including serological) responses. In addition to the primary endpoint, Global Response, Clinical Response and Mycological Response will be assessed as secondary endpoints at the disease specific primary time point and at additional time points, for the determination of efficacy by the independent DRC and the Investigator.

Other secondary efficacy assessments will include recurrence and survival. Recurrence will be evaluated at the 6-Week FU visit after EOT for all subjects, except VVC subjects, who will be assessed for recurrence at the 25-Day FU visit. Survival will be determined on Day 30 for patients with invasive candidiasis and candidemia, and on Day 42 for all subjects. Additional disease-specific efficacy endpoints will be evaluated for selected fungal diseases at additional time points.

Efficacy outcomes will be based on EORTC-MSG Consensus Criteria except for diseases not defined in the EORTC-MSG Consensus Criteria such as ABPA, CPA, CMC and VVC. The efficacy time points and outcome definitions for the primary and secondary endpoints are detailed in Table 16 in the full protocol. Criteria for the DRC assessment of response will be further detailed in the DRC Charter.

Phamacokinetic Evaluations: For subjects who are willing to participate in the PK sampling, up to three (3) blood samples will be collected at the following visits and sampling windows: Day 2 (one sample collected anytime post dosing), Days 3 to 5 (one sample collected predose on any of these days), and Days 7 to 10 (one sample collected predose on any of these days). Additional blood PK samples will be collected when clinically indicated.

Procedures for collecting, storing, and shipping plasma samples for PK are described in the study PK Manual. The sparse samples collected in this study will be analyzed using Population PK (Pop PK) analysis methods to estimate PK parameters (C_{max}, AUC, clearance/fraction absorbed [CL/F]) as applicable. Further analysis of possible metabolites may be performed.

Safety Evaluations: Safety will be evaluated throughout the study, including the following parameters: AEs, treatment discontinuations, general physical examination, vital signs, safety laboratory tests and concomitant medications. A final safety assessment will be conducted at the 35-Day FU visit (35 days after EOT) for VVC subjects and at the 6-Week FU (6 weeks after the EOT) for all other subjects.

Statistical Analyses:

All statistical analyses will be performed using SAS® version 9.3 or later. Descriptive statistics (i.e., number of subjects, mean, standard deviation, median, minimum, maximum) will be presented for all continuous variables; number and percentage of subjects will be presented for categorical variables. For parameters measured over time, observed data and changes from Baseline will be described for each time point.

Outcome analyses will include results by fungal disease, disease category, enrollment reason, and when relevant and sufficient number of cases allow, by pathogen and other clinical or microbiological characteristics such as MIC, FKS mutations, etc. Overall response will also be presented for all disease categories combined. Unless otherwise stated, data will be analyzed as is with no imputation. Details of the statistical analysis will be provided in a statistical analysis plan, which will be approved prior to final database lock.

Sample Size Determination: This is an exploratory study and no formal sample size calculations will be performed. A total of 220 subjects are estimated to be adequate for an assessment of the safety and tolerability of ibrexafungerp in subjects with documented eligible fungal diseases that have been refractory to, resistant to, have relapsed after SOC or subjects have intolerance to or demonstrated toxicities resulting from an approved SOC antifungal treatment.

Analysis Populations

The study populations to be used in the analyses are defined as follows:

- **Intent-to-Treat Population**: The intent-to-treat (ITT) population will include all subjects who are enrolled in the study and receive at least 1 dose of study drug.
- **Myco-ITT:** The Myco-ITT population will include all ITT subjects with confirmed pathogens and who also had all necessary cultures or mycology tests to estimate mycological response.
- **Per-Protocol Population:** The per-protocol (PP) population will include all ITT subjects who received enough drug to enable clinical efficacy judgment as determined by DRC, who have an EOT (TOC for VVC, CMC, CPA and ABPA) assessment and who have no major protocol violations.
- **Safety Population:** The safety population will include all subjects who receive at least one dose of study medication and have at least one safety assessment post Baseline.
- **Pharmacokinetic 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.

Efficacy Analysis

The primary efficacy endpoint is the percentage of subjects with Global Response (clinical, radiological and mycological) as determined by the DRC at TOC for VVC (Day 17), CMC (EOT or Day 84), CPA (EOT or Day 90) and ABPA (EOT or Day 90) (whichever comes first), and at EOT for all other diseases. Results will be presented separately for each disease category along with a 95% confidence interval (CI) for a single binomial proportion in the ITT, Myco-ITT and PP populations where sufficient cases are available. In addition, the number of subjects with a successful response across all disease categories will be summarized as a response rate and 95% CI. Secondary endpoints will be presented with 95% Cis for the ITT, Myco-ITT and PP populations using the same approach as for the primary endpoint. The estimated response rates and 95% CIs outlined will also be assessed relative to the external data described in the Study Design section above.

The percentage of subjects surviving at the defined time points will be presented for the ITT, Myco-ITT and PP populations. A Kaplan Meier plot will also be produced summarizing the survival curve over time and the median time to death. A subject without a reported death will be censored at the point of last time the subject was known to be alive.

For primary and overall secondary endpoints, presentations by pathogen will be conducted, if numbers allow. Data for all subjects will be presented by fungal disease, disease category, reason for enrollment and receipt of combination therapy (Yes/No).

If data are missing and the subject has not been deemed a success or failure the outcome will be categorized as unknown / not evaluable.

Data Review Committee: A DRC Charter will provide detailed criteria to be used for the baseline and outcome analysis of subjects in this study. The analysis criteria will be based on the definitions captured in Table 16 using EORTC-MSG Consensus Criteria as reference for all diseases except ABPA, CPA, CMC and VVC. Adaptations to the EORTC-MSG criteria adopted by the DRC will be documented in the DRC Charter.

Pharmacokinetics:

The concentration versus time data from the sparse PK samples collected in this study will be analyzed using a Pop PK model to estimate Cmax, AUC and CL/F, as applicable. The PK analysis will be conducted on the PK Population. Further analysis of possible metabolites may be performed.

Safety Analysis

All safety analyses will be conducted in the safety population; all safety variables will be listed.

Incidence and severity of treatment-emergent AEs, AEs leading to discontinuation and SAEs and their relationship to treatment will be summarized. Also data on AEs leading to death, AEs of special interest, AEs leading to withdrawal and AEs by severity will be summarized.

Early discontinuation of study drug treatment will be presented and will include the reasons for and timing of such discontinuations. Abnormal physical examinations associated with adverse events will be listed. Concomitant medications will be summarized.

Laboratory evaluations will be summarized as observed values and changes from Baseline; shifts with respect to the laboratory reference range will be summarized. Vital signs will be summarized as observed values and changes from Baseline.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class and preferred term. Concomitant medications will be classified based on the World Health Organization´s (WHO) Drug Dictionary terminology.

6.0 Schematic of Study Design

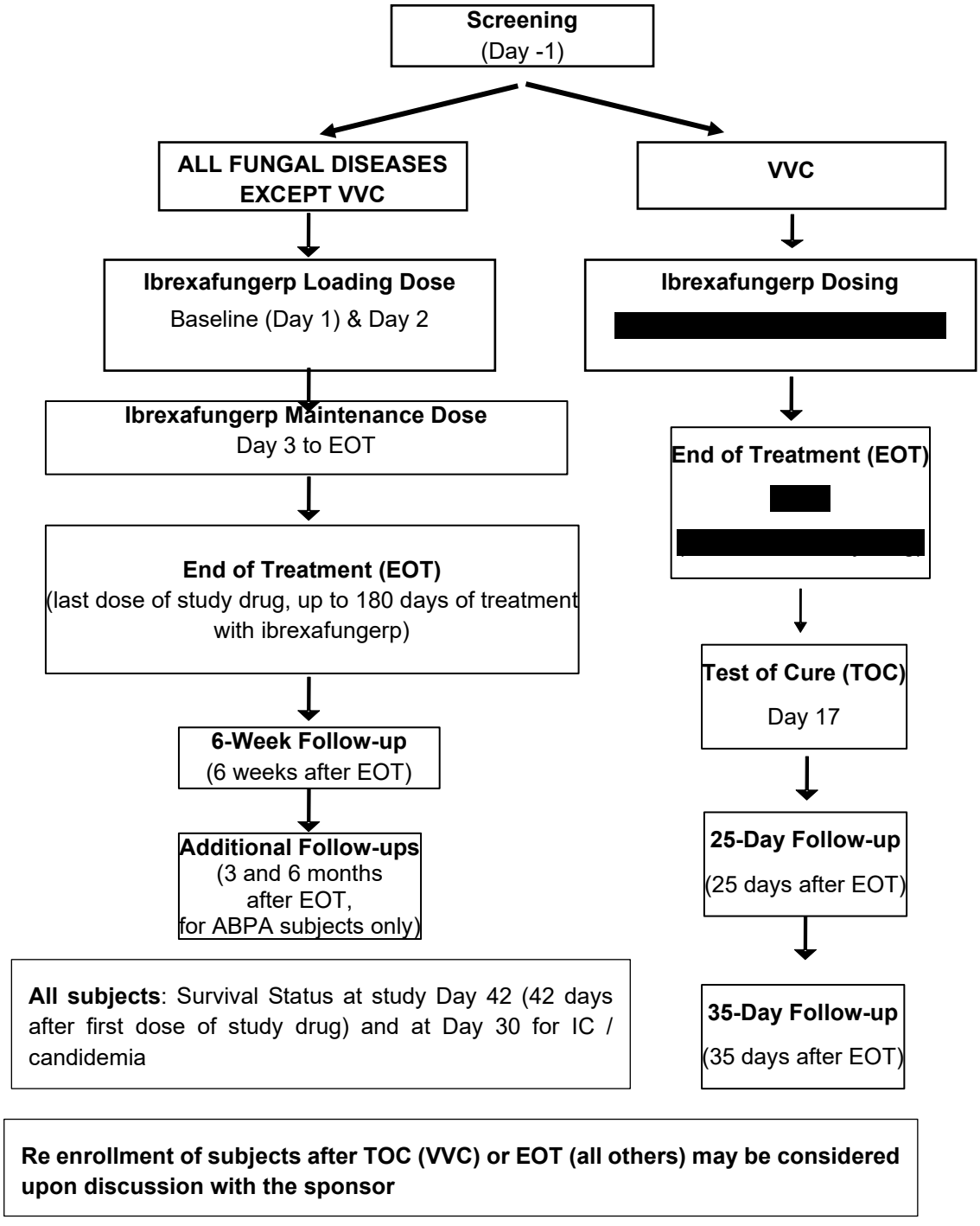

Figure 1 Schematic of Study Design

7.0 Background Information and Scientific Rationale

7.1 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.

Fungal diseases caused by *Candida* spp., *Aspergillus* spp., *Pneumocystis*, dimorphic fungi, etc., have limited treatment options and represent a growing threat, particularly to patients with compromised immune systems, including patients receiving cancer chemotherapy, hematopoietic stem cell transplantation and solid organ transplantation, and patients with advanced human immunodeficiency virus (HIV)-infection. Invasive fungal diseases caused by *Candida* and *Aspergillus* species are of principal concern. Despite advances in medical care, the overall mortality rate of invasive fungal infections remains high, particularly in the most profoundly immunocompromised patient populations[1,2,13].

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 clinical utility. The emergence of resistance (clinical and mycological) to azoles and more recently to echinocandins[3,4], and the toxicity associated with polyenes, signals the need for new agents that are well tolerated and that retain activity against resistant strains.

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 *in vitro* and *in vivo* activity against *Candida*, *Aspergillus* and other fungal genera. Ibrexafungerp offers an oral non-azole treatment alternative for these infections.

This includes e.g. patients with Candida infections who are failing therapy clinically or for whom azole therapy is not advisable due to infection with an isolate with a high likelihood of azole non-susceptibility (e.g. *C. glabrata, C. krusei, C. auris*), or other *Candida spp*. isolates with documented non-susceptibility to azoles based on MIC determination[6].

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 250 *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 a clinical alert by the CDC due to the global emergence of this fungal disease with limited therapeutic options and high mortality. In a recent study, Ibrexafungerp demonstrated potent *in vitro* activity against >100 different *C. auris* isolates and results showed potent activity

of ibrexafungerp against all strains at concentrations indicative of potential clinically-relevant effect.[5]

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*.

Activity against *Aspergillus* spp.

The spectrum and potency of activity of ibrexafungerp has been evaluated by several independent laboratories against a panel of clinically relevant *Aspergillus* isolates using CLSI and EUCAST methods. The studies included 41 *A. fumigatus*, 48 *A. flavus*, 21 *A. niger*, and 27 *A. terreus* wild-type isolates as well as 16 azole-resistant isolates: 14 *A. fumigatus*, and one each *A. niger*, and *A. terreus.* In these studies, microbiological outcome is reported as MEC (minimum effective concentration). Overall, ibrexafungerp was active against all the *Aspergillus* strains evaluated with MEC values similar to those obtained for caspofungin. Furthermore, there were no significant differences in the ibrexafungerp MEC values obtained between the wild-type and azole-resistant strains. Details are provided in Table 1.

Table 1 *In Vitro* Activity of Ibrexafungerp and Caspofungin Against *Aspergillus* spp.

***Aspergillus* spp**	**N**	**Microbiologic Outcome[a]**	**Ibrexafungerp**	**Caspofungin**
A. fumigatus				
WT	41	MEC Range	0.008 – 0.5	0.015 – 0.125
Azole-R	14		0.03 – 0.5	0.015 – 0.125
A. flavus				
WT	48	MEC Range	0.015 - 8	0.015 – 0.125
Azole-R	NT			
As. terreus				
WT	27	MEC Range	0.008 – 0.125	0.015 – 0.125
Azole-R	1		0.125	0.03
A. niger				
WT	29	MEC Range	0.008 – 0.125	0.015-0.06
Azole-R	1		0.06	0.06

Abbreviations: Azole-R = azole-resistant; MEC = minimum effective concentration;
NT = none tested; WT = wild type
a: Values in µg/mL

The potent *in vitro* activity of ibrexafungerp against *Aspergillus* species was confirmed in a recent study that included >500 clinical isolates. MEC_{50} and MEC_{90} values for the 311 isolates tested were <0.063 and 0.125 µg/mL, respectively.

Ibrexafungerp was evaluated for *in vitro* activity against 172 *Aspergillus* strains, including cryptic species and some with Cyp51 A mutants. MIC and MEC values were determined following EUCAST 9.2 and CLSI M38A methodologies. All strains were obtained from clinical samples (respiratory, cutaneous, biopsies, exudates, abscesses and wounds) between 2000 and 2017, and

included WT and Cyp51A mutants. Ibrexafungerp showed good activity with low MEC_{90} for almost all the species tested, both for EUCAST and CLSI. Ibrexafungerp displayed similar activity against WT and azole-R strains of *A. fumigatus*. Isolates of *Aspergillus alliaceus* were the only ones showing reduced susceptibility to ibrexafungerp, with MEC_{90} >16 μg/L (EUCAST) and 16 μg/L (CLSI). Overall, there was good agreement between results obtained using EUCAST and CLSI methodologies.

The *in vitro* activity of ibrexafungerp was evaluated alone and in combination with amphotericin B, isavuconazole, or voriconazole against a panel of clinical *A. fumigatus* isolates, which included four wild-type *A. fumigatus* strains and 2 strains with elevated amphotericin B and azole MICs (one of which has a CYP51 mutation at F46Y). The combination of ibrexafungerp with all three antifungals demonstrated synergy in most wild-type strains tested, and although ibrexafungerp retained activity against azole resistant isolates, it showed no synergistic effect against these strains. One exception was the combination of ibrexafungerp and amphotericin B, which was synergistic against the CYP51 mutant resistant strain.

Activity against Dimorphic Fungi

Ibrexafungerp was evaluated for *in vitro* activity against isolates of *Coccidioides* spp., *Blastomyces* spp. and *Histoplasma* spp. Ibrexafungerp was evaluated against 15 clinical isolates each of *Blastomyces dermatitidis* and *Histoplasma capsulatum,* and against 5 clinical isolates of *Coccidioides immitis.* The results of this evaluation revealed that the respective MICs for these dimorphic fungi ranged from <0.125 to 0.25 ug/ml.

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. Murine models of ibrexafungerp in disseminated candidiasis caused by *C. glabrata*, *C. auris,* and *C. tropicalis* indicated activity across multiple *Candida* species. 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.

In murine models of disseminated *A. fumigatus* infection, treatment with ibrexafungerp resulted in improved survival, similar to that achieved with voriconazole treatment groups.

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.

The efficacy of ibrexafungerp in combination with isavuconazole in the treatment of experimental invasive pulmonary aspergillosis in persistently neutropenic rabbits was evaluated and established the foundation for further clinical evaluation. A neutropenic New Zealand White rabbit model of

experimental invasive pulmonary aspergillosis was used. Treatment groups included rabbits receiving ibrexafungerp (formerly known as SCY-078, thus abbreviated here as "SCY") at 2,5 mg/kg/day IV (SCY2.5) and 7.5 mg/kg/day IV (SCY7.5), isavuconazole at 40 mg/kg/day orally (ISA40), the combination of SCY2.5 + ISA40, the combination of SCY7.5 + ISA40, or untreated control rabbits. Treatment started 24 hours after endotracheal administration of an *A. fumigatus* inoculum and continued QD for up to 12 days. Blood samples for galactomannan index (GMI) antigenemia and serum (1→3)-β-D-glucan (BDG) levels were obtained every other day. Rabbits treated with SCY2.5+ISA40 and SCY7.5+ISA40 had prolonged survival in comparison to those of SCY2.5-treated, SCY7.5-treated, ISA40-treated or untreated control rabbits ($p<0.05$). In addition, groups of SCY2.5+ISA40 and SCY7.5+ISA40 demonstrated lower pulmonary infarct scores in comparison to those of single therapy ISA40. These outcome variable data correlated directly with a significant decline of GMI antigenemia and serum BDG levels during therapy in comparison to progressive GMI and BDG levels of untreated control rabbits. These preclinical data indicate a synergistic response resulting from the co-administration of ibrexafungerp with an azole antifungal.

Nonclinical experience

The toxicity and toxicokinetic profile of ibrexafungerp following a once daily (QD) oral (gavage) administration to Sprague-Dawley rats for 26 weeks or to Beagle dogs for 39 weeks was assessed. Additionally, the reversibility of any changes following a 12-week period post dosing cessation was evaluated in both species. For each study, clinical assessments consisted of mortality, clinical observations, body weight, food consumption and ophthalmology. Electrocardiograms were also conducted in dogs. Blood and urine samples were collected for clinical pathology and blood plasma was analyzed for toxicokinetics. Following the end of the 26- or 39-week dosing period and the 12-week recovery periods, animals were euthanized and organ weights and macroscopic observations were recorded. Histopathological examination was performed on a comprehensive list of tissues from all animals.

In rats, no new toxicities or target organs of toxicity were identified (compared to experience in shorter terms studies), and the no-observed-adverse-effect-level (NOAEL) was established, which corresponded to mean maximum concentration (C_{max}) and AUC up to the last measurable concentration (AUC_{last}) values on Day 182 of 3290 ng/mL and 73,700 hr•ng/mL in males, and 4060 ng/mL and 87,300 hr•ng/mL in females, respectively. Likewise, in dogs, no new toxicities or target organs of toxicity were identified (compared to experience in shorter terms studies) and the NOAEL was established, which corresponded to mean C_{max} and AUC_{last} values on Day 273 of 1600 ng/mL and 26,700 hr•ng/mL in males, and 2390 ng/mL and 46,100 hr•ng/mL in females, respectively.

Therefore, as no new toxicities were identified following daily oral dose administration to rats and dogs for up to 6 and 9 months, respectively, per ICH M3(R2) dose administration duration in the clinical setting for greater than 6 months is supported.

The *in vitro* studies indicated that ibrexafungerp metabolism was predominantly oxidative, with cytochrome P450 (CYP) 3A being the primary enzyme involved in its oxidative metabolism. Strong inhibitors of CYP3A would be expected to increase plasma levels of ibrexafungerp and its concurrent administration should be avoided.

Clinical experience

To date, the oral formulations of ibrexafungerp have been evaluated in over 1,500 subjects and patients included in multiple Phase 1 and two Phase 2 studies.

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.

Two Phase 2 studies of oral ibrexafungerp in patients with vulvovaginal candidiasis (VVC) have been completed. Both were multicenter, randomized, active-controlled, evaluator or double-blind studies of oral ibrexafungerp in adult female patients with VVC. The results from both studies were consistent with oral ibrexafungerp achieving high clinical cure and mycological eradication rates. Specifically, in the Phase 2b study DOVE (204) in subjects with acute VVC, a [redacted] of ibrexafungerp resulted in a clinical cure rate of 52% at day 10 (TOC) and 70% at Day 25 with mycological eradication achieved by 63% of subjects by day 10. In these studies, ibrexafungerp was well tolerated with the most common AEs being mild gastrointestinal events. The high clinical cure rates observed are supportive of the clinically relevant antifungal activity of ibrexafungerp in this form of *Candida* infection.

According to the Infectious disease society of America (IDSA) treatment guidelines,[6] patients with severe acute *Candida* vulvovaginitis, fluconazole, 150 mg, given every 72 hours for a total of 2 or

3 doses, is recommended. Based on the anticipation that the VVC patients that would need treatment in this study would have severe disease, [redacted] is recommended in this protocol for acute VVC.

A preliminary efficacy review of the 20 subjects who completed therapy under this study, SCY-078-301, was conducted by an external expert panel (Data Review Committee, DRC). These 20 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, with a mean duration of ~37 days. Per DRC evaluation at end of treatment, 11 patients achieved a Complete or Partial Global Response and six patients a stable-disease response. Only two patients showed progression of disease and one patient's outcome was considered indeterminate.

Several drug-drug interaction studies have been conducted. Ketoconazole (a strong inhibitor of CYP3A) induces a significant (5-fold) increase in ibrexafungerp exposure while diltiazem (a moderate inhibitor of CYP3A) induces a mild to moderate (<3 fold) increase in ibrexafungerp exposure. Ibrexafungerp did not have any effect on rosiglitazone (a CYP2C8 substrate) exposure, had only a mild effect (less than a 0.5-fold increase) on the AUC of tacrolimus (a CYP3A and P-gp substrate) and had no effect on the C_{max} of tacrolimus.

Based on the cumulative *in vivo* animal efficacy data and animal and human safety data, the target plasma exposure for clinical efficacy and safety in invasive candidiasis is 15.4 µM•hr (11.2 µg•hr/mL). 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 efficacy and safety 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_{0-24} ≥11.2 µg•hr/mL in the majority of subjects. 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_{0-24} 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_{0-24} 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 [redacted] This alternative dosing regimen results in the same exposure (AUC) and C_{avg} with a minor reduction in Cmax, in comparison to the primary dosing regimen described above.

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.

7.2 Rationale for the Study

This study is being conducted to evaluate the efficacy, safety and PK of ibrexafungerp in male and female subjects ≥18 years of age with documented severe fungal diseases for whom SOC antifungal treatment is not appropriate due to refractoriness, resistance, intolerance, relapse, toxicities, need for oral therapy or other reasons.

Eligible subjects must be selected based on study criteria and be approved for selection by the Sponsor or Sponsor designee.

Subjects must have a documented eligible fungal disease that has been refractory to, has relapsed after, or the subject has intolerance to or demonstrated toxicities resulting from an approved SOC antifungal treatment, or has an isolate resistant to, or that has a high MIC and is unlikely to respond to SOC antifungal treatment. Subjects are also eligible if, in the judgement of the Investigator, continued IV antifungal therapy is not feasible or desirable due to clinical or logistical circumstances or if other oral antifungal alternatives are not appropriate. Refractoriness, defined as persistent clinical, radiological or mycological evidence of fungal disease, and intolerance, including presence of, history of or anticipated toxicities (e.g. drug-to-drug interactions) associated with administration of SOC antifungal agents, will be determined by the Investigator.

The primary efficacy endpoint of the study is Global Response (composite assessment of clinical, radiological and mycological responses) as determined by a Data Review Committee (DRC). The primary endpoint will be determined at the TOC visit for VVC, CMC, CPA and ABPA and at the EOT visit for all other fungal diseases.[7,8] Clinical response will be evaluated by the signs and symptoms of the infection and/or imaging scans, if applicable. Mycological response will be assessed by mycological testing (fungal culture, KOH and other fungal stains, T2 testing) and/or serological testing (including GMI, *Coccidioides* titers, and β-D-glucan levels, among others),[9] if applicable. Recurrence will be assessed at the 25-Day FU visit (25 days after EOT) for subjects with VVC and at the 6-Week FU visit (42 days after EOT) for all other subjects as a secondary efficacy endpoint. Recurrence is defined as Global Response at EOT (TOC for VVC) but re-emergence of the baseline fungal disease (with the same fungal species and involving the same site) during the post treatment follow-up.

8.0 Study Objectives

8.1 Primary Objectives

The primary objectives listed below apply to all eligible fungal diseases:

- To evaluate the efficacy of ibrexafungerp in the treatment of severe fungal diseases by a Data Review Committee (DRC) at the primary time point for the fungal disease
- To evaluate the safety of ibrexafungerp

8.2 Secondary Objectives

8.2.1 Overall Secondary Objectives

The overall secondary objectives listed below apply to all eligible fungal diseases:

- To evaluate the efficacy of ibrexafungerp as determined by the DRC at other time points
- To evaluate the efficacy of ibrexafungerp as determined by the Investigator
- To determine the efficacy of ibrexafungerp by pathogen
- To determine the efficacy of ibrexafungerp by fungal disease and disease category
- To evaluate the efficacy of ibrexafungerp by recurrence of the baseline fungal disease
- To evaluate the efficacy of ibrexafungerp by reason for enrollment (refractory, resistance, relapse, intolerance, toxicity, need for oral therapy)
- To determine All-Cause Mortality (ACM)
- To evaluate the pharmacokinetics (PK) of ibrexafungerp by population PK analysis

8.2.2 Disease-Specific Secondary Objectives

- To evaluate the efficacy of ibrexafungerp as determined by other disease-specific endpoints (Table 2)

9.0 Study Endpoints

9.1 Primary Endpoints

The primary endpoints listed below apply to all eligible fungal diseases:

- Efficacy as measured by the percentage of subjects with Global Response at TOC for VVC (Day 17), CMC (EOT or Day 84), CPA (EOT or Day 90) and ABPA (EOT or Day 90) (whichever comes first) and at
  EOT for all other diseases as determined by a DRC
- Safety as measured by: physical examination, vital signs, AEs, and laboratory tests

9.2 Secondary Endpoints

9.2.1 Overall Secondary Endpoints

The overall secondary endpoints listed below apply to all eligible fungal diseases:

- The percentage of subjects who achieve Global Response at additional time points as applicable for each disease, disease category and reason for enrollment (Table 16), as determined by the DRC and by the Investigator
- The percentage of subjects who achieve Clinical Response by pathogen at time points applicable for each disease, disease category and reason for enrollment (Table 16), as determined by the DRC and the Investigator
- The percentage of subjects who achieve Mycological Response by pathogen at time points applicable for each disease, disease category and reason for enrollment (Table 16), as determined by the DRC and the Investigator
- The percentage of subjects who achieve Clinical Response by fungal disease, disease category and reason for enrollment at time points applicable for each disease (Table 16), as determined by the DRC and the Investigator
- The percentage of subjects who achieve Mycological Response by fungal disease, disease category and reason for enrollment at time points applicable for each disease (Table 16), as determined by the DRC and the Investigator
- The percentage of subjects with a recurrence of the baseline fungal disease at the 25-Day FU for VVC and at the 6-Week FU for all other diseases as determined by the DRC
- ACM at Day 30 (Invasive candidiasis and candidemia) and Day 42 for all diseases
- Time to death from any cause
- Describe ibrexafungerp plasma concentrations

9.2.2 Disease-Specific Secondary Endpoints

Disease-specific secondary endpoints, as assessed by the DRC (Table 2)

Table 2 Disease -Specific Secondary Endpoints

Disease-Specific Secondary Endpoints
Acute Invasive candidiasis / Candidemia • Completion of study drug antifungal treatment (i.e. no recurrence, no use of other antifungal treatment, no discontinuation for any reason) **Acute or Chronic Severe Mucocutaneous Candidiasis** • Percentage subjects with mycological cure at Day 84 • Percentage subjects with clinical response by Day 30 and Day 84 • Percentage of subjects with continued symptom relief at 6-week FU **Chronic Pulmonary Aspergillosis (CPA) disease-specific endpoints** o Six-Minute Walk Test and MRC Dyspnea Score at Day 90 and Day 180 o Weight change at Day 90 and Day 180 o Improvement in inflammatory markers (CRP, plasma viscosity, albumin, platelet count, disease-specific immunoglobulin levels) at Day 90 and Day 180 o Change in total IgG and *Aspergillus* IgG at Day 90 and Day 180, if elevated at Baseline o All-cause mortality at Day 90, Day 120 and Day 180 o Recurrence at Day 180 **Allergic Bronchopulmonary Aspergillosis (ABPA) disease-specific endpoints**: o Percentage of subjects who exhibit a Global Response at Day 42 o Percentage of subjects with Clinical Improvement (as measured on a 4-point scale) at TOC, Day 90, Day 180, then every 3 months while on therapy, and 6-Month FU o Percent decline in total IgE (baseline IgE minus time point IgE/baseline IgE) at Day 42 and Day 90 o Number of subjects who experience an ABPA exacerbation at the 3-Month and 6-Month FUs o Time to first ABPA exacerbation o Change in lung function (FEV1 and FVC) at Day 42 o Number of Asthma exacerbations and ABPA exacerbations at the 3-Month and 6-Month FUs o All-cause mortality at Day 90, Day 120 and Day 180 **Invasive Pulmonary Aspergillosis (IPA) disease-specific endpoint** o The percentage of subjects who attain a GMI decrease including absolute and percent reduction from Baseline to Weeks 1, 2, 4 and 6, when feasible o Time to achieve a clinically meaningful GMI absolute and percent decrease o All-cause mortality at Day 84

Disseminated/invasive dimorphic fungal disease-specific endpoint

- All-cause mortality at Day 84

Other emerging fungi including yeasts and molds disease-specific endpoint

- All-cause mortality at Day 84

Abbreviations: CRP=c-reactive protein; FEV1 = forced expiratory volume during the first second; FVC = forced vital capacity; FU = Follow-up; GMI=galactomannan index; IgE=immunoglobulin E; MRC=Medical Research Council; TOC=test of cure

10.0 Study Design

10.1 Overall Description of the Study

This is a multicenter, open-label, non-comparator, single-arm study to evaluate the efficacy, safety and PK of ibrexafungerp in male and female subjects ≥18 years of age with documented severe fungal diseases for whom SOC antifungal treatment is not appropriate due to refractoriness, resistance, intolerance, relapse, toxicities, need for oral therapy or other reasons.

Subjects must have a documented eligible fungal disease that has been refractory to, has relapsed after, or subject has intolerance to or demonstrated toxicities resulting from an approved SOC antifungal treatment as listed in Table 5 (Eligible Fungal Diseases), or has an isolate resistant to, or that has a high MIC and is unlikely to respond to antifungal SOC. Subjects are also eligible if, in the judgement of the Investigator, continued IV antifungal therapy is not feasible or desirable due to clinical or logistical circumstances or if other oral antifungal alternatives are not appropriate. Subjects should meet these and other study criteria to be considered for enrollment. Inclusion of each subject in the study must be approved by the Sponsor (or Sponsor designee) prior to initiation of study drug.

The study will be conducted at approximately 40 sites globally and is planned to enroll and treat approximately 220 (+10%) subjects.

Study Schedule

For all subjects except VVC subjects, there will be a Screening visit, a Baseline visit (also considered Day 1), several scheduled visits depending on the subject's fungal disease, an EOT visit and a follow-up visit 6 weeks after EOT. For ABPA subjects there will be additional follow-up visits 3 months and 6 months after EOT. . For CMC, CPA and ABPA subjects there will be a TOC visit on EOT or Day 84 for CMC subjects or Day 90 for CAP and ABPA subjects, whichever comes first. Following Screening, eligible subjects will receive the study drug loading dose on Days 1 and 2 and the study drug maintenance dose from Day 3 up to EOT. A summary of the overall treatment and follow-up schedule for these subjects is provided in Table 3.

Table 3 Summary of Overall Treatment and Follow-Up Schedule for All Subjects Except VVC Subjects

Pre-study Activities	Ibrexafungerp Loading Dose	Ibrexafungerp Maintenance Dose	TOC	EOT	6-Week Follow-Up	Additional Follow-Ups
Screening[a] (Days -1 [-3])	Day 1[a] (Baseline) & Day 2	Day 3 to EOT	EOT or Day 84 (CMC) EOT or Day 90 (CPA and ABPA) whichever comes first	Last dose of study drug (up to 180 days from Day 1)	6 weeks (±7 days) after EOT	3 and 6 months after EOT for ABPA subjects only

Abbreviations: ABPA = allergic bronchopulmonary aspergillosis; CMC = chronic mucocutaneous candidiasis; CPA = chronic pulmonary aspergillosis; EOT = end of treatment; TOC = test of cure
a: Screening and Baseline (Day 1) may occur on the same day.

Subjects with VVC will have a Screening visit, a Baseline/Day 1 visit, and scheduled visits on [redacted] 25-day FU (Day 32) and 35-day FU (Day 42). VVC subjects will receive treatment [redacted]
The EOT and 35-Day FU visits may be a phone contact for asymptomatic subjects. A summary of the overall treatment and follow-up schedule for VVC subjects is provided in Table 4.

Table 4 Summary of Overall Treatment and Follow-Up Schedule for VVC Subjects

Pre-study Activities	Ibrexafungerp Dosing	EOT (Phone/on site)	TOC	25-Day FU	35-Day FU (Phone/on site)
Screening[a] (Day -1)	[redacted]	[redacted]	Day 17 (±3)	Day 32 (25 days after EOT; 32 days after first dose)	Day 42 (35 days after EOT; 42 days after first dose)

Abbreviations: EOT = end of treatment; FU = follow up; TOC = test of cure; VVC = vulvovaginal candidiasis
a: Screening and Baseline (Day 1) may occur on the same day.

Study Treatments

Eligible subjects (excluding VVC subjects) will receive ibrexafungerp monotherapy given as an initial loading dose of 750 mg BID during the first two days of treatment (Day 1 and Day 2) and then subsequent oral doses of 750 mg QD for up to 180 days depending on fungal disease. Ibrexafungerp given as combination therapy will be required for all subjects with refractory or relapsing IPA, mucormycosis and other molds with unpredictable ibrexafungerp activity based on Investigator's judgement and contingent on Sponsor approval. The treatment duration may be extended beyond 180 days, if needed, for certain fungal diseases. Sponsor approval must be obtained for any extension of treatment beyond 180 days. For subjects receiving extended treatment, a 4-week visit schedule may be followed. Subjects who have a recurrence after EOT may also be considered for re enrollment upon discussion with the sponsor. Subjects who are re

enrolled will follow the protocol defined visit schedule.

Subjects with VVC will receive oral doses of [redacted] Subjects treated for VVC who have a recurrence after TOC may receive additional cycles of ibrexafungerp treatment, similar to the initial regimen, upon discussion with the sponsor.

Study Assessments

Efficacy, PK and safety will be evaluated in this study.

Efficacy evaluations will consist of clinical evaluations of the signs and symptoms of infection, mycological testing (including, but not limited to, fungal culture, KOH and other fungal stains, and T2 testing), imaging (e.g., CT, MRI, X-Ray or ultrasound) and serological testing (including, among others, ß-D-glucan levels, GM and fungal antibody titers) as applicable for each fungal disease. Additional procedures (esophagoscopy, spirometry, St. George's Respiratory Questionnaire [SGRQ]6-Minute Walk Test and Medical Research Council [MRC] Dyspnea Scale) will be conducted for selected fungal diseases.

Efficacy will be assessed primarily in terms of Global Response at TOC for VVC (Day 17), CMC (EOT or day 84), CPA (EOT or Day 90) and ABPA (EOT or Day 90) (whichever comes first), and at EOT for all other fungal diseases, as determined by an independent DRC. Global Response will be a composite global outcome composed of clinical (including radiological, when applicable) and mycological (including serological) responses. In addition to the primary endpoint, Global Response, Clinical Response and Mycological Response will be assessed as secondary endpoints at the primary time point for the determination of efficacy (TOC) for VVC, CMC, CPA and ABPA, and EOT for all other eligible fungal diseases) and at additional time points by the independent DRC and the Investigator. Efficacy outcome definitions and time points for each fungal disease are listed in Table 16 and will be defined in the DRC Charter.

Other secondary efficacy assessments will include recurrence and survival. Recurrence will be evaluated at the 6-Week FU visit after EOT for all subjects, except VVC subjects, who will be assessed for recurrence at the 25-Day FU visit. Survival will be determined primarily on Day 30 for IC/Candidemia and on Day 42 for all subjects. Additional disease-specific efficacy endpoints will be evaluated for selected fungal diseases at additional time points (Table 2).

PK: The PK data obtained from this study will be part of the Population PK analyses that will be performed. For subjects who are willing to participate in the PK sampling, blood samples will be collected on Day 2 (one sample collected anytime post dosing), Days 3 to 5 (one sample collected predose on any of these days) and Days 7 to 10 (one sample collected predose on any of these days). Additional blood PK samples will be collected when clinically indicated.

Subjects will be evaluated for safety throughout the study, including parameters such as physical exam, vital signs, AEs and concomitant medications, and safety laboratory tests (hematology,

blood chemistry and urinalysis). A final safety assessment will be conducted at the 35-Day FU visit (35 days after EOT) for VVC subjects and at the 6-Week FU (6 weeks after the EOT) for all other subjects.

Results from the study will be analyzed against historical and concurrent SOC-treated subjects, who will be selected from literature reviews and other data resources.

10.2 Blinding, Randomization and Stratification

This is an open-label study.

10.3 Study Duration

Each subject is expected to complete the study, including all follow-up survival visits, within approximately 222 days from Baseline/Day 1.

10.4 Number of Centers

Approximately 40 study centers will participate in the study worldwide.

11.0 Study Population

The study population will include male and female adult subjects ≥18 years of age with documented eligible severe fungal diseases for whom SOC antifungal treatment is not appropriate due to refractoriness, resistance, intolerance, relapse, toxicities, need for oral treatment, or other reasons.

11.1 Inclusion Criteria

Subjects must fulfill all of the following criteria at Screening and/or Baseline to be eligible for study admission:

1. Subject is a male or female adult ≥18 years of age on the day the study informed consent form (ICF) is signed.
2. Subject has a documented eligible fungal disease that has been refractory or resistant to SOC, has relapsed after, or the subject has intolerance to or demonstrated toxicities resulting from an approved SOC antifungal treatment (as defined in Table 5). The subject is also eligible if, in the judgement of the Investigator, long-term IV antifungal therapy is not feasible or desirable due to clinical (isolate is resistant to or has a high MIC and is unlikely to respond to antifungal SOC) or logistical circumstances or if other antifungal alternatives are not appropriate.

Table 5 Eligible Fungal Diseases

	Eligibility Criteria	
Fungal Disease	**Diagnostic Criteria**	**Refractoriness/Resistance/Intolerance[a]/Toxicity[b]/Relapse[c] Criteria**
Acute or **chronic invasive candidiasis, including candidemia**	• Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site showing yeast cells—for example, *Candida* species showing pseudohyphae or true hyphae OR • Recovery of a *Candida* spp. by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 h ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process OR • Blood culture positive for *Candida* spp. OR • Alternative approved diagnostic method such as T2 testing or ß-D-glucan levels (two consecutive positive test results), and at least one of the following: temperature ≥38°C or <36°C, systolic blood pressure <90 mmHg or a decrease of >30 mmHg from normal baseline, local signs or symptoms or radiologic findings of invasive candidiasis	For **acute invasive candidiasis, including candidemia** refractoriness is defined as meeting one or more of the following criteria: • Persistence of mycological evidence of *Candida* infection after >3 days of SOC antifungal therapy. Acceptable mycological evidence for this study includes: o Persistently positive culture from a normally sterile site o Persistently positive T2 test o ß-D-glucan with elevated values equal to or increasing from Baseline (i.e., before start of SOC antifungal therapy) • Antifungal susceptibility results indicating that the *Candida* isolate is not susceptible to the SOC antifungal therapy being administered, indicating a high risk of therapeutic failure • Antifungal susceptibility results or local epidemiology indicating high risk of antifungal resistance with increased risk of therapeutic failure to SOC (e.g., *Candida auris*) For **chronic disseminated candidiasis** refractoriness is defined as any of the following: • Persistent clinical manifestations such as debilitating fever after 12 weeks of initiating SOC antifungal treatment • Lack of changes in radiological imaging lesions >12 weeks after starting SOC antifungal treatment

	Eligibility Criteria	
Fungal Disease	**Diagnostic Criteria**	**Refractoriness/Resistance/Intolerance[a]/Toxicity[b]/Relapse[c] Criteria**
Acute or **chronic severe mucocutaneous candidiasis**, including: • **Esophageal candidiasis (EC)** • **Oropharyngeal candidiasis (OPC)** • **Chronic mucocutaneous candidiasis (CMC)** • **Vulvovaginal candidiasis (VVC)**	• **EC:** Clinical manifestations and endoscopic findings consistent with EC plus potassium hydroxide (KOH) or fungal stain from biopsy or brushing indicating yeast infection. • **OPC, CMC**: Evidence of clinical manifestations and mycological documentation (positive fungal stain from biopsy or positive *Candida* spp. culture obtained from the affected site). • **VVC**: Evidence of clinical manifestations with total composite signs and symptoms score of 4 or more in the vulvovaginal signs and symptoms (VSS) Scale (Section 21.4 [Appendix D]) and a positive *Candida* spp. culture obtained from a vaginal sample.	For **EC** and **OPC**, refractoriness is defined as meeting the following criteria: • Lack of clinical improvement or worsening of infection after receipt of SOC antifungal therapy for at least 7 consecutive days For **CMC**, refractoriness is defined as meeting the following criteria: • Lack of clinical improvement or worsening of the mucocutaneous manifestations of CMC after receipt of SOC antifungal therapy for at least 21 consecutive days For **VVC**, refractoriness is defined as meeting any of the following criteria: • Lack of clinical improvement or worsening of the infection after receipt of SOC antifungal therapy with documentation of persistence of *Candida* spp. in a vaginal sample obtained after completion of SOC antifungal therapy • Recurrent VVC caused by *Candida glabrata* • Recurrent VVC caused by any *Candida* species with a MIC for fluconazole ≥ 16 µg/mL

	Eligibility Criteria	
Fungal Disease	**Diagnostic Criteria**	**Refractoriness/Resistance/Intolerance[a]/Toxicity[b]/Relapse[c] Criteria**
Disseminated/invasive dimorphic fungi: • Coccidioidomycosis • Histoplasmosis • Blastomycosis	• Recovery in culture from a specimen obtained from the affected site, in a host with a temporally related illness consistent with a fungal infectious disease process OR • If a culture is negative or not obtained, histopathologic or direct microscopic demonstration of appropriate morphological forms for dimorphic fungi having truly distinctive appearance OR • Positive blood culture OR • Demonstration of fungal antibody in a two-dilution rise measured in two consecutive blood samples tested concurrently in the setting of a temporally related infectious disease process	For **disseminated/invasive dimorphic fungi**, refractoriness is defined as meeting any of the following criteria: • Relapse after therapy with a SOC antifungal agent (azole or amphotericin B) • Intolerance, anticipated intolerance including high risk for drug interactions, or current or past toxicity to administered antifungal • Failure of current therapy as judged by lack of decline in fungal serology titers or persistence of signs and symptoms after a minimum of 1 month of SOC antifungal therapy • Isolate with a MIC indicating a high probability of therapeutic failure for the intended antifungal agent (e.g., fluconazole MIC > 8 µg/mL)

	Eligibility Criteria	
Fungal Disease	**Diagnostic Criteria**	**Refractoriness/Resistance/Intolerance[a]/Toxicity[b]/Relapse[c] Criteria**
Chronic Pulmonary Aspergillosis (CPA)	**CPA** diagnosed according to the European Respiratory Society 2016 guideline, including: • Thoracic imaging (preferably by CT) consistent with CPA, such as: o Aspergilloma o Chronic cavitary pulmonary aspergillosis o Subacute invasive aspergillosis (1-3 months) AND • Direct evidence of *Aspergillus* infection or an immunological response to *Aspergillus* spp. o Percutaneous biopsy showing fungal hyphae on microscopy or growing *Aspergillus* spp. from a pulmonary lesion, OR o Respiratory samples showing hyphae consistent with *Aspergillus* and/or growing *Aspergillus* spp. and/or with a positive *Aspergillus* PCR AND o High *Aspergillus* IgG in a serum sample AND • Active mycobacterial infection ruled out • Disease present for at least 3 months • Disease requires antifungal treatment for CPA, in the opinion of the Investigator	For **CPA**, refractoriness is defined as meeting any of the following criteria: • Suboptimal clinical response (per the Investigator's judgment) of CPA signs and symptoms after receipt of SOC antifungal therapy for at least 6 weeks, including: o Significant hemoptysis o Weight loss o Persistent fatigue o Productive cough • Presence of new or worsened CPA signs and symptoms (expected to respond to antifungal treatment) while receiving SOC antifungal therapy for at least 6 weeks • Persistence of azole-resistant *Aspergillus* spp. positive sputum or BAL cultures after at least 3 months of SOC antifungal therapy • Radiologic evidence of lack of improvement, such as: o New cavities o Increased peri-cavity infiltrates o New fungal ball

	Eligibility Criteria	
Fungal Disease	**Diagnostic Criteria**	**Refractoriness/Resistance/Intolerance[a]/Toxicity[b]/Relapse[c] Criteria**
Allergic Bronchopulmonary Aspergillosis (ABPA)	• Presence of all of the following: (1) asthma; (2) immediate cutaneous hyperreactivity on *Aspergillus* skin test or serum *A. fumigatus*-specific IgE > 0.35 kUA/L; and (3) elevated serum total IgE > 1,000 IU/mL (2.4 mg/L). AND • Presence of two of the following features: (1) precipitating antibodies against *A. fumigatus* in serum; (2) fixed or transient radiographic pulmonary opacities; (3) peripheral blood eosinophil count > 1,000 cells/µL; (4) bronchiectasis on chest HRCT scan, (5) infection with azole-resistant but ibrexafungerp-susceptible *Aspergillus* spp.	Not responsive, intolerant or demonstrated toxicity to SOC glucocorticoids or azole therapy as judged by the Investigator
Invasive Pulmonary Aspergillosis (IPA)	**Mycological evidence:** • Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site showing hyphae forms accompanied by evidence of associated lung damage OR • Recovery of an *Aspergillus* spp. by culture of a sample obtained by a sterile procedure from a normally sterile site (excluding BAL) showing a clinical or radiological abnormality consistent with a pulmonary invasive aspergillosis OR • Alternative approved diagnostic method from serum or BAL, such as PCR or GMI test (for serum GMI: two consecutive positive test results; for BAL, one positive test)	For **IPA**, refractoriness is defined as meeting the following criteria: • Suboptimal response (per the Investigator's judgment) to an approved SOC antifungal treatment for IPA (i.e., voriconazole, isavuconazole, posaconazole, or amphotericin B at the doses recommended per their label), defined as radiological, serological or clinical signs of lack of response or increased fungal burden, such as any of the following: o Increased size or number of radiologic infiltrates not associated with resolution of neutropenia o Increased GMI levels o Lack of clinically meaningful reduction in serum GMI levels compared to a sample obtained prior to initiation of an acceptable antifungal therapy after at least 7 days of antifungal therapy Monotherapy with ibrexafungerp is not recommended for refractory or relapsing IPA. All subjects enrolled for refractory or relapsing IPA should receive combination antifungal therapy.

	Eligibility Criteria	
Fungal Disease	**Diagnostic Criteria**	**Refractoriness/Resistance/Intolerance[a]/Toxicity[b]/Relapse[c] Criteria**

	PLUS
	
	Clinical evidence
	
	• At least one of the following clinical signs or symptoms: temperature ≥38°C or <36°C, systolic blood pressure <90 mmHg or a decrease of >30 mmHg from normal baseline, local signs or symptoms
	AND
	• radiologic findings compatible with pulmonary invasive aspergillosis (Chest CT or MRI)
	
	PLUS
	
	Subject Risk Factors, such as:
	
	• Recent history of neutropenia, or
	• Allogeneic stem cell transplant recipient, or
	• Prolonged (>3 weeks) corticosteroid therapy, or
	• Recent treatment with other recognized T-cell immunosuppressant, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies or nucleoside analogues during the past 90 days
	• Other underlying condition known to have increased risk for invasive aspergillosis (e.g. influenza, pneumonia)
		The following combination options are allowed:
		
		• addition of ibrexafungerp to any ongoing antifungal
		• replacement of one (toxic/ineffective) element of a two antifungal combination therapy with ibrexafungerp
		• replacement of current monotherapy with a new combination, generally:
		  ○ replacement of amphotericin B monotherapy with an azole plus ibrexafungerp combination, or
		  ○ replacement of an azole monotherapy with an amphotericin B plus ibrexafungerp combination
		• continuation of an azole plus echinocandin combination where the subject could go home on an oral regimen by replacing the parenteral echinocandin with ibrexafungerp
		
		Subjects with IPA and intolerance to other standard of care options can be considered for enrollment to receive ibrexafungerp monotherapy, upon discussion with the Sponsor.

	Eligibility Criteria	
Fungal Disease	**Diagnostic Criteria**	**Refractoriness/Resistance/Intolerance[a]/Toxicity[b]/Relapse[c] Criteria**
Other emerging fungi including yeasts and molds (e.g., sachromycetes, scopulariopsis)	• Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site showing fungal cells. OR • Recovery of a fungal species by culture of a sample obtained by a sterile procedure from a normally sterile site, wound or lesion consistent with known pathophysiology of the organism AND • Radiological imaging showing evidence consistent with an infectious disease process AND • Fungus (genus species) is known to be generally susceptible to ibrexafungerp *in vitro* OR • Fungal susceptibility of the isolate showing MICs for ibrexafungerp ≤ 4 ug/mL	For **other emerging fungi**, refractoriness is defined as meeting any of the following criteria: • Subject intolerant of available therapeutic options • Suboptimal response per the Investigator's judgement • Limited or no therapeutic options available For subjects without culture isolate available (to confirm susceptibility to ibrexafungerp), combination therapy should be considered and discussed with the Sponsor.

	Eligibility Criteria	
Fungal Disease	**Diagnostic Criteria**	**Refractoriness/Resistance/Intolerance[a]/Toxicity[b]/Relapse[c] Criteria**

Abbreviations: ABPA=allergic bronchopulmonary aspergillosis; ALT= alanine aminotransferase; AST=aspartate aminotransferase; BAL=bronchoalveolar lavage; CMC=chronic mucocutaneous candidiasis; CPA=chronic pulmonary aspergillosis; CT=computerized tomography; EC=esophageal candidiasis; GMI=galactomannan index; HRCT= high resolution computerized tomography; Ig=immunoglobulin; IPA=invasive pulmonary aspergillosis; MIC=minimum inhibitory concentration; MRI=magnetic resonance imaging; OPC=oropharyngeal candidiasis; PCR= polymerase chain reaction; SOC=standard of care; TNF = tumor necrosis factor; VSS=vulvovaginal signs and symptoms; VVC=vulvovaginal candidiasis.

a: **Intolerance** for any of the eligible diseases above is defined as presence or history of administration-related AEs (e.g., infusion reaction, hypersensitivity reactions, etc.) to the standard antifungal being administered or intended for treatment of the current fungal disease.

b: **Toxicity** for any of the eligible diseases above is defined as the degree to which a substance (antifungals) can damage an individual as well as cause a negative effect on a substructure of an individual such as a system or organ. The toxicity should be of a severity or prognosis such that, as per the Investigator´s judgement, it is in the best interest of the subject to modify his/her antifungal therapy. Example of toxicities include:

- Nephrotoxicity defined as elevation of serum creatinine level by 2 times the baseline value or any value above the upper limit of normal (ULN), in a repeat test at least 24 hours apart.
- Hepatotoxicity defined as elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >5 times ULN.
- Other events not related to the subject's condition and that started after initiation of the standard antifungal agent, such as visual disturbances, cutaneous reactions, neurological reactions, histamine reactions, etc.
- Drug-drug interactions of the standard antifungal agent with other therapies being received by the subject, which are either associated with a documented toxicity or are likely to result in toxicity.

c: **Relapse** is defined as deterioration or worsening of a fungal disease after an initial improvement to therapy.

3. Subject is able to tolerate medication orally or through a nasogastric (NG) tube or percutaneous endoscopic gastrostomy (PEG) tube.
4. Subject and/or legal guardian is/are able to understand and sign a written ICF, which must be obtained prior to treatment and any study-related procedures.
5. Subject and/or legal guardian 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 US, a Health Insurance Portability and Accountability Act [HIPAA] authorization form).
6. Subject and/or legal guardian is able to understand and follow all study-related procedures including study drug administration.
7. Subject is not pregnant and is highly unlikely to become pregnant or to impregnate a partner since he/she meets at least one of the following criteria:

    a. Subject is a female subject who is not of reproductive potential and is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as one who: (1) has reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels in the postmenopausal range as determined by the local laboratory, or 12 months of spontaneous amenorrhea); (2) is 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy; or (3) has undergone bilateral tubal ligation. Spontaneous amenorrhea does not include cases for which there is an underlying disease that causes amenorrhea (i.e., anorexia nervosa).

    b. Subject is a male subject who is not of reproductive potential and is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as one who has undergone a successful vasectomy. A successful vasectomy is defined as (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.

    c. Subject is a male or female subject who is of reproductive potential and agrees to remain abstinent if it is the subject's preferred method of contraception, or, if sexually active, use (or have their partner use) 2 acceptable methods of contraception starting from the time of consent through 28 days after the completion of study therapy. Acceptable methods of birth control are hormonal contraception (including but not limited to oral, injectable or implantable methods), intrauterine device, diaphragm with spermicide, condom, and vasectomy. Hormonal contraception (including but not limited to oral, injectable or implantable methods), must not be used alone as a method of contraception because it is unknown if the effect of ibrexafungerp may reduce the efficacy of hormonal contraceptives.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are NOT acceptable methods of contraception.

NOTE: Women of childbearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin) prior to enrollment (performed by the site's local laboratory).

11.2 Exclusion Criteria

A subject will be excluded from participation in the study if he or she meets any of the following exclusion criteria at Screening and/or Baseline:

1. Subject has an invasive fungal disease with central nervous system involvement unless the subject is planned to receive combination therapy with ibrexafungerp and other antifungal.
2. Subject has an inappropriately controlled fungal disease source (e.g., persistent catheters, devices, identified undrained abscess) that is likely to be the source of the fungal disease.
3. Subject is hemodynamically unstable and/or requiring vasopressor medication for blood pressure support.
4. Subject has abnormal liver test parameters: AST or ALT >10 x ULN and/or total bilirubin >5 x ULN.

   Note: Subjects with unconjugated hyperbilirubinemia with a diagnosis of Gilbert's disease **are not excluded**.
5. Subject is unlikely to survive 30 days.
6. Subject has any other condition or laboratory abnormality that, in the judgment of the Investigator, would put the subject at unacceptable risk for participation in the study or may interfere with the assessments included in the study.
7. Subject requires treatment with the prohibited medications.
8. Subject has known hypersensitivity to ibrexafungerp.
9. Subject is pregnant or lactating.
10. Subject has received any other investigational drug (i.e., new chemical entity) within at least 30 days (or 5 and a half half-lives of the investigational product) before signing the ICF.
11. Subject is an employee of SCYNEXIS, Inc., the Investigator, or contract research organization involved in the study, or an immediate family member (partner, offspring, parents, siblings, or sibling's offspring) of an employee involved in the study.

12. Subject or legal representative is/are unable to provide written informed consent for any reason.
13. Subject is unlikely to comply with protocol requirements.

11.3 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 and/or subject's legal guardian;
- Investigator or Sponsor decision that withdrawal is in the subject's best interest;
- Deterioration of the clinical condition or delayed response requiring, in opinion of the Investigator, alternative therapy;
- Occurrence of an AE that, in the opinion of the Investigator, warrants discontinuation of the subject from the study drug;
- Pregnancy;
- Lost to follow up (every attempt should be made to contact the subject).

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).

For VVC subjects, all TOC procedures should be performed for subjects who discontinue from the study before the TOC visit, and all 25-Day FU procedures should be performed for subjects who discontinue from the study after the TOC visit but before the 25-Day FU visit.

For all other fungal diseases, at the time of discontinuation, all EOT procedures should be performed for subjects who discontinue from treatment on or before the EOT visit and the 6-Week FU visit should also be completed. All 6-Week FU procedures should be performed for subjects who discontinue from the study after the EOT visit and on or before the 6-Week FU visit. All follow up visits should be completed for discontinued subjects regardless of need for additional antifungal therapy.

11.4 Replacement of Discontinued Subjects

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

12.0 Study Treatments

12.1 Study Treatment Groups

This is an open-label, non-comparator, single-arm study. All subjects will receive ibrexafungerp monotherapy except subjects with refractory or relapsing invasive pulmonary aspergillosis (IPA), who will receive combination therapy. Combination therapy may also be administered to other

subjects based on Investigator's judgement and contingent on Sponsor approval. Subjects will receive ibrexafungerp on an inpatient or outpatient basis, as needed for each fungal disease.

12.1.1 Ibrexafungerp Monotherapy for All Fungal Diseases, Excluding VVC

Subjects will receive ibrexafungerp monotherapy given as an initial loading dose of 750 mg (3 tablets of 250 mg each) given BID (total daily dose = 1500 mg) during the first 2 days of treatment and then subsequent oral doses of 750 mg (3 tablets of 250 mg each) QD for up to 180 days, depending on fungal disease.

Table 6 Ibrexafungerp Monotherapy Dosing Regimen (Excluding VVC)

	Treatment Days	Ibrexafungerp Dosing Regimen	Total Ibrexafungerp Daily Dose
Loading Dose	Study Days 1 and 2	**750 mg BID:** 750 mg (3 tablets x 250 mg) AM 750 mg (3 tablets x 250 mg) PM	1500 mg
Maintenance Dose	Study Day 3 to EOT	**750 mg QD:** 750 mg (3 tablets x 250 mg)	750 mg
[redacted]	[redacted]	[redacted]	[redacted]

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

Treatment beyond 180 days may be permitted under certain circumstances to be agreed upon by the Investigator and the Sponsor on a per-subject basis. Subjects with a recurrence after TOC (VVC) or EOT (all other diseases) may be considered for re-enrollment upon discussion with the Sponsor.

If subjects cannot swallow the whole tablet, the tablets may be split. In the event subjects experience gastrointestinal intolerance on the 750 mg QD dose, the tablets may be split and/or administered at 10 to 20-minute intervals. [redacted]

12.1.2 Ibrexafungerp Monotherapy for VVC

Subjects with VVC will receive ibrexafungerp monotherapy given as oral doses of [redacted] Subjects treated for VVC who have a recurrence after TOC may receive additional cycles of ibrexafungerp treatment similar to the initial regimen, upon discussion with the sponsor.

Table 7 Ibrexafungerp Monotherapy Dosing Regimen for VVC

Treatment Days	Ibrexafungerp Dosing Regimen	Total Ibrexafungerp Daily Dose
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AM = morning; PM = evening; VVC = vulvovaginal candidiasis

12.1.3 Ibrexafungerp Combination Therapy

Monotherapy with ibrexafungerp is not recommended for refractory or relapsing IPA. All subjects enrolled for refractory or relapsing IPA, mucormycosis or other molds with unpredictable ibrexafungerp activity should receive ibrexafungerp given as combination therapy. Subjects with IPA and intolerance to other SOC options can be considered for enrollment to receive ibrexafungerp monotherapy, upon discussion with the Sponsor.

For subjects who have infections due to other emerging fungi, including yeasts and molds, but have no culture isolate available (to confirm susceptibility to ibrexafungerp), combination therapy should be considered and discussed with the Sponsor. Combination therapy will also be allowed for other subjects based on Investigator's judgement and contingent on Sponsor approval.

Acceptable antifungal therapy includes voriconazole, isavuconazole, posaconazole, fluconazole or amphotericin B (AMB) at the doses recommended per their label. When used in combination with the azoles, the dose of ibrexafungerp should be reduced from 750 mg to 500 mg.

Table 8 Ibrexafungerp – Azole Combination Therapy Dosing Regimen

	Treatment Days	Additional Antifungal	+	Ibrexafungerp Dosing Regimen	Total Ibrexafungerp Daily Dose
Loading Dose	Study Days 1 and 2	Per label	+	**500 mg BID:** 500 mg (2 tablets x 250 mg) AM 500 mg (2 tablets x 250 mg) PM	1000 mg
Maintenance Dose	Study Day 3 to EOT	Per label	+	**500 mg QD:** 500 mg (2 tablets x 250 mg)	500 mg

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

The following combination options are allowed:

- addition of ibrexafungerp to any ongoing antifungal therapy
- replacement of one (toxic/ineffective) element of a two-antifungal combination therapy with ibrexafungerp

- replacement of current monotherapy with a new combination, generally:
  - replacement of AMB monotherapy with an azole plus ibrexafungerp combination, or
  - replacement of an azole monotherapy with an AMB plus ibrexafungerp combination
- continuation of an azole plus echinocandin combination where the subject could go home on an oral regimen by replacing the parenteral echinocandin with ibrexafungerp

12.1.4 Dietary Requirements

Oral study drug should be taken with approximately 8 oz/240 mL of water, preferably with food. For subjects on continuous feeding via an NG or PEG tube, the drug should be crushed and administered with approximately 8 oz/240 mL of water. The tube should be closed at least one hour before drug administration and should be flushed with approximately 20 mL of water before and after drug administration.

12.2 Study Drugs

12.2.1 Ibrexafungerp Description

Study Drug Identifier: Ibrexafungerp

Empirical 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: (1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-15-[[(2R)-2-amino-2,3,3-trimethylbutyl]oxy]-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]

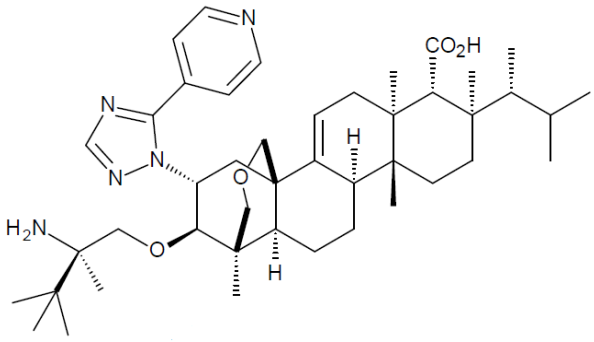

Figure 2 Chemical Structure of Ibrexafungerp Citrate

12.2.2 Formulation, Packaging and Labelling

Ibrexafungerp citrate drug product for oral administration will be supplied as compressed oral tablets containing 250 mg of ibrexafungerp active ingredient on a free base basis. In addition to the active ingredient, the oral tablet formulation also contains silicified microcrystalline cellulose, crospovidone, mannitol, colloidal silicon dioxide, magnesium stearate (non-bovine), and butylated hydroxyanisole. Ibrexafungerp is packaged in bottles containing 30 tablets.

Labels on the bottles of ibrexafungerp will include information as required by regional regulations and may include:

- Sponsor information
- Protocol number
- Protocol visit number
- Place to write the subject number
- Route of administration
- Lot number
- Product name and potency
- Contents, e.g. number of tablet count per bottle
- Storage conditions
- Name of manufacturer and date of manufacture
- Caution statement according to local regulations: "Caution: New Drug – Limited by Law to Investigational Use Only”

12.2.3 Storage and Stability

The pharmacist or appropriate designee at each clinical research site will be responsible for the study drug. Ibrexafungerp tablets are to be stored at room temperature: between 15°C and 25°C with allowable limited excursions of up to 30°C.

For long-term storage at the site, study drug supplies must be kept in a secure area (e.g., locked cabinet) and stored at room temperature.

The site will be required to keep a temperature log to establish a record of compliance with these storage conditions. All study drug will be kept in a secure cabinet or room with access restricted to necessary clinic personnel.

12.3 Drug Accountability

The Investigator or designee will inventory and acknowledge receipt of all shipments of the study drug. 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. At the conclusion of the study, after final 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.

The study drug supplied for this study is only for use in subjects who were properly consented and enrolled under this protocol.

A study site designee (e.g., pharmacist, study nurse/coordinator) will:

- Record the treatment in the drug accountability log.
- Count the number of tablets per bottle before dispensing to subject.
- Report and document any study medication issues such as contamination, crushed or broken tablets, incorrect labelling.
    - All product quality complaints should be reported to the Sponsor.
- Collect and count the number of tablets remaining at the EOT visit.

Review subject diary card and remaining study drug count, record any unused or remaining drug in the drug accountability log and eCRF, and note any discrepancies and reason for discrepancies.

12.4 Subject Compliance with Study Drug Dosing

Subjects who are discharged from the hospital will be instructed to have the study medication (including empty bottles/units) with them at each visit. Compliance will be assessed based on remaining study drug as compared to what should have been taken and the subject diary where the subject will enter the details of dosing. Details of treatment including any missing dose will be recorded on 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 problems with tolerability.

13.0 Non-Study Treatments

13.1 Prior and Concomitant Medications

All medications (including prescription and over-the-counter medications, supplements, and herbal products) taken from 30 days before Baseline/Day 1 through TOC (Day 17) for VVC and EOT for all other fungal diseases will be recorded on the eCRF. Immunosuppressants (e.g.,

chemotherapy, corticosteroids, T-Cell immunosuppressants) used up to 90 days prior to subject enrollment will be recorded on the eCRF. Antifungal medications administered for the treatment of the eligible fungal infection if received for ≥7 days in the preceding 6 months prior to enrollment will also be recorded on the eCRF. In individual cases, timelines beyond 6 months or treatments less than 7 days may be requested for the record as clinically relevant, as judged by the Investigator and the Sponsor. Only the use of other antifungal medications, antibiotics for any reason or medications to treat an AE will be recorded after EOT (TOC for VVC subjects) and through the last observation in the study (35-Day FU for VVC, 6-Month FU for ABPA and 6-Week FU for all other fungal diseases). Start and stop times of concomitant medications taken during antifungal therapy will be recorded on the eCRF. Subjects will also record any new concomitant medications taken between visits in the subject diary.

See Section 13.2 and Section 13.3 for prohibited medications and medications to be administered with caution, respectively.

13.2 Prohibited Medications

Medications not permitted include the following:

- Non-study systemic or topical antifungal therapy except in subject subgroups where combination therapy is allowed or where an exception was granted by the Sponsor on a per-subject basis
- Other investigational drug(s)
- Strong CYP3A4/5 inhibitors, CYP3A4/5 inducers, and select P-gp substrates (refer to Appendix B [Section 21.2] for the full list of prohibited medications).

See Appendix B [Section 21.2] for the full list of prohibited medications

13.3 Medications to be Administered with Caution and Monitored as Appropriate

CYP3A4 moderate 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 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.

Refer to Appendix B (Section 21.2) for further details.

13.4 Study Restrictions

There are no study restrictions other than those described in Sections 11.2 (Exclusion Criteria), Section 12.1.4 (Dietary Requirements), Section 13.2 (Prohibited Medications) and Section 13.3 (Medications to be Administered with Caution).

14.0 Study Procedures

The following sections provide a description of the individual study procedures to be performed during the conduct of the study. Detailed schedules of study assessments for VVC and for all other fungal diseases are provided in Section 15.0.

Study days, weeks and months are counted relative to the first dose of study drug (Baseline [Day 1]). For follow-up visits, days, weeks and months are counted relative to the EOT visit. The Screening visit and Baseline (Day 1) visit may occur on the same day.

14.1 General Procedures

14.1.1 Informed Consent

Every study subject or legally authorized representative must provide written informed consent prior to participating in any screening evaluations or any other study activities (see Section 19.3).

14.1.2 Enrollment and ID Assignment

At Screening, all subjects who have signed an ICF will receive an 8-digit subject identification (ID) number that will be composed of a 3-digit study number (301) 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 301-01-001. 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 301-02-002. This number will be unique to each subject and will be used to identify the subject throughout the study. Non-U.S. sites will have a 3-digit site identification number, instead of a 2-digit number for U.S. sites.

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.

For subjects who signed an ICF (i.e., are assigned a subject number) but were NOT treated because they did not meet all of the inclusion/exclusion criteria, the Screening visit pages of the eCRF will be completed. The criteria that were not met for enrollment will be documented on the eCRF.

All eligible subjects must be approved by the Sponsor (or Sponsor designee) for enrollment. An Eligibility Form will be used to request eligibility confirmation from the Sponsor or Sponsor designee.

14.1.3 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 and ethnicity will also be collected. For subjects with ABPA, the number of Asthma and ABPA Exacerbations in the six months prior to enrollment should be recorded. For subjects with chronic pulmonary aspergillosis (CPA), the latest available result on the Six-Minute Walk Test and St. George's Respiratory Questionnaire prior to Screening should be recorded on the eCRF. Data available to support inclusion / exclusion criteria collected as SOC prior to signature of the ICF will be collected as appropriate in the EDC.

14.1.4 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed to ensure that the subject qualifies for the trial at Screening and at Baseline/Day 1.

14.1.5 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 for all female subjects of childbearing potential, except those with VVC. Pregnancy tests may be conducted more often (e.g., on a monthly basis), per local regulations.

14.1.6 Prior and Concomitant Medications

Refer to Section 13.0 and Section 21.2 for details.

14.1.7 Study Drug Dispensing, Collection and Accountability Review

For subjects who are not hospitalized, the study drug will be dispensed at Baseline/Day 1 and every 14 days. Study drug will be collected for accountability review every 14 days up to EOT, at EOT and at unscheduled visits (see Section 12.4 for further details regarding treatment compliance evaluation). Any unused study drug will be re-dispensed to the subject.

For VVC subjects, study drug will be dispensed at Baseline/Day 1 and will be collected at EOT (Day 7), when treatment compliance will be assessed.

14.1.8 Study Drug Dosing

For all subjects except VVC subjects, study drug doses will be administered daily through EOT, as needed, depending on the fungal disease. Subjects with VVC will receive ibrexafungerp on [redacted]

Further details of the study treatment and dietary requirements for administration of ibrexafungerp monotherapy and combination therapy are provided in Section 12.1.1, Section 12.1.2 and Section 12.1.3.

14.1.9 Subject Diaries

Non-hospitalized subjects will complete a subject diary up to their EOT visit. The subjects will record the date/time of study medication dosing, daily symptoms, other medical concerns or complaints, and concomitant medications.

For all subjects except VVC subjects, diaries will be dispensed at Baseline/Day 1 and will be reviewed every 14 days during treatment up to EOT, at unscheduled visits, and at EOT, when they will be collected. For VVC subjects, diaries will be dispensed at Baseline/Day 1 and will be collected at TOC.

14.2 Efficacy Procedures

14.2.1 Targeted Physical Examination, Including Clinical Evaluation of Signs and Symptoms

A targeted examination of the fungal disease site, including the signs and symptoms of the fungal infection, will be conducted for all subjects, excluding VVC subjects, at Screening and Baseline/Day 1 (prior to treatment), and at the per-protocol visits displayed in Table 9.

Table 9 Schedule of Visits for Targeted Physical Examinations by Fungal Disease (Excluding VVC)

Study Days	Every 14 days during Tx[a]	D42	[c]D84	[d]D90	D180	EOT	Unsch. Visits	FU 1 (6-WK)	FU 2 & FU 3
Allowable window	±2 d	±7 d	±7 d	±7 d	±14 d	±3 d	AP	± 7 d	AP
Acute or Chronic IC	X	X				X	X	X	
EC, OPC	X	X				X	X	X	
CMC[c]	X	X	X			X	X	X	
D/I DF	X	X	X			X	X	X	
CPA[d]	Day 14	X		X	X[b]	X	X	X	
ABPA[d]	Day 14	X		X	X[b]	X	X	X	X
IPA	X	X	X			X	X	X	
Other emerging fungi	X	X	X			X	X	X	

Abbreviations: ABPA=allergic bronchopulmonary aspergillosis; AP = as applicable; CMC=chronic mucocutaneous candidiasis; CPA=chronic pulmonary aspergillosis; D=day; DF=dimorphic fungi; D/I= disseminated/ invasive; EC=esophageal candidiasis; EOT=end of treatment; FU=follow up; FU 1=6-Week FU; FU 2=3-Month FU; FU 3=6-Month FU; IC=invasive candidiasis; IPA=invasive pulmonary aspergillosis; OPC=oropharyngeal candidiasis; Tx=treatment; unsch.=unscheduled; VVC=vulvovaginal candidiasis; WK=week

a: As clinically indicated for disease.

b: Efficacy procedures for CPA and ABPA subjects will be performed every 3 months following Day 180 if the subject is still on treatment.

c: For CMC subjects, D84 is TOC visit unless EOT occurs first

d: For CPA and ABPA subjects, D90 is TOC visit unless EOT occurs first

For subjects with VVC, targeted physical exams will be done at Screening, Baseline/Day 1 (prior to treatment), [redacted] TOC (Day 17 [±3]) and 25-Day FU visit (25 days after EOT). A targeted physical exam (vaginal examination) will also be conducted at the 35-Day FU visit (35 days after EOT) if the subject is symptomatic. The EOT visit and the 35-Day FU visits will be a phone contact only if the subject is asymptomatic.

Note: For subjects who are suspected to have a relapse of infection during the study follow-up period, evaluations relevant to the signs and symptoms of infection should be performed before starting non-study antifungal therapy. The results of these studies should be documented on the eCRF. Subjects who have a recurrence after TOC (VVC) or EOT (all other diseases), may be considered for re-enrollment upon discussion with the Sponsor.

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

- General signs and symptoms:
  - Fever, defined as oral temperature ≥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 <90 mmHg or a >30 mmHg decrease below normal baseline)

- Tachycardia
- Local signs and symptoms of inflammation

- Disease-specific signs and symptoms:
  - OPC: White patches or plaques on the tongue and other oral mucous membranes, redness or soreness in the affected areas, difficulty swallowing, cracking at the corners of the mouth (angular cheilitis)
  - EC: White plaques and/or ulcers on the lining of the esophagus or narrowing of the lumen, pain when swallowing, difficulty swallowing, heartburn
  - CMC: Extensive scaling, skin lesions, thickened nails
  - Other signs and symptoms of candidiasis and other fungal diseases, as applicable

Subjects who are discharged from hospital during ibrexafungerp therapy will record their signs and symptoms daily on subject diaries, and the signs and symptoms will also be assessed by the site staff at the study visits. The site will assess whether the signs and symptoms recorded on the subject diary are related to the fungal disease.

14.2.2 Mycological Testing

14.2.2.1 Vulvovaginal Candidiasis

Samples for fungal culture will be collected at Screening, EOT (Day 7), TOC (Day 17 [±3]) and 25-Day FU (25 days after EOT; 32 days after first dose). Additional samples will be obtained, if applicable, at Baseline/Day 1 and at any unscheduled visits. For symptomatic subjects, samples will also be collected at the 35-Day FU visit (35 days after EOT; 42 days after first dose).

14.2.2.2 All Other Fungal Diseases Excluding Vulvovaginal Candidiasis

Mycological samples will be obtained for all subjects at Screening and/or Baseline/Day 1 (prior to treatment), and as applicable for each subject and fungal disease while on therapy. In addition, samples will be collected at the per-protocol visits displayed in Table 10.

Table 10 Schedule of Visits for Mycological Assessments by Fungal Disease (Excluding VVC)

Study Days	D42	D84[b]	D90[c]	D180	EOT	Unsch. Visits	FU 1 (6-WK)	FU 2 & FU 3
Allowable window	±7 d	±7 d	±7 d	±14 d	±3 d	AP	± 7 d	AP
Acute or Chronic IC	X				X		X	
EC, OPC	X				X		X	
CMC[b]	X	X			X		X	
D/I DF	X	X			X		X	
CPA[c]			X	X[a]	X		X	
ABPA								
IPA	X	X			X		X	
Other emerging fungi	X	X			X		X	

Abbreviations: ABPA=allergic bronchopulmonary aspergillosis; AP = as applicable; CMC=chronic mucocutaneous candidiasis; CPA=chronic pulmonary aspergillosis; D=day; DF=dimorphic fungi; D/I= disseminated/ invasive; EC=esophageal candidiasis; EOT=end of treatment; FU=follow up; FU 1=6-Week FU; FU 2=3-Month FU; FU 3=6-Month FU; IC=invasive candidiasis; IPA=invasive pulmonary aspergillosis; OPC=oropharyngeal candidiasis; Tx=treatment; unsch.=unscheduled; VVC=vulvovaginal candidiasis; WK=week

Note: Mycological response will be assessed by fungal culture, KOH and other fungal stains, T2 testing, and serological testing (including, GMI, *Coccidioides* titers, and β-D-glucan levels, among others [Section 14.2.4]), if applicable.

a: Efficacy procedures for CPA subjects will be performed every 3 months following Day 180 if the subject is still on treatment.

b: For CMC subjects, D84 is TOC visit, unless EOT occurs first

c: For CPA and ABPA subjects, D90 is TOC visit unless EOT occurs first

14.2.2.2.1 *Candida* Infections Excluding VVC

Blood cultures: Two sets of blood cultures will be collected at Screening and repeated daily or every other day until blood cultures are negative for at least 48 hours (if it is only possible to obtain 1 set of blood cultures, a reason should be documented). Blood should be drawn peripherally [directly from a vein]; however, if this is not possible, blood may be drawn from a central IV catheter. Follow-up cultures will be performed as clinically indicated.

Non-blood cultures: Follow-up cultures from subjects who have non-blood sites of *Candida* infection should be performed as clinically indicated.

EC: Follow-up KOH or fungal stains and/or mycological cultures from biopsy or brushing indicating yeast infection will be performed as clinically indicated.

OPC and CMC: Follow-up KOH or fungal stains and/or mycological cultures for *Candida* spp. obtained from the affected site will be performed as clinically indicated.

Urine cultures: for subjects with urinary tract infections, urine samples for fungal cultures are recommended to be collected every 48-72 hours until negative.

For subjects diagnosed exclusively by T2 testing:

- The diagnosis should be based on two consecutively positive T2 tests.
- For subjects diagnosed based on positive T2 tests, in addition to Screening, samples for T2 testing will be collected every 48 hours until negative.

14.2.2.2.2 Other Fungal Diseases

Baseline mycological assessment (Screening) of the subject's fungal disease will be performed according to best local practice using local laboratories, including suitable samples for fungal culture and isolation as well as samples from the infected site for histology and cytology. Outside of these time points, mycological assessment will be performed as clinically indicated and/or in line with standard clinical management for the subject's specific fungal disease and anatomic site involved. The results of all mycological assessments, both culture and non-culture based (including negative results), performed during the study and relevant to the fungal infection will be recorded on the eCRF.

14.2.2.3 General Notes for Mycological Testing

The study site's local microbiology laboratory will perform identification and *in vitro* susceptibility testing as per their local standards. The Investigator should ensure that fungal isolates obtained from all cultures performed during the study period (and wherever possible, the isolate from the initial positive culture) are sent to the central microbiology laboratory, as described in the laboratory manual. The central microbiology laboratory will repeat the identification and perform *in vitro* susceptibility testing of the isolates as per CLSI M27-A4 and or EUCAST guidelines.[10,11] Baseline isolated pathogens and subsequent isolates will be subjected to ibrexafungerp susceptibility testing. The central laboratory will include standard of care antifungals in the drug panels to determine resistance patterns.

Further evaluation to identify the potential mechanism of resistance may be performed. Isolates may be maintained in a repository for potential future use, for subjects that provide consent for future use.

Identification of the fungi isolate by local and central laboratory may be performed using acceptable methods such us culture, PCR, matrix-assisted laser desorption/ionization (MALDI-TOF) or others that are approved for such use or are considered acceptable in the state of the art and current guidelines.

Table 11: Fungal Isolates to be Collect for the Study.

Fungal isolate	Definition	When to Send to Central Laboratory
Initial Isolate	The isolate from the culture that resulted in the initial diagnosis of invasive fungal disease will be considered the "initial" isolate. All subjects except those diagnosed solely based on non-culture tests like T2, PCR or serological tests will have an isolate from an initial culture.	End of Study for each subject.
Screening Isolate	Subjects with refractory or resistant fungal disease will have cultures that are positive after the initial positive culture (thereby qualifying the subjects as "refractory or resistant" for study eligibility). This will be referred to as the "Screening" Isolate.	For subjects refractory or resistant to an echinocandin, the isolate should be sent at the time of enrollment per the laboratory manual instructions. Otherwise, screening isolates may be sent at End of Study for each subject.
Study Isolate	All fungal isolates recovered during study while the subject is receiving ibrexafungerp or during the follow-up window.	End of Study for each subject.

For subjects who are suspected to have a relapse of infection during the study follow-up period, cultures should be collected and other evaluations relevant to the signs and symptoms of infection should be performed before starting non-study antifungal therapy. Results of all mycological tests, including both culture and non-culture based (including negative results), relevant to the fungal infection under treatment should be documented on the eCRF.

Sites should make every attempt to save the initial isolate for the study. However, it is not mandatory to have the initial isolate for enrollment. In the absence of baseline isolates, all post-Baseline pathogens collected in the context of clinical failure and associated with the fungal disease will be stored and shipped to central laboratory for identification of fungal species and susceptibility testing. If the identities of the pathogens differ between the central and local laboratories, the central laboratory results will take precedence over the local results for all study purposes.

Other procedures and assessments will be performed as clinically indicated for the individual subject:

- Suitable samples for fungal culture and isolation (blood/ tissue cultures).
- Follow-up culture samples from non-bloodstream infections are not mandatory but, if obtained, results should be recorded. Histological or cytological findings are regarded as supportive evidence of invasive fungal disease and should be recorded, if available.
- For outcome assessment of fungal blood stream infections, confirmed (two consecutive) negative blood cultures are required.
- All isolates should be identified to species level. All baseline and EOT isolates will be stored and shipped for central retesting. The central laboratory results will be considered definitive.
- Biopsy/biological fluid samples from the infected site for histology and cytology.

14.2.3 Imaging

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 for all subjects at Screening as applicable for each subject and fungal disease. Imaging scans will also be collected at the recommended per-protocol visits displayed in Table 12. In addition to the scheduled time points, imaging scans will be collected anytime during therapy, as clinically indicated. The window for EOT imaging may range from ± 3 to ± 7 days, depending on the fungal disease.

Data available to support patient eligibility collected as SOC prior to signature of the ICF will be collected as appropriate in the EDC. Baseline radiological assessments for invasive fungal diseases should be performed ideally within 72 hours of Screening. However, assessments performed up to 7 days before/after the first administration of study medication may be used to confirm the diagnosis of the fungal disease if none exists within the ideal window. Radiological assessments should ideally be made by CT scan (HRCT if available) or MRI. The same radiologic methodology used at Baseline should be used for subsequent assessments. For lung, bone and abdominal infections, imaging at EOT is strongly recommended, since they are critical for outcome assessment.

Bronchoscopic assessments should be performed as clinically indicated. When performing bronchoscopic examinations, samples obtained should be sent for the following tests: culture, histology/cytology and GM. If BAL samples are obtained at Baseline, an additional sample should be stored for shipping to the central laboratory. For other time points, any residual BAL sample after routine SOC testing is complete should be stored for shipping to the central laboratory.

The results of these imaging studies should be documented on the eCRF.

Table 12 Schedule of Visits for Recommended Imaging Assessments by Fungal Disease, if obtained for Routine Care (Excluding VVC)

Study Days	D42	D84[d]	D90[e]	D180	EOT	Unsch. Visits	FU 1 (6-WK)	FU 2 & FU 3
Allowable window	±7 d	±7 d	±7 d	±14 d	± 3 to ± 7	AP	± 7 d	AP
Acute or Chronic IC[a]	X				X		X	
EC, OPC[a]	X				X		X	
CMC[a, d]	X	X			X		X	
D/I DF	X	X			X		X	
CPA[e]			X	X[b]	X		X	
ABPA[e]	X		X	X[b]	X		X	X
IPA[c]	X	X			X		X	
Other emerging fungi[a]	X	X			X		X	

Abbreviations: ABPA=allergic bronchopulmonary aspergillosis; AP = as applicable; CMC=chronic mucocutaneous candidiasis; CPA=chronic pulmonary aspergillosis; D=day; DF=dimorphic fungi; D/I= disseminated/ invasive; EC=esophageal candidiasis; EOT=end of treatment; FU=follow up; FU 1=6-Week FU; FU 2=3-Month FU; FU 3=6-Month FU; IC=invasive candidiasis; IPA=invasive pulmonary aspergillosis; OPC=oropharyngeal candidiasis; Tx=treatment; unsch.=unscheduled; VVC=vulvovaginal candidiasis; WK=week

a: If applicable.

b: Efficacy procedures for CPA and ABPA subjects will be performed every 3 months following Day 180 if the subject is still on treatment.

c: For IPA subjects, a chest CT scan within -7 days of Baseline and ±3 to ±7 days of EOT is required.

d: For CMC subjects, D84 is TOC unless EOT occurs first

e: For CPA and ABPA subjects, D90 is TOC unless EOT occurs first

14.2.4 Serological Testing

Serological tests will be obtained for all subjects, excluding VVC subjects, at Screening and at Baseline/Day 1 (prior to treatment), as applicable for each subject and fungal disease. Samples will also be collected at the recommended per protocol visits displayed in Table 13.

Table 13 Schedule of Visits for Recommended Serological Assessments by Fungal Disease (Excluding VVC)

Study Days	D3-D5	D7-D10	Every 14 days during Tx	D42	D84	D90	D180	EOT	Unsch. Visits	FU 1 (6-WK)	FU 2 & FU 3
Allowable window	±2 d	±2 d	±2 d	±7 d	±7 d	±7 d	±14 d	±3 d	AP	± 7 d	AP
Acute or Chronic IC											
EC, OPC											
CMC											
D/I DF[a]			Day 14	X	X						
CPA[b]	← as applicable →					X	X[c]	X		X	
ABPA[d]	← as applicable →			X		X	X[c]	X		X	X
IPA[e]	X	X	X	X							
Other emerging fungi[a]											

Abbreviations: ABPA=allergic bronchopulmonary aspergillosis; AP = as applicable; CMC=chronic mucocutaneous candidiasis; CPA=chronic pulmonary aspergillosis; D=day; DF=dimorphic fungi; D/I= disseminated/ invasive; EC=esophageal candidiasis; EOT=end of treatment; FU=follow up; FU 1=6-Week FU; FU 2=3-Month FU; FU 3=6-Month FU; IC=invasive candidiasis; IPA=invasive pulmonary aspergillosis; OPC=oropharyngeal candidiasis; Tx=treatment; unsch.=unscheduled; VVC=vulvovaginal candidiasis; WK=week

a: Serological tests will be conducted as clinically indicated.

b: Change in total IgG and *Aspergillus*-specific IgG will be evaluated if elevated at Baseline.

c: Efficacy procedures for CPA and ABPA subjects will be performed every 3 months following Day 180 if the subject is still on treatment.

d: Serum samples will be collected for total IgE .

e: Serum samples will be collected for GM determination at Week 1, Week 2, Week 4 and Week 6.

For subjects diagnosed exclusively by ß-D-glucan tests:

- The diagnosis should be based on two consecutively positive ß-D-glucan tests.
- Samples for ß-D-glucan testing will be collected every 72 hours until negative.

For subjects with CPA:

- Serum samples will be collected at Day 90 and Day 180 for Ig, *Aspergillus*-specific IgG and total IgG.

For subjects with ABPA:

- Serum samples will be collected for total IgE at Day 42, Day 90, Day 180 and every 3 months following Day 180 while receiving study medication, at EOT and at the 3-Month FU and 6-Month FU visits.

For subjects with invasive aspergillosis, including IPA:

- A single value of ≥ 0.7 or two consecutive values each of ≥ 0.5 - < 0.7 (i.e., from two separate blood draws) will be considered a positive result unless deemed false positive due to the presence of known interacting agents. Subjects with serum GM meeting the

protocol-defined requirements drawn within 10 days prior to first dose of study medication are eligible for enrollment.

- BAL for GM specimens may be processed locally, but an additional aliquot of BAL fluid will be collected for shipment to the central laboratory as well, when feasible. A single GM value ≥1 will be considered a positive result unless deemed false positive due to the presence of known interacting agents. For the current invasive aspergillosis episode, the results available for all previous GM determinations in the preceding 3 months (e.g. before enrollment) will be collected on the eCRF.

For subjects with IPA:

- Serum samples will be collected at Week 1, Week 2, Week 4 and Week 6 for GM determination.

14.2.5 Esophagoscopy

Esophagoscopies will be conducted at Screening in all subjects who have EC. Results of the most recent esophagoscopy that confirmed the diagnosis must be available for Screening. A repeat esophagoscopy is not required at Screening if the subject's signs and symptoms of EC have persisted since initial diagnosis. A repeat esophagoscopy is required at EOT for all subjects, if this complies with SOC. Additional esophagoscopies are recommended at the Day 42 and 6-Week FU visits only if symptoms have recurred and following local standard practices. Esophagoscopies should be performed at any unscheduled visits, if clinically indicated per local standard practices. Results from all esophagoscopies conducted during the subject's participation in the study should be included in the study database.

14.2.6 Spirometry

A spirometry test will be conducted at Screening or Baseline/Day 1 (prior to treatment) for all ABPA subjects. A repeat spirometry will be conducted at Day 42.

14.2.7 St. George's Respiratory Questionnaire (SGRQ)

For subjects with CPA, the latest available result on the St. George's Respiratory Questionnaire prior to Screening should be recorded on the eCRF as part of their medical history. Additionally, subjects with CPA will be administered the St. George's Respiratory Questionnaire at Screening or Baseline/Day 1 (prior to treatment), Day 90, Day 180, every 3 months while on therapy beyond Day 180, at EOT and at the 6-Week FU visits.

14.2.8 Six-Minute Walk Test and Medical Research Council (MRC) Dyspnea Scale

For CPA subjects, the latest available result on the Six-Minute Walk Test prior to Screening should be recorded on the eCRF as part of their medical history. Additionally, subjects with CPA will undergo a Six-Minute Walk Test at Screening or Baseline/Day 1 (prior to treatment), Day 90, and Day 180. Subject's disability will be graded using the MRC Dyspnea Scale at the same time points.

14.2.9 Recurrence

Recurrence will be assessed at the 25-Day FU visit (25 days after EOT, 32 days after first dose) for subjects with VVC and at the 6-Week FU (42 days after EOT) for all other subjects as a secondary efficacy endpoint. For CPA subjects, recurrence will also be assessed at Day 180.

14.2.10 Survival

Survival status (collected as ACM) will be recorded at Day 30 for IC/candidemia subjects and at Day 42 for all diseases. ACM will be also recorded at Day 84 for subjects with IPA, disseminated/invasive dimorphic fungi and other emerging fungi, and at Day 90, Day 120 and Day 180 for subjects with CPA and ABPA**.** Information on survival status on Days 42, 84, 90, 120 and 180 will be collected for all subjects, irrespective of when treatment was discontinued. If the subject has died, the date and cause of death along with the reporting of SAE details will be recorded on the eCRF.

14.2.11 Assessment of Efficacy

Efficacy procedures will depend on each fungal disease. Efficacy will be assessed primarily in terms of Global Response at TOC for VVC, CMC, CPA and ABPA, and at EOT for all other fungal diseases. Global Response at other time points and Clinical Response and Mycological Response will also be assessed as secondary endpoints. In addition, secondary efficacy assessments will include disease-specific endpoints for selected fungal diseases. See Section 14.2 for detailed efficacy procedures and Section 18.4.1 for a detailed discussion of efficacy assessments.

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

- Clinical signs and symptoms of fungal disease (Section 14.2.1)
- Mycological testing (including, but not limited to, fungal cultures, T2 testing, KOH and other fungal stains) (Section 14.2.2)
- Radiological assessments including esophagoscopy and other imaging scans, as applicable (e.g., X-ray, ultrasound, CT and MRI) (Section 14.2.3 and Section 14.2.5)
- Serological testing (including, but not limited to, GM, *Coccidioides* titers, or ß-D glucan levels) (Section 14.2.4)

Additional procedures (i.e., spirometry, SGRQ, 6-Minute Walk Test and MRC Dyspnea Scale) will be conducted for selected fungal diseases. See Section 14.2.6, Section 14.2.7 and Section 14.2.8, respectively.

14.3 Safety Procedures

14.3.1 Vital Signs

Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate, weight and body temperature, will be measured at Screening, Baseline/Day 1, EOT and unscheduled visits as appropriate. For CPA subjects, weight will also be determined at the Day 180 visit.

14.3.2 General Physical Examination

A general physical exam will be done at Screening and EOT. A general physical exam will also be conducted at the 6-Week FU for all subjects, except VVC subjects. The physical examination will include an abbreviated assessment of general appearance, skin, eyes, heart, chest and abdomen.

14.3.3 Clinical Laboratory Safety Assessments

Clinical laboratory tests will include hematology, blood chemistry and urinalysis.

For all fungal diseases except VVC, samples for clinical laboratory tests will be collected at Screening, every 14 days up to EOT if clinically indicated, at EOT, at the 6-Week FU if clinically indicated, and at unscheduled visits if clinically indicated. If indicated, these may be done more frequently as follow-up to a laboratory abnormality.

In addition to the above, if still on treatment, CPA subjects will have blood drawn on Day 90 and Day 180 for albumin, platelet count, CRP and plasma viscosity assessment.

For VVC subjects, safety labs will be collected at Screening, [redacted] and 25-Day FU (32 days after first dose). Safety labs will be repeated at any unscheduled visit, if applicable.

The following laboratory parameters will be determined:

Hematology

▪ White blood cell (WBC) count[a]	▪ Hemoglobin
▪ Red blood cell (RBC) count	▪ Hematocrit
▪ Platelet count[b]	▪ C-reactive protein[b]
	▪ Plasma viscosity[b]

a: Differential WBC count will include percentages for segmented neutrophils, lymphocytes, monocytes, eosinophils and basophils, and absolute counts for neutrophils, lymphocytes, monocytes, eosinophils and basophils.

b: On Day 90 and Day 180 for CPA subjects only.

Blood Chemistry

▪ Sodium	▪ Glucose
▪ Potassium	▪ Albumin[a]
▪ Alkaline Phosphatase	▪ Aspartate aminotransferase (AST/SGOT)
▪ Chloride	▪ Alanine aminotransferase (ALT/SGPT)
▪ Blood urea nitrogen (BUN)	▪ Gamma glutamyl transferase (GGT)
▪ Creatinine	▪ Lactate dehydrogenase (LDH)
▪ Total creatine phosphokinase (CPK)	▪ Bilirubin (total, direct, and indirect)
▪ Total protein	▪ Prothrombin (PT) and international normalized ratio (INR)

a: On Day 90 and Day 180 for CPA subjects only if still on treatment.

Urinalysis

▪ Appearance (clarity, color)	▪ Glucose
▪ Specific gravity	▪ Ketones
▪ pH	▪ Protein
▪ Blood	▪ Leukocytes
▪ Bilirubin	▪ Urobilinogen

Reflex Microscopic Evaluation

▪ Bacteria	▪ Mucous
▪ Casts	▪ RBC
▪ Crystals	▪ WBC
▪ Epithelial cells	

14.3.4 Adverse Events

All AEs will be collected and evaluated from the time the informed consent is signed throughout the duration of the study and up to the last observation in the study. AEs and SAEs will be reviewed at all scheduled and unscheduled study visits from the time the informed consent is signed. See Section 16.0 for details regarding safety assessment and monitoring.

14.4 Pharmacokinetic Procedures

For subjects who are willing to participate in the PK sampling, up to three (3) blood samples should be collected at the following visits and sampling windows: Day 2 (one sample collected anytime post dosing), Days 3 to 5 (one sample collected predose on any of these days), and Days 7 to 10 (one sample collected predose on any of these days). Additional blood PK samples will be collected when clinically indicated.

Procedures for collecting, storing, and shipping plasma samples for PK are described in the study PK Manual. The sparse samples collected in this study will be analyzed using Population PK (Pop PK) analysis methods to estimate PK parameters (C_{max}, AUC, clearance/fraction absorbed [CL/F]) as applicable. Further analysis of possible metabolites may be performed.

In addition to blood samples, other fluid and tissue samples may be collected for ibrexafungerp PK determination when clinically indicated. Tissue samples collected as part of SOC procedures (e.g., biopsies) may be sent for drug concentration analysis, when available.

15.0 Study Schedules

Detailed schedules of all study visits and procedures for all subjects (except VVC subjects) are presented in Table 14 and detailed schedules of all study visits and procedures for VVC subjects are presented in Table 15.

Table 14 Schedule of Treatment Visits and Procedures (All Fungal Diseases Except VVC)

|PROCEDURE Visit	**Screen[a]**	**BL/ D1[a]**	**D2 (PK Only)**	**D3-D5**	**D7-D10**	**Study Day 14 and then Every 14 days during Tx**	**D42**	**D84[t]**	**D90[u]**	**D120**	**D180**	**EOT**	**Unsch. Visits**	**FU 1[b]** (6-WK)	**FU 2-FU 3[b]**
Days (allowable window)	-1 (-3)	Prior to Tx		±2 d	±2 d	±2 d	±7 d	±7 d	±7 d	±14 d	±14 d	±3 d	AP	± 7d	AP
GENERAL															
Informed Consent	X														
Subject Enrollment and ID Assignment	X														
Medical History and Demographics	X														
Inclusion/Exclusion Criteria	X	X													
Pregnancy Test[s]	X											X			
Prior and Concomitant Medications	X ----------														X
Study Drug Dispensing[c]		X				X									
Study Drug Collection and Accountability Review						X						X	X		
Study Drug Dosing		X	X	X----------									X[d]		
Subject Diary Dispensing and Collection		X				X						X	X		
EFFICACY															
Targeted PE including S&S[v]	X	X				X	X[d]	X[d]	X[e,f]		X[e,f]	X[d]		X[d]	X[f]
Mycological Testing[g,j]	X[d]	X[d]	← X[d] →					X[d]	X[e]		X[e]	X[d]		X[d]	
Imaging[h]	X[d,r]						X[d]	X[d]	X[e,f]		X[e,f]	X[d,i]		X[d,i]	
Serological Testing[j,k]	X[d]	X[d]	← X[d] →				X[d]	X[d]	X[e,f]		X[e,f]	X[d]		X[d]	X[f]
Esophagoscopy[l]	X[m]						X[l]					X[l]	X[l]	X[l]	
Spyrometry	X[f]	X[f]					X[f]								
SGRQ	X[e]	X[e]							X[e]		X[e]	X[e]		X[e]	
6-Minute Walk Test	X[e]	X[e]							X[e]		X[e]				
MRC Dyspnea Scale	X[e]	X[e]							X[e]		X[e]				

|PROCEDURE Visit	**Screen[a]**	**BL/ D1[a]**	**D2 (PK Only)**	**D3-D5**	**D7-D10**	**Study Day 14 and then Every 14 days during Tx**	**D42**	**D84[t]**	**D90[u]**	**D120**	**D180**	**EOT**	**Unsch. Visits**	**FU 1[b]** (6-WK)	**FU 2-FU 3[b]**
Days (allowable window)	-1 (-3)	Prior to Tx		±2 d	±2 d	±2 d	±7 d	±7 d	±7 d	±14 d	±14 d	±3 d	AP	± 7d	AP
Assessment of Recurrence											X[e]			X	
Subject Status (alive/ deceased)							X	X[o]	X[e,f]	X[e, f]	X[e, f]				
Assessment of Efficacy							X[d]	X[d]	X[d]		X[d]	X[d]		X[d]	X[f]
SAFETY															
Vital Signs	X	X									X[p]	X	X		
General Physical exam	X											X		X	
Clinical Laboratory Safety Assessments	X					X[n]	X[n]	X[n]	X[n, e]	X[n]	X[n,e]	X	X[n]	X[n]	
AEs	X----------														----------X
PHARMACOKINETIC															
PK Assessments[q]			X	X	X										

Abbreviations: AE = adverse event; ABPA = allergic bronchopulmonary aspergillosis; AP = as applicable; CPA=chronic pulmonary aspergillosis; d = day; D = Day; EC=esophageal candidiasis; eCRF=electronica case report form; EOT = End of Treatment; FU = Follow-up; ID = identification; IPA = invasive pulmonary aspergillosis; MRC = Medical Research Council; PK=pharmacokinetic; Screen. = Screening; S&S = signs and symptoms; SGRQ = St. George's Respiratory Questionnaire; Tx = treatment; Unsch. = unscheduled; W = Week.

Note: Study days, weeks and months are counted relative to the first dose of study drug (Baseline [Day 1]). For FU visits, weeks, months and years are counted relative to the EOT visit.

a. Screening and Baseline (Day 1) may occur on the same day.
b. FU visits will occur 6 weeks (6-Week FU = FU 1), 3 months (3-Month FU = FU 2) and 6 months (6-Month FU = FU 3) after the EOT visit. FU visits FU 2 and FU 3 will be conducted for ABPA subjects only.
c. For subjects who are not hospitalized.
d. As applicable based on fungal disease.
e. For CPA subjects. Efficacy procedures for CPA subjects will be performed every 3 months following Day 180 if the subject is still on treatment.
f. For ABPA subjects. Efficacy procedures for ABPA subjects will be performed every 3 months following Day 180 if the subject is still on treatment.
g. For urinary tract infections, urine samples for fungal cultures are recommended to be collected every 48-72 hours until negative.
h. In addition to the scheduled time points, imaging scans will be collected anytime during therapy, as clinically indicated.
i. The window for EOT imaging may range from ± 3 to ± 7 days, depending on fungal disease.
j. For subjects diagnosed exclusively by ß-D-glucan tests, the diagnosis should be based on two consecutively positive T2 or ß-D-glucan tests. For those subjects diagnosed based on positive T2 tests, samples for T2 testing will be collected every 48 hours until negative. For those subjects diagnosed based on positive ß-D-glucan tests, samples for ß-D-glucan testing will be collected every 72 hours until negative.
k. For disseminated/invasive dimorphic fungi subjects, serological tests may be conducted at other time points, as clinically indicated.
l. For EC subjects only. A repeat esophagoscopy is required at EOT for all subjects, if allowable per SOC practice. Additional esophagoscopies are recommended at the Day 42 and 6-Week FU visits only if symptoms have recurred and following local standard practices. Esophagoscopies should be performed at any unscheduled visits, if clinically indicated per local standard practices.

|PROCEDURE Visit	**Screen[a]**	**BL/ D1[a]**	**D2 (PK Only)**	**D3-D5**	**D7-D10**	**Study Day 14 and then Every 14 days during Tx**	**D42**	**D84[t]**	**D90[u]**	**D120**	**D180**	**EOT**	**Unsch. Visits**	**FU 1[b]** (6-WK)	**FU 2-FU 3[b]**
Days (allowable window)	-1 (-3)	Prior to Tx		±2 d	±2 d	±2 d	±7 d	±7 d	±7 d	±14 d	±14 d	±3 d	AP	± 7d	AP

m. For subjects who have EC, results of the most recent esophagoscopy that confirmed the diagnosis must be available for Screening. A repeat esophagoscopy is not required at Screening if the subject's signs and symptoms of EC have persisted since initial diagnosis.
n. If clinically indicated.
o. For IPA subjects, subjects with disseminated/invasive dimorphic fungi and subjects with other emerging fungi.
p. At Day 180, weight will be determined for CPA subjects only. No other vital sign measurements will be collected for CPA or any other subjects.
q. Sparse PK samples for Population PK analysis will be collected during the following time windows on Day 2 (anytime post dosing); between Days 3 to 5 (predose) and between Days 7 to 10 (predose). Additional blood PK samples will be collected when clinically indicated. The time of dosing and sample collection must be recorded on the subject diary and eCRF. In addition to blood samples, other fluid and tissue samples may be collected for ibrexafungerp PK determination when clinically indicated. Tissue samples collected as part of SOC procedures (e.g., biopsies) may be sent for drug concentration analysis, when available.
r. Baseline radiological assessments for invasive fungal disease should be performed ideally within 72 hours of Screening. However, assessments performed up to 7 days before/after the first administration of study medication may be used to confirm the diagnosis of the fungal disease if none exists within the ideal window.
s. Pregnancy tests may be conducted more often (e.g., on a monthly basis), per local regulations.
t. For CMC D84 is TOC unless EOT occurs first
u. For CPA and ABPA D90 is TOC unless EOT occurs first
v. Targeted Physical Examinations (clinical evaluation of signs and symptoms) should be performed if subject comes in for PK assessments

Table 15 Schedule of Treatment Visits and Study Procedures for VVC

Study Visit/ Day	**Screen[a]**	**BL/ Day 1[a]**	D4	**EOT** D7	**TOC** D17	**25-DAY FU** D32[b]	**35-DAY FU[c]** D42	**Unsch** Visits
Study Procedures	-1 (-3)	Prior to Tx		Phone/ On-site[c]	± 3 days		Phone/ On-site[c]	
GENERAL								
Informed Consent	X							
Subject Enrollment and ID Assignment	X							
Medical History and Demographics	X							
Inclusion/Exclusion Criteria	X	X						
Pregnancy Test	X							
Prior and Concomitant Medications	X----------						----X	X
Study Drug Dispensing		X						
Study Drug Collection and Review								
Subject Diary Dispensing and Collection		X			X			
EFFICACY								
Targeted PE including Clinical Evaluation of Signs and Symptoms of Infection	X	X		X	X	X	If applic.[d]	
Mycological Testing (fungal culture)	X	If applic.		X	X	X	If applic.[d]	If applic.
Assessment of Recurrence						X		
Subject Status (alive/ deceased)							X	
Assessment of Efficacy				X	X	X	X	
SAFETY								
Vital Signs	X	X		X				X
General Physical exam	X			X				
Clinical Laboratory Safety Assessments	X			X		X		If applic.
Adverse events	X----------							----X
PHARMACOKINETIC								
PK Assessments[e]			X[e]	X[e]				

Abbreviations: applic. = applicable; BL = Baseline; D = day; eCRF = electronic case report Form; EOT = end of treatment; FU = Follow-up; ID = identification; PE = physical exam; PK = pharmacokinetic; Screen = Screening; TOC = test of cure; Tx = treatment; Unsch. = unscheduled.

a. Screening and Baseline/ Day 1 can occur on the same day.
b. The 25-Day FU visit will occur on study Day 32 (i.e., 32 days after the first dose of study drug and 25 days after EOT).
c. The 35-Day FU visit will occur on study Day 42 (i.e., 42 days after the first dose of study

Study Visit/ Day	Screen[a]	BL/ Day 1[a]	D4	EOT D7	TOC D17	25-DAY FU D32[b]	35-DAY FU[c] D42	Unsch Visits
Study Procedures	-1 (-3)	Prior to Tx		Phone/ On-site[c]	± 3 days		Phone/ On-site[c]	

drug and 35 days after EOT). This will be a telephone call and only a full on-site visit if the subject is symptomatic.

d. Vaginal examination and samples for mycological testing to be done if the subject is still symptomatic.

e. For subjects who give consent, sparse PK samples for Population PK analysis should be collected during the following time windows between Days 3 to 5 (predose) and between Days 7 to 10 (predose). The time of dosing and sample collection must be recorded on the subject diary and eCRF. Additional PK samples will be collected when clinically indicated.

16.0 Safety Assessments and Monitoring

16.1 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 will be considered an AE and should be recorded in the eCRF, whether or not it is related to the study drug. For non-fungal infection-related AEs (e.g., bacterial sepsis, bacterial intra-abdominal abscess) the positive cultures related to the AE should also be recorded on the eCRF.

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 (Day 1) that worsen after signing the informed consent or following the initiation of treatment with study medication

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)
- 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

16.2 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.

16.3 Events of Clinical Interest

The following are considered events of clinical interest (ECIs) if they occur after dosing, and must be reported by the site when it becomes aware of the ECI:

- ALT or AST >8 x ULN, if new compared to Baseline, confirmed by repeat testing
- ALT or AST >5 x ULN for more than 2 weeks and if new compared to Baseline, confirmed by repeat testing

- ALT or AST >3 x ULN and total bilirubin >2 x ULN and if new compared to Baseline, confirmed by repeat testing
- ALT or AST >3 x ULN, confirmed by repeat testing, with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)]

16.4 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 diary and in the subject medical record.

16.5 Pregnancy

Female subjects who become pregnant should be immediately discontinued from the study and 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.

16.6 Unexpected Adverse Event

An AE is considered “unexpected” if it is not listed in the Investigator’s Brochure 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 Investigator’s Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s Brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or

as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

16.7 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.

16.8 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 less likely 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.

16.9 Adverse Event Collection Timeframe

For subjects who receive study drug, AEs will be collected and evaluated from the time the informed consent is signed throughout the duration of the study and up to the last observation in the study.

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.

For subjects who experience a severe AE or a SAE that is deemed related to the study drug, a blood sample should be drawn (if possible) for determination of the concentration of ibrexafungerp.

16.10 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.

16.11 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).

16.12 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.

In case of any technical issues in EDC system, the investigator will fill the Paper SAE form, sign it and send the scanned copy via email to the dedicated centralized email ID:

safety.scynexis@awinsals.com or send via Fax +1 844-769-3213 within 24 hours of their awareness. Site can also reach out at AWINSA's safety hotline +1 760-372-7230.

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.

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.

16.13 Procedures for Emergency Unblinding

This is an open-label study.

17.0 Data Collection, Study Monitoring and Record Management

17.1 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, but no later than 5 days after each visit/time point.

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, if allowed per local regulations, a designated sub-investigator, following review of the data in the eCRF, will confirm the validity of each subject's data by signing the eCRF.

17.2 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 (PI) must make all the subject 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.

17.3 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;
- 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 Investigator's Brochure 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;
- a CD or DVD containing final subject CRF 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; and
- monitoring visit log.

17.4 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.

18.0 Analytical Plan

All statistical analyses will be performed using SAS® version 9.3 or later.

Descriptive statistics (i.e., number of subjects, mean, standard deviation, median, minimum, maximum) will be presented for all continuous variables; number and percentage of subjects will be presented for categorical variables. For parameters measured over time, observed data and changes from Baseline will be described for each time point.

All analyses for ibrexafungerp will present the results by fungal disease, disease category and enrollment category. Overall response will be presented for all disease categories combined.

Unless otherwise stated, data will be analyzed as is with no imputation. Details of the statistical analysis will be provided in a statistical analysis plan, which will be approved prior to final database lock.

18.1 Sample Size Determination

This is an exploratory study and no formal sample size calculations will be performed. A total of 220 subjects are estimated to be adequate for an assessment of the safety and tolerability of ibrexafungerp in subjects with documented eligible fungal diseases that have been refractory or resistant to, have relapsed after SOC, or subjects have intolerance to or demonstrated toxicities resulting from an approved SOC antifungal treatment.

18.2 Analysis Populations

The study populations to be used in the analyses are defined as follows:

- Intent-to-Treat Population: The intent-to-treat (ITT) population will include all subjects who are enrolled in the study and receive at least 1 dose of study drug.
- MITT: the Myco-ITT population will include all ITT subjects with confirmed pathogens and who also had all necessary cultures or mycology tests to estimate mycological response.

- Per-Protocol Population**:** The per-protocol (PP) population will include all ITT subjects who receive enough study drug (ibrexafungerp) to enable clinical efficacy judgement as determined by the DRC, who have an EOT (TOC for VVC, CMC, CPA and ABPA) assessment and who have no major protocol violations.
- Safety Population**:** The safety population will include all subjects who receive at least one dose of study medication and have at least one safety assessment post Baseline.
- Pharmacokinetic 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.

18.3 Interim Analyses and Supplemental Analysis

No interim analyses are planned for this study. If subjects on long-term treatment (CMC, ABPA and CPA) are ongoing at the time of planned data base lock, their data up to TOC visit will be included in the analyses, and data collected after TOC will be reported in a Supplementary Analysis.

18.4 Efficacy

18.4.1 Enrollment Categories

The following enrollment categories as detailed in Table 5, will be utilized. Each subject's enrollment reason will be assessed by the DRC and the Investigator:

- Refractory
- Intolerant
- Resistant (includes step-down cases)
- Toxicities
- Relapse

18.4.2 Efficacy Assessments

Response will be assessed by the DRC and by the Investigator. The primary efficacy endpoint of the study is the percentage of subjects who achieve Global Response at TOC for VVC (Day 17), CMC (Day 84), CPA (Day 90), ABPA (Day 90) and at EOT for all other diseases, as determined by the DRC. In cases where EOT for CMC, CPA or ABPA subjects occurs before the planned TOC days, EOT will be TOC assessment. Secondary efficacy endpoints include the percentage of subjects who achieve Global Response, Clinical Response and Mycological Response by pathogen and by disease category (type of fungal disease) at several time points as assessed by the DRC and by the Investigator. The percentage of subjects with a recurrence, ACM and time to death will also be assessed. See Section 9.0 for detailed study endpoints and Section 14.2 for efficacy procedures.

Efficacy outcomes will be based on the definitions captured in Table 16 and Table 17. Criteria for the DRC assessment of response will be further detailed in the DRC Charter. Criteria for the Investigator is outlined in Section 18.4.5.

18.4.2.1 Efficacy Time Points and Outcome Definitions

The efficacy time points and outcome definitions for the primary and secondary endpoints are detailed in Table 16.

Table 16 Efficacy Time Points and Outcome Definitions for Primary and Secondary Endpoints

Fungal disease	**Primary time point** (Secondary time points)	**Primary Outcome Definition**	Secondary Outcome Definitions *(disease-specific outcome definitions, if not previously defined)*[a, e]
Acute or **chronic invasive candidiasis, including candidemia**	**EOT** (EOT, Day 42, 6-Week FU)	**Global Response = Global Response** based on MSG-EORTC outcome response definitions[b, e]	Global Response (as defined) Clinical Response (including radiological outcome) and Mycological Response = Clinical and Mycological Responses based on MSG-EORTC outcome response definitions[b]
Acute or **chronic severe mucocutaneous candidiasis**, including: • **Esophageal candidiasis (EC)** • **Oropharyngeal candidiasis (OPC)** • **Chronic mucocutaneous candidiasis (CMC)** • **Vulvovaginal candidiasis (VVC)**	For EC and OPC: **EOT** (EOT, Day 42, 6-Week FU)	For EC and OPC: **Global Response = Global Response** based on MSG-EORTC outcome response definitions[b]	For EC and OPC: Global Response (as defined) Clinical Response (including radiological outcome if done as SOC) and Mycological Response = Clinical and Mycological Responses based on MSG-EORTC outcome response definitions[b]
	For CMC: **TOC (Day 84 or EOT, whichever occurs first)** (EOT, Day 42, Day 84, 6-Week FU)	For CMC: **Global Response = Global Response** based on MSG-EORTC outcome response definitions[b]	For CMC: Global Response (as defined) Clinical Response (including radiological outcome) and Mycological Response = Clinical and Mycological Responses based on MSG-EORTC outcome response definitions[b]
	For VVC: **TOC (Day 17)** (Day 17, 25-Day FU [Day 32], 35-Day FU [Day 42])	For VVC: **Global Response = Clinical Success**, defined as at least 50% reduction from baseline in total composite score, without use of additional antifungal	For VVC: Global Response (as defined) Clinical Response = Clinical Cure, defined as complete resolution of all signs and symptoms (VSS = 0) without use of additional antifungal (Reference FDA guidelines 2016); Resolved VVC infection (score <3) Mycological Response = mycological eradication for the baseline pathogen Symptom resolution at FU (clinical cure, resolved infection, clinical success) Responder outcome (Clinical Cure and mycological eradication) at TOC and FU

Fungal disease	**Primary time point** (Secondary time points)	**Primary Outcome Definition**	Secondary Outcome Definitions *(disease-specific outcome definitions, if not previously defined)*[a, e]
Disseminated/invasive dimorphic fungi: • Coccidioidomycosis • Histoplasmosis • Blastomycosis	**EOT** (EOT, Day 42, Day 84, 6-Week FU)	**Global Response = Global Response** based on MSG-EORTC outcome response definitions[b]	Global Response (as defined) Clinical Response (including radiological outcome) and Mycological Response = Clinical and Mycological Responses based on MSG-EORTC outcome response definitions[b]
Chronic Pulmonary Aspergillosis (CPA)	**TOC (Day 90 or EOT, whichever occurs first)** (EOT, Day 90, Day 180, every 3 months while on Tx if beyond Day 180, 6-Week FU)	**Global Response = Successful Overall CPA Response**, defined as subjects who are judged to have shown improvement of the disease by clinical, radiological and mycological parameters and those that achieved stable disease after entering the study with a rapidly progressing condition.	Global Response (as defined) Clinical Response = defined as a decrease in the St. George's Respiratory Questionnaire (SGRQ) score by ≥4 points SGRQ outcomes will be categorized as follows: • Improvement: Decrease in SGRQ by ≥4 points • Stability: Change in SGRQ between: increase by <4 to decrease by <4 • Deterioration: Increase in SGRQ by ≥4 point Radiological Response will be assessed using chest CT scan and will be categorized as: • Radiological Improvement: >30% decrease in volume of fungus ball AND/OR 20% decrease in cavity wall thickening AND/OR 20% improvement in pleural thickening. • Radiological Deterioration: >30% increase in volume of fungus ball AND/OR 20% increase in cavity wall thickening AND/OR 20% increase in pleural thickening. Subjects with measurements fulfilling any of the criteria for radiological deterioration will be classified as deteriorated, even if they also fulfil a criterion for improvement. • Radiological Stability: No notable change in radiological image. Mycological Response = reduction in *Aspergillus* IgG by ≥20% AND/OR negative sputum culture for *Aspergillus*

Fungal disease	Primary time point (Secondary time points)	Primary Outcome Definition	Secondary Outcome Definitions *(disease-specific outcome definitions, if not previously defined)*[a, e]
Allergic Bronchopulmonary Aspergillosis (ABPA)	**TOC (Day 90 or EOT, whichever occurs first)** (EOT, Day 90, Day 180, every 3 months while on Tx if beyond Day 180, 6-Week FU)	**Global Response = Composite ABPA Response**, defined as >75% improvement from Baseline in cough and dyspnea, partial (≥50%) or total clearance of chest radiographic lesions (if present prior to treatment initiation), AND decline in serum total IgE by ≥ 25%[c,d]	Global Response (as defined) Clinical Response = >75% improvement from Baseline in cough and dyspnea AND partial (≥50%) or total clearance of chest radiographic lesions (if present prior to treatment initiation Mycological Response = decline in serum total IgE by ≥ 25% ***Disease-specific outcome definitions not previously defined:*** *Clinical Improvement in cough and dyspnea is documented on a four point scale, as follows:* *1. no improvement or worsening;* *2. mild improvement (<25% reduction from Baseline);* *3. moderate improvement (25%-75% reduction from Baseline); and* *4. significant improvement (>75% reduction from Baseline).* *ABPA exacerbation: clinical and/or radiological worsening along with doubling of the serum total IgE over the previous Baseline value* *Asthma exacerbation: clinical worsening in cough and dyspnea with no radiological worsening or doubling of serum total IgE.*
Invasive Pulmonary Aspergillosis (IPA)	**EOT** (EOT, Day 42, Day 84, 6-Week FU)	**Global Response = Global Response** based on MSG-EORTC outcome response definitions[b]	Global Response (as defined) Clinical Response (including radiological outcome) and Mycological Response = Clinical and Mycological Responses based on MSG-EORTC outcome response definitions[b]
• **Other emerging fungi including yeasts and molds** (e.g., **s**achromycetes, scopulariopsis)	**EOT** (EOT, Day 42, Day 84, 6-Week FU)	**Global Response = Global Response** based on MSG-EORTC outcome response definitions[b]	Global Response (as defined) Clinical Response (including radiological outcome) and Mycological Response = Clinical and Mycological Responses based on MSG-EORTC outcome response definitions[b]

Abbrev: ABPA = allergic bronchopulmonary aspergillosis; CMC=chronic mucocutaneous candidiasis; CPA=chronic pulmonary aspergillosis; CT = computed tomography; EC=esophageal candidiasis; EOT=end of treatment; FDA = Food and Drug Administration; FU = Follow-up; Ig = immunoglobulin; IPA = invasive pulmonary aspergillosis; MSG-EORTC = Mycosis Study Group and European Organization for Research and Treatment of Cancer

Fungal disease	**Primary time point** (Secondary time points)	**Primary Outcome Definition**	Secondary Outcome Definitions *(disease-specific outcome definitions, if not previously defined)*[a, e]

Consensus Criteria; OPC=oropharyngeal candidiasis; SGRQ = St. George's Respiratory Questionnaire; TOC = Test of Cure; Tx = treatment; VVC=vulvovaginal candidiasis.

a: See disease-specific secondary endpoints in Section 9.2.2 for disease-specific time points.

b: Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria. Clin Infect Dis. 2008;47(5):674–683. Doi:10.1086/590566

c: Agarwal R, Dhooria S, Singh Sehgal I, et al. A randomized trial of itraconazole vs prednisolone in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. Chest. 2018;153(3):656-664. Doi:10.1016/j.chest.2018.01.005.

d: Agarwal R, Dhooria S, Singh Sehgal I, et al. A randomized trial of voriconazole and prednisolone monotherapy in acute-stage ABPA complicating asthma. Eur Respir J. 2018; in press. Doi:10.1183/13993003.01159-2018.

e: When the MSG_EORTC criteria is not fully applicable for a specific case, the DRC will adjudicate outcome based on acceptable criteria, per their judgement.

As specified in Table 16, the EORTC-MSG[12] outcome definitions will be used for the assessment of efficacy for all fungal diseases except for ABPA, CPA, CMC and VVC. EORTC-MSG general criteria for global responses to antifungal therapy are provided in Table 17.

Table 17 EORTC-MSG General Criteria for Global Responses to Antifungal Therapy with adaptations [a and b]

Global Response	Outcome Criteria
Success	Complete Response: Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease and radiological abnormalities, and mycological evidence of eradication of disease [a] *For subjects who were enrolled for step-down therapy and who were asymptomatic at baseline: no new symptoms or signs suggestive of disease and no new positive cultures.*
	Partial Response: Survival within a prespecified period of observation, improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden, and no new positive cultures, as assessed by a quantitative and validated laboratory marker
Failure	Stable Response: Survival within a prespecified period of observation and minor or no improvement in fungal disease, but no evidence of progression, as determined on the basis of a composite of clinical, radiological and mycological criteria.
	Progression of Fungal Disease: Evidence of progressive fungal disease based on a composite of clinical, radiological and mycological criteria
	Death: Death during the prespecified period of evaluation, regardless of attribution
[b] **Not Evaluable**	Outcome cannot be assessed due to missing data

[a] Definition added for subjects enrolled for step-down therapy

[b] Category added for non-evaluable subjects due to missing data

When the MSG_EORTC criteria is not fully applicable for a specific case, the DRC will adjudicate outcome based on acceptable criteria, per their judgement.

18.4.2.2 Recurrence

Recurrence is defined as Global Response at EOT but re-emergence of the baseline fungal disease during the post treatment follow-up. Re-emergence of the fungal disease is required to be with the same species and involving the same site that was initially identified at Baseline.

Recurrence will be assessed at the 25-Day FU visit (25 days after EOT, 32 days after first dose) for subjects with VVC and at the 6-Week FU (42 days after EOT) for all other subjects as a secondary efficacy endpoint. For CPA subjects, recurrence will also be assessed at Day 180.

18.4.2.3 Survival

Survival status (collected as ACM) will be recorded at Day 30 for IC/Candidemia and at Day 42 for all. ACM will be also recorded at Day 84 for subjects with IPA, disseminated/invasive dimorphic fungi and other emerging fungi, and at Day 90, Day 120 and Day 180 for subjects with CPA and ABPA**.**

Information on survival status on Day 30 (IC/Candidemia), Days 42, 84, 90, 120 and 180 will be collected for all subjects, irrespective of when treatment was discontinued. If the subject has died, the date and cause of death along with the reporting of SAE details will be recorded on the eCRF.

18.4.3 Efficacy Analyses

The primary efficacy endpoint is the percentage of subjects with Global Response (clinical, radiological and mycological) as determined by the DRC at TOC for VVC (Day 17), CMC (EOT or Day 84), CPA and ABPA (EOT or Day 90) (whichever comes first), and at EOT for all other diseases. Results will be presented separately for each disease category along with a 95% confidence interval (CI) for a single binomial proportion in the ITT, Myco-ITT and PP populations where sufficient cases are available. In addition, the number of subjects with a successful response across all disease categories will be summarized as a response rate and 95% CI.

Secondary endpoints will be presented with 95% CIs for the ITT, Myco-ITT and PP populations using the same approach as for the primary endpoint.

The estimated response rates and 95% CIs outlined will also be assessed relative to the external data described in Section 10.1.

The percentage of subjects surviving at the defined time points will be presented for the ITT, Myco-ITT and PP populations. A Kaplan Meier plot will also be produced

summarizing the survival curve over time and the median time to death. A subject without a reported death will be censored at the point of last time the subject was known to be alive.

For primary and overall secondary endpoints, presentations by pathogen will be conducted, if numbers allow.

Data for all subjects will be presented by fungal disease, disease category, reason for enrollment and receipt of combination therapy (Yes/No). If data are missing and the subject has not been deemed a success or failure the outcome will be categorized as unknown/not evaluable.

18.4.4 Data Review Committee

A DRC Charter will provide detailed criteria to be used for the baseline and outcome analysis of subjects in this study. The analysis criteria will be based on EORTC-MSG Consensus Criteria[12] for all diseases except ABPA, CPA, CMC and VVC. Adaptations to the EORTC-MSG criteria adopted by the DRC will be documented in the DRC Charter.

18.4.5 Investigator's Assessment of Overall Response

The Investigator will be asked to provide his/her opinion of the subject's response as follows:

Clinical Response (all non-radiological clinical symptoms and physical findings)**:**

1. Resolution of all attributable clinical symptoms and physical findings (i.e., resolution of all clinical symptoms and physical findings of fungal disease present at Baseline and/or resolution of those that appeared at a subsequent visit)
2. Resolution of some attributable clinical symptoms and physical findings (i.e., resolution of some but not all clinical symptoms and/or physical findings of fungal disease present at Baseline and/or of those that appeared at a subsequent visit)
3. No resolution of any attributable clinical symptoms and physical findings and/or worsening (i.e., no resolution or worsening of any clinical symptoms and/or physical findings of fungal disease present at Baseline and/or of those that appeared at a subsequent visit)
4. Results not available/subject unevaluable (i.e., visit and/or assessment of clinical symptoms and physical findings of fungal disease was not performed at any time point)
5. No attributable signs and symptoms at Screening (i.e., no clinical symptoms or physical findings of fungal disease present at Baseline)

Radiological Response:

1. ≥90% improvement
2. ≥50 to < 90% improvement
3. ≥25 to < 50% improvement
4. < 25% improvement
5. No signs on radiological images at Screening
6. Results not available (i.e., visit and/or radiological assessment was not performed at any time point)

Mycological Response:

1. Eradication (eradication of the original causative organism cultured or identified by histology/cytology/serology at Baseline)
2. Presumed eradication (missing documentation of the eradication of the original causative organism at Baseline plus resolution of all or some clinical symptoms and physical findings of fungal disease present at Baseline and/or of those that appeared at a subsequent visit)
3. Persistence (persistence of the original causative organism cultured or identified by histology/cytology at Baseline or emergence of a new causative organism)
4. Presumed persistence (missing documentation of the persistence of the original causative organism at Baseline plus no resolution or worsening of any clinical symptoms and physical findings of fungal disease present at Baseline and/or of those that appeared at a subsequent visit)
5. No mycological follow-up results available, for whatever reason (no diagnostic test done at any time point)
6. No mycological evidence at Screening (up to Day 7) (any negative diagnostic test(s) obtained or not done at Baseline [from Screening up to Day 7, inclusive])

Mycological response will be confirmed by the DRC and will include central laboratory results.

If relevant mycology findings occur after successful mycological response (proven or presumed eradication), an evaluation will be made as to whether the infection is recurrent (same species as at Baseline) or emergent (different species compared with Baseline). Subjects with recurrent or emergent infection will be classified as mycological failure from the visit onwards where positive cultures were reported, i.e. positive cultures before the FU Visit will be categorized as mycological failure and overall non-successful response on the primary efficacy assessment.

18.5 Pharmacokinetics

18.5.1 Pharmacokinetic Assessments

See Section 14.4 for details.

18.5.2 Pharmacokinetic Analyses

The concentration versus time data from the sparse PK samples collected in this study will be analyzed using a Pop PK model to estimate Cmax, AUC and CL/F, as applicable.

The PK analysis will be conducted on the PK Population.

Further analysis of possible metabolites may be performed.

18.6 Safety

18.6.1 Safety Assessments

Safety will be evaluated throughout the study, including the following parameters: AEs, treatment discontinuations, general physical examination, vital signs, safety laboratory tests and concomitant medications. Prior and concomitant medications are discussed in Section 13.1. Other safety procedures are described in Section 14.3.

18.6.2 Safety Analyses

All safety analyses will be conducted in the safety population; all safety variables will be listed.

Incidence and severity of treatment-emergent AEs, AEs leading to discontinuation and SAEs and their relationship to treatment will be summarized. Also data on AEs leading to death, AEs of special interest, AEs leading to withdrawal and AEs by severity will be summarized.

Early discontinuation of study drug treatment will be presented and will include the reasons for and timing of such discontinuations. Abnormal physical examinations associated with adverse events will be listed. Concomitant medications will be summarized.

Laboratory evaluations will be summarized as observed values and changes from Baseline; shifts with respect to the laboratory reference range will be summarized.

Vital signs will be summarized as observed values and changes from Baseline.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class and preferred term. Concomitant medications will be classified based on the World Health Organization´s (WHO) Drug Dictionary terminology.

19.0 Ethics and Protection of Human Patients

19.1 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 and/or other national and local ethical and legal requirements, as applicable.

19.2 Institutional Review Board/Ethics Committee Review

The PI or 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.

19.3 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 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. In the case of a minor, according to the local definition (e.g., below 16 or 18 years of age), a parent or legal representative should also sign and date the ICF. Additional local regulatory requirements may be applicable for participation of subjects below the age of consent. 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.

19.4 Future Use of Samples

Fungal isolates collected during the study will be sent to a central laboratory and will be maintained for as long as they deem useful to conduct *in vivo* and/or *in vitro* testing of new or existing medication antifungals or analysis of mechanisms of action/resistance.

Human biological samples collected from this study such us plasma or tissue for PK determination of ibrexafungerp or its metabolites and/or fungal pathogen identification will be maintained in a central repository for as long as deemed useful for the specified research purposes.

All samples will be identified only by a coded number to maintain subject confidentiality. Researchers requesting samples or information from the repository must have a research protocol approved by an Institutional Review Board (IRB)/Ethics Committee (EC). Human biological samples will only be retained for subjects who provide consent for future use.

19.5 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.

19.6 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.

19.7 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.

20.0 References

1. Schmiedel Y, Zimmerli S. Common invasive fungal diseases: an overview of invasive candidiasis, aspergillosis, cryptococcosis, and *Pneumocystis* pneumonia. Swiss Med Wkly. 2016; 146:w14281.

2. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care- associated infections. NEJM 2014;370:1198-208.

3. Centers for Disease Control and Prevention [Internet]. Atlanta, GA: Centers for Disease Control and Prevention. Fungal Diseases: Invasive Candidiasis Statistics; [updated 2016 Dec 12; cited 2016 Dec 27]; [about 5 screens]. Available from: http://www.cdc.gov/fungal/diseases/candidiasis/invasive/statistics.html.

4. Farmakiotis D, Kyvernitakis A, Tarrand JJ et al. Early initiation of appropriate treatment is associated with increased survival in cancer patients with *Candida glabrata* fungaemia: a potential benefit from infectious disease consultation. Clin Microbiol Infect [Internet]. 2015 [cited 2016 Dec 27];21(1):79-86. Available from: http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(14)00020-2/pdf. doi: 10.1016/j.cmi.2014.07.006.

5. Larkin E, Hager C, Chandra J, Mukherjee PK, et al. The Emerging *Candida auris*: Characterization of Growth Phenotype, Virulence Factors, Antifungal Activity, and Effect of SCY-078, a Novel Glucan Synthesis Inhibitor, on Growth Morphology and Biofilm Formation. Antimicrob Agents Chemother. 2017 Feb 21.

6. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. CID 2016:62(4):e1-50.

7. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole Treatment for Less-Common, Emerging, or Refractory Fungal Infections. Clin Infect Dis 2003; 36 (9): 1122-1131. doi: 10.1086/374557.

8. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomized double-blind trial. Lancet 2007; 369: 1519–27.

9. Odabasi Z, Mattiuzzi G, Estey E, et al. β- d -Glucan as a Diagnostic Adjunct for Invasive Fungal Infections: Validation, Cutoff Development, and Performance in Patients with Acute Myelogenous Leukemia and Myelodysplastic Syndrome. Clin Infect Dis 2004; 39 (2): 199-205. doi: 10.1086/421944.

10. CLSI. 2012. Reference method for broth dilution antifungal susceptibility testing of yeasts; 4th informational supplement. CLSI document M27-S4. Clinical and Laboratory Standards Institute, Wayne, PA.

11. European Committee on Antimicrobial Susceptibility Testing (EUCAST) Guidelines.

12. Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and

European Organization for Research and Treatment of Cancer Consensus Criteria. Clin Infect Dis. 2008;47(5):674–683. doi:10.1086/590566.

13. Andes DR, Safdar N, Baddley JW et al. Impact of Treatment Strategy on Outcomes in Patients with Candidemia and Other Forms of Invasive Candidiasis: A Patient-Level Quantitative Review of Randomized Trials. Clinical Infectious Diseases 2012;54:80:1110-22.

21.0 Appendices

21.1 Appendix A: Protocol Revision History

21.1.1 Protocol Amendment 3

Current Version and Date: Protocol Amendment 3 (Protocol Version 4.0) dated 21 November 2022. Revision to Protocol dated 13 AUGUST 2019 (Amendment 2) listed below.

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

Protocol Amendment 3	
Main affected Protocol Sections	**Change and Rationale**
○ Synopsis	Updated based on changes listed in this Revision History
○ Background	Updated with more recent information
○ Study Objectives ○ Study Endpoints Overall Description of the study	Additions and clarifications as applicable for fungal diseases. Changes implemented throughout the document
○ Primary study objective ○ Primary endpoints	To evaluate the efficacy of ibrexafungerp in the treatment of severe fungal diseases by a Data Review Committee (DRC) at the primary time point **for the fungal disease** Efficacy as measured by the percentage of subjects with Global Response at TOC for VVC (Day 17), **CMC (EOT or Day 84), CPA (EOT or Day 90) and ABPA (EOT or Day 90) (whichever comes first)** and at EOT for all other diseases as determined by a DRC
○ Overall secondary objectives and ○ Secondary endpoints	○ To determine the efficacy of ibrexafungerp by **fungal disease** and disease category ○ **To evaluate the efficacy of ibrexafungerp by reason for enrollment (refractory, resistance, relapse, intolerance, toxicity, need for oral therapy)** ○ ACM **at Day 30 (Invasive candidiasis and candidemia) and** Day 42 for all diseases
○ Disease specific secondary endpoints	**ADDED - Acute Invasive candidiasis / Candidemia** ○ **Completion of study drug antifungal treatment (i.e. no recurrence, no use of other antifungal treatment, no discontinuation for any reason)** **ADDED Acute or Chronic Severe Mucocutaneous Candidiasis** ○ **Percentage subjects with mycological cure at Day 84** ○ **Percentage subjects with clinical response by Day 30 and Day 84**

Protocol Amendment 3	
Main affected Protocol Sections	**Change and Rationale**
	○ **Percentage of subjects with continued symptom relief at 6-week FU** Chronic Pulmonary Aspergillosis ○ **ADDED Recurrence at Day 180**
○ Study Treatments and overall Description of the Study	Added allowance of re-enrollment in cases of recurrence **Subjects who have a recurrence after TOC (VVC subjects) or EOT (other subjects), may be considered for re enrollment upon discussion with the sponsor** Clarified combination therapy requirement Ibrexafungerp given as combination therapy will be required for all subjects with refractory or relapsing IPA**, mucormycosis and other molds with unpredictable ibrexafungerp activity.**
○ Study Population and enrollment reasons	Clarification of enrollment reasons: Subject has a documented eligible fungal disease that has been refractory **or resistant** to SOC, has relapsed after, or the subject has intolerance to or demonstrated toxicities resulting from an approved SOC antifungal treatment (as defined in Table 5). The subject is also eligible if, in the judgement of the Investigator, long-term IV antifungal therapy is not feasible or desirable due to clinical **(isolate is resistant to or has a high MIC and is unlikely to respond to antifungal SOC)** or logistical circumstances or if other antifungal alternatives are not appropriate
○ Study Procedures	Medical History and Imaging – added **Data available to support inclusion/exclusion criteria collected as SOC prior to signature of the ICF will be collected as appropriate in the EDC** Imaging – updated to remove central reading Radiological assessments should ideally be made by CT scan (HRCT if available) or MRI ~~and all radiological images and local reports pertaining to the fungal disease will be forwarded to the central reading laboratory for independent review.~~ Esophagoscopy – added A repeat esophagoscopy is required at EOT for all subjects, **if this complies with SOC.** Tissue simples - added

Protocol Amendment 3	
Main affected Protocol Sections	**Change and Rationale**
	Tissue samples collected as part of SOC procedures (e.g., biopsies) may be sent for drug concentration analysis, when available.
○ Analytical Plan	Clarified as follows: All analyses for ibrexafungerp will ~~initially~~ present the results by **fungal disease**, disease category **and enrollment category**. **Overall response will be presented** for all disease categories combined.
○ Sample size	Increased from 200 to **220 (+10%)**
○ Analysis Population	Added Myco-ITT and clarified PP ○ **Myco-ITT: the Myco-ITT population will include all ITT subjects with confirmed pathogens and who also had all necessary cultures or mycology tests to estimate mycological response.** ○ Per-Protocol Population: The per-protocol (PP) population will include all ITT subjects who receive **enough study drug (ibrexafungerp) to enable clinical efficacy judgement as determined by the DRC**, who have an EOT (TOC for VVC, **CMC, CPA and ABPA**) assessment and who have no major protocol violations ~~that would impact the assessment of efficacy~~.
○ Interim Analysis and Supplementary Analysis	Added a clause for Supplemental Analyses No interim analyses are planned for this study. **If subjects on long-term treatment (CMC, ABPA and CPA) are ongoing at the time of planned data base lock, their data up to TOC visit will be included in the analysis, and data collected after TOC will be reported in a Supplementary Analysis.**
○ Enrollment Categories	Added **Section 18.4.1 Enrollment Categories** **The following enrollment categories as detailed in Table 5, will be utilized. Each subject's enrollment reason will be assessed by the DRC and the Investigator:** ○ **Refractory** ○ **Intolerant** ○ **Resistant (includes step-down cases – need for oral therapy)** ○ **Toxicities** ○ **Relapse**
○ Efficacy Assessment	Updated as follows: The primary efficacy endpoint of the study is the percentage of subjects who achieve Global Response at TOC for VVC (Day 17), **CMC (Day 84), CPA (Day 90), ABPA (Day 90)** and at

Protocol Amendment 3	
Main affected Protocol Sections	**Change and Rationale**
	EOT for all other diseases, as determined by the DRC. **In cases where EOT for CMC, CPA or ABPA subjects occurs before the planned TOC days, EOT will be TOC assessment.**
○ Efficacy Timepoints and Outcome Definitions for primary and secondary endpoints	Primary Efficacy Timepoints changed as follows: **CMC: TOC (Day 84 or EOT, whichever comes first)** **CPA: TOC (Day 90 or EOT, whichever comes first)** **ABPA: TOC (Day 90 or EOT, whichever comes first)** Outcome definitions changed as follows: ○ EC and OPC Clinical Response (including radiological outcome **if done as SOC)** ○ VVC Primary Outcome Definition: Global Response = Clinical **Success** ~~Improvement~~, defined as **at least 50% reduction from baseline in** ~~complete or partial resolution of signs and symptoms with~~ total composite score ~~not >1~~, without use of additional antifungal ○ VVC Secondary Outcome Definition: Global Response (as defined) Clinical Response = Clinical Cure, defined as complete resolution of all signs and symptoms **(VSS = 0)** without use of additional antifungal (Reference FDA guidelines 2016); **Resolved VVC infection (score <3)** Mycological Response = mycological eradication for the baseline pathogen **Symptom resolution at FU (clinical cure, resolved infection, clinical success)** **Responder outcome (Clinical Cure and mycological eradication) at TOC and FU** EORTC-MSG table for General Criteria for Global Responses to Antifungal therapy (Table 17) – additions as follows: ○ Global Response - Success definition for step-down therapy added: **For subjects who were enrolled for step-down therapy and who were asymptomatic at baseline: no new symptoms or signs suggestive of disease and no new positive cultures.** ○ Partial Response: Survival within a prespecified period of observation, improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden, **and**

Protocol Amendment 3	
Main affected Protocol Sections	**Change and Rationale**
	no new positive cultures, as assessed by a quantitative and validated laboratory marker o Added a category "Not Evaluable" **Not Evaluable – Outcome cannot be assessed due to missing data** o Added a statement: **When the MSG_EORTC criteria is not fully applicable for a specific case, the DRC will adjudicate outcome based on acceptable criteria, per their judgement.**
o Survival	Updated: Survival status (collected as ACM) will be recorded at **Day 30 for IC/Candidemia and** at Day 42 for all.
Protocol Amendment 3	
Administrative and/or General Changes	
o Cover Page, headers and footers	o Updated protocol version details.
o Contact Information o Protocol Approvals	o Updated contact and protocol approval details.
o Spelling and typographic errors	o Corrected throughout
o Section 16.12 SAE Reporting procedures for Investigators	o Contact information for Pharmacovigilance Service Provider and SAE reporting process updated
o References	o Updated reference list.
o Appendices	o Added Protocol Amendment 3 under Revision History (Section 21.1.1) o Renumbered appendices accordingly.

21.1.2 Protocol Amendment 2

Current Version and Date: Protocol Amendment 2 (Protocol Version 3.0) dated 13 AUGUST 2019

Revisions to Protocol dated 23 MAR 2017 (Amendment 1) listed below.

Protocol Amendment 2	
Main Affected Protocol Sections	**Change and Rationale (Major changes shown as underlined font)**
Overall document	Updated protocol organization to current template organization.
o Synopsis	o Updated based on major and minor/general changes listed in this Revision History.
o Schematic of Study Design	o Updated to reflect current study design.
o Background Information	o Updated to describe current ibrexafungerp knowledge.
o Study Objectives o Study Endpoints o Rationale for the study o Overall Description of the Study	o Revised study objectives and endpoints to account for all eligible diseases. o Added disease-specific objectives and endpoints for selected fungal diseases.
o Overall Description of the Study	o Updated to reflect current study design
o Study Duration o Overall Description of the Study	o Updated to a total study duration of approximately 222 days for each subject.
o Inclusion Criteria	o Clarified that subjects must fulfill all inclusion criteria at Screening and/or Baseline (as applicable). o Added the following fungal diseases as eligible for inclusion in the study: ▪ vulvovaginal candidiasis (VVC) ▪ disseminated/invasive dimorphic fungi (coccidioidomycosis, histoplasmosis, blastomycosis) ▪ chronic pulmonary aspergillosis (CPA) ▪ allergic bronchopulmonary aspergillosis (ABPA) ▪ invasive pulmonary aspergillosis (IPA) ▪ other emerging fungi including yeasts and molds (e.g., sachromycetes, scopulariopsis)

Protocol Amendment 2	
Main Affected Protocol Sections	**Change and Rationale (Major changes shown as underlined font)**
	○ Added eligibility criteria for the above-listed fungal diseases. ○ Updated relapse and refractoriness criteria for eligible fungal diseases. ○ Added "and/or legal guardian" to inclusion criteria No. 5 and No. 6. ○ Revised contraception wording.
○ Exclusion Criteria	○ Clarified that subjects will be excluded if they meet any of the exclusion inclusion criteria at Screening and/or Baseline (as applicable). ○ Revised exclusion criterion No. 1 to clarify that subjects will be excluded if they have an invasive fungal disease with central nervous system involvement, unless they are planned to receive combination therapy with ibrexafungerp and other antifungal. ○ Removed exclusion criteria for subjects with VVC and invasive fungal diseases of the bone and/or joint. ○ Removed exclusion criteria based on absolute neutrophil count and QTcF interval.
○ Discontinuation Criteria	○ Added instructions for discontinuation procedures to be conducted depending on time of discontinuation.
○ Study Treatments ○ Overall Description of the Study	○ Added a dedicated section (Study Treatment Groups) for study treatments, as per current protocol template, including subsections with detailed dosing instructions and dietary requirements for: ▪ ibrexafungerp monotherapy for all fungal diseases except VVC ▪ ibrexafungerp monotherapy for VVC, and ▪ ibrexafungerp combination therapy for certain subgroups of subjects ○ Clarified that for subjects on continuous feeding via an NG or PEG tube, the tube should be flushed with approximately 20 mL of water before and after drug administration. ○ Clarified that ibrexafungerp will be packaged in bottles containing 30 tablets and that ibrexafungerp should be stored at a maximum temperature of 25°C with allowable excursions to 30°C.
○ Non-Study Treatments	○ Developed a separate, dedicated section for non-study treatments, as per current protocol template.
○ Prior and Concomitant Medications	○ Revised the time period for recording prior and concomitant medications depending on fungal disease.

Protocol Amendment 2	
Main Affected Protocol Sections	**Change and Rationale (Major changes shown as underlined font)**
	○ Clarified specific time period for recording prior use of immunosuppressants and antifungals.
○ Study Procedures	○ Reorganized study procedures as General Procedures, Efficacy Procedures, Safety Procedures and Pharmacokinetic Procedures to match new order in Schedule of Study Procedures. ○ Added clarification that study days, weeks and months are counted relative to the first dose of study drug (Baseline [Day 1]) and that, for follow-up visits, days, weeks and months are counted relative to the EOT visit. Clarified that Screening and Baseline/Day 1 may occur on the same day.
○ Informed Consent	○ Added "legally authorized representative" as potential person giving consent.
○ Enrollment and ID Assignment ○ Study Rationale ○ Overall Description of the Study ○ Appendix B	○ Added clarification that an Eligibility Form will be used to request eligibility confirmation from the Sponsor. ○ Name changed from "Enrollment Form" to "Eligibility Form". ○ Included updated sample Eligibility Form in Appendix B. ○ Clarified that non-US sites will have a 3 digit ID number for their sites. ○ Clarified subject enrollment may also be approved by a Sponsor designee.
○ Medical History and Demographics	○ Added drug monitoring, if applicable, and details to be collected for ABPA and CPA subjects.
○ Pregnancy Test	○ Added urine testing in addition to serum testing as an option for pregnancy tests and a mandatory pregnancy test at EOT for all female subjects, except VVC subjects. ○ Clarified that pregnancy tests may be conducted more often (e.g., on a monthly basis), per local regulations.
○ Prior and Concomitant Medications	○ Separated AE and medication procedures to accommodate to the new organization of the Schedule of Study Procedures. ○ Cross-referred to Non-Study Treatments section and Appendix B, for clarity.
○ Study Drug Dispensing, Collection and Accountability Review	○ Clarified that, for non-hospitalized subjects excluding VVC subjects, study drug will be dispensed at Baseline/Day 1 and then collected and redispensed every 14 days up to EOT. Also clarified that any unused study drug will be redispensed to the subject.

Protocol Amendment 2	
Main Affected Protocol Sections	**Change and Rationale (Major changes shown as underlined font)**
	o Added dispensing and collection details for VVC (dispensed at Baseline/Day 1 and collected at EOT).
o Study Drug Dosing	o Added entire procedure with overall details for study drug dosing.
o Subject Diaries	o Clarified that, for all subjects except VVC subjects, diaries will be reviewed every 14 days up to EOT and collected and reviewed at EOT. o For VVC subjects, diaries will be collected at TOC.
o Targeted Physical Exam	o Added timepoints specific for each fungal disease. o Clarified that, if a relapse is suspected, the examination should occur before starting any new antifungal treatment.
o Mycological Testing	o Added timepoints and requirements specific for each fungal disease. o Added instructions for urinary tract infections. o Provided general requirements for baseline mycological, identification and susceptibility testing and testing during the study. o Added discussion regarding the requirements for fungal isolates and incorporated table to define Initial, Screening and Study Isolates. o Clarified that, if a relapse is suspected, samples for fungal culture should be collected before starting any new antifungal treatment.
o Imaging	o Added recommended timepoints and requirements specific for each fungal disease. o Clarified radiological requirements for enrollment and for the duration of the study. o Added requirements for bronchoscopies.
o Serological	o Added recommended timepoints and requirements specific for each fungal disease.
o Esophagoscopy	o Clarified timepoints and requirements for EC subjects.
o Spirometry	o Added as new procedure (required for ABPA subjects).
o Saint George's Respiratory Questionnaire	o Added as new procedure (required for CPA subjects).
o Six-Minute Walk Test and MRC Dyspnea Scale	o Added as new procedures (required for CPA subjects).
o Recurrence	o Added as a procedure with timepoints and requirements specific for each fungal disease.
o Survival	o Added as a procedure with timepoints and requirements specific for each fungal disease.

Protocol Amendment 2	
Main Affected Protocol Sections	**Change and Rationale (Major changes shown as underlined font)**
○ Assessment of Efficacy	○ Updated based on current endpoints and added fungal diseases. ○ Moved outcome definitions to the efficacy portion of the Analytical Plan section of the protocol.
○ Vital Signs	○ Added weight to vital sign measurements. ○ Clarified that, for CPA subjects, weight will also be determined at the Day 180 visit.
○ General Physical Examination	○ Clarified that this procedure is not applicable for VVC subjects.
○ 12-Lead ECG	○ ECGs will no longer be conducted for the study. Removed ECG procedure throughout the study.
○ Clinical Laboratory Safety Assessments	○ Added timepoints and requirements specific for each fungal disease and for the determination of ECIs.
○ Adverse Events ○ Adverse Event Collection Timeframe	○ Separated AE and medication procedures to accommodate to the new organization of the Schedule of Study Procedures. ○ Clarified that all AEs will be collected from signature of the informed consent to the last observation in the study.
○ PK Procedures ○ Overall Description of the Study	○ Removed “optional” for Day 2 sampling to clarify that all PK sampling is optional (i.e., for consenting subjects only). ○ Added that additional blood PK samples will be collected when clinically indicated. ○ Clarified that, in addition to blood samples, other fluid and tissue samples may be collected for ibrexafungerp PK determination when clinically indicated.
○ Study Schedules ○ Overall Description of the Study	○ Developed two separate schedules: one for VVC and a separate one for all other fungal diseases. ○ Reorganized study procedures for both schedules as General Procedures, Efficacy Procedures, Safety Procedures and Pharmacokinetic Procedures. ○ <u>For all diseases except VVC</u>: added study visits for Day 42, Day 84, Day 90, Day 120, Day 180, 3-month FU and 6-month FU and added spirometry, SGRQ, MRC Dyspnea Scale, 6-Minute Walk Test, Recurrence, Survival and Study Drug Dosing as study procedures based on revised endpoints and newly incorporated eligible fungal diseases. ○ <u>For VVC</u>: developed a schedule with VVC-specific procedures and the following VVC-specific visits: Day 4, EOT (Day 7), TOC (Day 17), 25-Day FU (32 days after first dose) and 35-day FU (42 days after first dose).

Protocol Amendment 2	
Main Affected Protocol Sections	**Change and Rationale (Major changes shown as underlined font)**
	○ For all fungal diseases: removed 12-lead ECG for all fungal diseases including VVC. ○ Updated schedules based on changes made to the procedure descriptions and footnotes accordingly.
○ Definition of an Adverse Event	○ Clarified that for non-fungal infection-related AEs (e.g., bacterial sepsis, bacterial intra-abdominal abscess) the positive cultures related to the AE should also be recorded on the eCRF.
○ Events of Clinical Interest	○ Clarified that an event will be considered an ECI if it occurs after dosing. ○ Removed QTc elevations as ECIs. ○ Removed INR elevations as ECIs.
○ Causality Assessment	○ Clarified definition for Related AEs as those with a temporal relationship with the study drug that makes causality possible and less likely due to another cause.
○ AE Collection Timeframe	○ Clarified that blood samples should be drawn (if possible) to determine ibrexafungerp concentrations for subjects who experience a severe AE or a SAE if such AE is deemed related to the study drug therapy.
○ SAE Reporting Requirements	○ Clarified that the PI will be responsible for reporting SAEs that require reporting to both local and/or central IRBs.
○ Data Collection and Reporting	○ Clarified that, following review of the data in the eCRF, a designated sub-investigator may confirm the validity of each subject's data if allowed per local regulations.
○ Analytical Plan	○ Clarified that all analyses for ibrexafungerp will initially present results by disease category, and will then present results for all disease categories combined.
○ Sample Size Determination ○ Overall Description of the Study	○ Increased sample size to a total of 200 subjects.
○ Analysis Populations	○ For the PK Population, added that in addition to including all enrolled subjects who provide at least one PK sample, this population will include subjects with no deviations significant enough to affect the interpretability of PK data. ○ The ITT Population was redefined to include all subjects who are enrolled in the study and receive at least 1 dose of study drug.

Protocol Amendment 2	
Main Affected Protocol Sections	**Change and Rationale (Major changes shown as underlined font)**
	○ The PP Population was redefined to include all ITT subjects who receive at least 5 days (1 day for VVC) of study drug (ibrexafungerp), who have an EOT (TOC for VVC) assessment and who have no major protocol violations that would impact the assessment of efficacy.
○ Interim Analysis	○ Added section to clarify that no interims analyses are planned for the study.
○ Efficacy Assessments	○ Added this as an entire new section, based on current protocol template.
○ Efficacy Timepoints and Outcome Definitions	○ Included table of efficacy timepoints and outcome definitions for primary and secondary endpoints for each fungal disease, as follows: ▪ Efficacy timepoint and outcome definitions for the primary efficacy endpoint ▪ Efficacy timepoints and outcome definitions for the overall secondary endpoints ▪ Outcome definitions for disease-specific secondary efficacy endpoints ○ Added EORTC-MSG table of General Criteria for Global Responses to Antifungal Therapy.
○ Recurrence ○ Survival	○ Added as new sections.
○ Efficacy Analyses	○ Updated to address changes in eligible fungal diseases and study endpoints. ○ Revised to clarify that results (percentage with 95% CIs) for the response rates of the primary and secondary endpoints will be presented separately for each disease category, across all disease categories and by pathogen (if numbers allow). ○ Clarified that the estimated response rates and 95% CIs outlined will also be assessed relative to external data. ○ Data for all subjects will be presented by disease category and then by disease category and receipt of combination therapy. ○ Revised confidence interval details to clarify that endpoints will be presented with 95% confidence intervals to fully outline the estimated responses and their uncertainty. ○ Described analyses for ACM and time to death.
○ Data Review Committee	○ Added as new section. ○ Provided summary description of guidelines to be used by the DRC.

Protocol Amendment 2	
Main Affected Protocol Sections	**Change and Rationale (Major changes shown as underlined font)**
○ Investigator's Assessment of Overall Response	○ Incorporated general guidelines for assessment of clinical, radiological and mycological response by the investigators.
○ Pharmacokinetic Assessments ○ Safety Assessments	○ Added as new sections based on current protocol template.
○ Safety Analyses	○ Clarified that summary tables by severity will be provided for AEs leading to death, AEs of special interest, AE's leading to withdrawal and AEs. ○ Removed ECG from safety variables.
○ Informed Consent	○ Added clarification that in the case of a minor, according to the local definition (e.g., below 16 or 18 years of age), a parent or legal representative should also sign and date the ICF and that additional local regulatory requirements may be applicable for participation of subjects below the age of consent.
○ Future Use of Samples	○ Added as new section based on current protocol template.
○ Prohibited Medications and Medications to be administered with Caution ○ Appendix B	○ Clarified that no antifungal treatment other than the study drug is allowed during the study except in subject subgroups where combination therapy is allowed or where an exception was granted by the Sponsor on a per-subject basis. ○ Clarified that 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. ○ Clarified that 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, and that additional ibrexafungerp PK and/or therapeutic drug monitoring may be needed in these cases. ○ Added fluconazole as a prohibited medication and clarified that fluconazole, itraconazole, posaconazole and voriconazole are prohibited except in subject subgroups where combination therapy is allowed or where an exception was granted by the Sponsor on a per-subject basis. ○ Updated windows for prohibited medications. ○ Updated medications to be taken with caution. ○ Removed CYPC8 Substrates as prohibited medications. ○ Added vinblastine and talinolol as prohibited P-gp substrates.

Protocol Amendment 2	
Main Affected Protocol Sections	**Change and Rationale (Major changes shown as underlined font)**
	o Removed moderate CYP3A4 inhibitors and OATP1B3. substrates as medications to be administered with caution. o Clarified that the administration of either sirolimus or tacrolimus should be offset by no less than 2 hours with the administration of ibrexafungerp. o Clarified that 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. o Added tacrolimus to the list of drugs for which dosing adjustments and subsequent monitoring should be undertaken in accordance with product prescribing information for the respective agents.
o Appendix C	o Updated the sample eligibility form and clarified that eligibility form provided is a sample form that may be modified as needed.
o Appendix D	o Added Vulvovaginal Signs and Symptoms (VSS) Scale.

Protocol Amendment 2	
Minor, Administrative and/or General Changes	
o Global Changes	o Changed “SCY-078” to “ibrexafungerp”. o Changed “Treatment Day” to “Day”. o Changed “Data Monitoring Committee” to “Data Review Committee”. o Changed “Week-6 FU” to “6-Week FU”. o Minor stylistic changes.
o Cover Page, headers and footers	o Updated protocol version details.
o Contact Information o Protocol Approvals	o Updated contact and protocol approval details.
o Abbreviations	o Updated list of abbreviations and abbreviations used in text.
o References	o Updated reference list.
o Appendices	o Moved Revision Histories to Appendix A.

Protocol Amendment 2	
Minor, Administrative and/or General Changes	
	o Renumbered appendices accordingly.

21.1.3 Protocol Amendment 1

Current Version and Date: Protocol Amendment 1 (Protocol Version 2.0) dated 23 Mar 2017

Revisions to Protocol dated 30 Nov 2016 (original protocol) listed below:

MAJOR CHANGES	
Main Affected Protocol Sections	**Change and Rationale** (Major changes shown as underlined font)
o Inclusion Criteria o Table of Eligible Fungal Diseases o Other sections as applicable	Added clarification that subjects may be male or female and updated definition of eligible fungal diseases for clarity as follows: 2. Subject has a documented eligible acute or chronic invasive candidiasis (including candidemia) and/or acute or chronic severe mucocutaneous candidiasis (excluding VVC) (as defined in Table 1) that is refractory to or intolerant of, or has toxicities associated with at least one approved Standard of Care (SoC) antifungal treatment. The subject is also eligible if, in the judgement of the investigator, long-term IV antifungal therapy is not feasible or desirable due to clinical or logistical circumstances or if other oral antifungal alternatives are not appropriate. Added requirements for alternative diagnostic criteria for invasive candidiasis, as follows: Or Alternative approved diagnostic method such as T2 or ß-D-glucan (two consecutive positive test results) and at least one of the following: temperature ≥38°C or <36°C, systolic blood pressure <90 mmHg or a decrease of >30 mmHg from normal baseline, local signs or symptoms or radiologic findings of invasive candidiasis Revised refractoriness criteria based on ß-D-glucan to clarify that elevated values (rather than persistently high values) equal to or increasing from baseline meet criteria for refractory invasive candidiasis including candidemia.

MAJOR CHANGES	
Main Affected Protocol Sections	**Change and Rationale** (Major changes shown as underlined font)
	Revised requirements for acceptable contraceptive methods and added definitions of male and female subjects who are not of reproductive potential, for clarity. Clarified women of childbearing potential must have a negative pregnancy test before enrollment.
o Exclusion Criteria	Added an exclusion criterion to clarify that subjects with invasive fungal disease of the bone and/or joint are excluded if they are expected to require treatment for more than 90 days. Added an exclusion criterion to clarify that subjects with vulvovaginal candidiasis are not eligible for the study except for subjects with chronic mucocutaneous candidiasis including vulvovaginal involvement. Deleted the exclusion criterion excluding subjects with a life expectancy $\leq$ 3 days. Clarified that subjects with unconjugated hyperbilirubinemia with diagnosis of Gilbert's disease are not excluded. Removed exclusion criterion that allowed neutropenic patients to participate in the study if they were expected to recover in 3-5 days following initiation of G-CSF treatment.
o Study Objectives o Other sections as applicable	Efficacy objectives revised based on updated definitions of treatment outcomes (see Study Procedures, Efficacy Assessments). Efficacy exploratory objective simplified. Pharmacokinetic exploratory objective revised as follows: • To evaluate the pharmacokinetics (PK) of SCY-078 by population PK analysis

MAJOR CHANGES	
Main Affected Protocol Sections	**Change and Rationale** (Major changes shown as underlined font)
○ Study Endpoints ○ Other sections as applicable	Efficacy endpoints revised based on updated definitions of treatment outcomes (see Study Procedures, Efficacy Assessments). Primary efficacy endpoint revised as follows: • Efficacy as measured by the percentage of subjects with global success (complete or partial global response) at EoT as determined by the DMC Efficacy endpoints revised to clarify that outcomes will be determined by the DMC. Primary safety endpoint added. Pharmacokinetic exploratory endpoint revised as follows: • SCY-078 plasma concentrations by population PK analysis
○ Study Procedures, Targeted Physical Examination, including Clinical Evaluation of Signs and Symptoms ○ Other sections as applicable	Clinical evaluation of signs and symptoms included under targeted physical examination for convenience. Signs and symptoms of infection revised as follows: • General signs and symptoms: ○ Fever defined as oral temperature ≥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 a >30 mmHg decrease below normal baseline) ○ Tachycardia ○ Local signs and symptoms of inflammation • Disease-specific signs and symptoms: ○ OPC: White patches or plaques on the tongue and other oral mucous membranes; redness or soreness in the affected areas; difficulty swallowing; cracking at the corners of the mouth (angular cheilitis) ○ EC: White plaques and/or ulcers on the lining of the esophagus or narrowing of the lumen, pain when swallowing, difficulty swallowing; heartburn ○ CMC: Extensive scaling, skin lesions, thickened nails • Other signs and symptoms of candidiasis

MAJOR CHANGES	
Main Affected Protocol Sections	**Change and Rationale** (Major changes shown as underlined font)
○ Study Procedures, Study-specific Testing, Mycological Testing ○ Other sections as applicable	Clarified mycological testing procedures to be performed during the study for eligible fungal diseases, as follows: Blood cultures: […] Blood should be drawn peripherally [directly from a vein]; however, if this is not possible, blood may be drawn from a central IV catheter). […] Non-blood cultures: Follow-up cultures from subjects who have non-blood sites of *Candida* infection should be performed as clinically indicated. EC: Follow-up KOH or fungal stains and/or mycological cultures from biopsy or brushing indicating yeast infection will be performed as clinically indicated. OPC and CMC: Follow-up KOH or fungal stains and/or mycological cultures for *Candida* spp. obtained from the affected site will be performed as clinically indicated. Clarified that local identification and susceptibility testing may be done according to the local lab´s standards and that central testing will be done as per CLSI M27-A3 guidelines.
○ Study Procedures, Study-specific Testing, Radiological Testing and Esophagoscopy	Study procedure identified as “Radiological Testing” changed to “Imaging” for clarity. Clarified that, for subjects whose diseases are assessed by imaging or esophagoscopy, imaging scans/esophagoscopies must be available at Screening and must be performed for End of Treatment. The remaining imaging scans/esophagoscopies may be done as clinically indicated.

MAJOR CHANGES	
Main Affected Protocol Sections	**Change and Rationale** (Major changes shown as underlined font)
○ Study Procedures, Pharmacokinetic Assessments ○ Other sections as applicable	PK sampling times and windows clarified, as follows: Up to three (3) blood samples will be collected at the following visits and sampling windows: Treatment Day 2 (one sample collected anytime post dosing [optional]), Treatment Days 3 to 5 (one sample collected predose on any of these days), and Treatment Days 7 to 10 (one sample collected predose on any of these days)
○ Study Procedures, 12-Lead Electrocardiogram ○ Other sections as applicable	Visit 4 ECG assessment removed
○ Study Procedures, Efficacy Assessments ○ Other sections as applicable	Updated definitions for the assessment of treatment outcomes for consolidation with other protocols in the SCY-078 development program, as follows: Global outcome will be scored as global success (complete global response or partial global response) or global failure (stable disease or progressive disease) Global success: Global success is defined as a complete global response or a partial global response • Complete global response is defined as a complete clinical response (the resolution of all clinical signs and symptoms and/or radiological abnormalities from baseline attributable to *Candida* infection) and a mycological response (mycological clearance (direct and/or negative cultures [when obtainable] and/or normal serological results [when appropriate]) • Partial global response is defined as a partial clinical response (major improvement of all clinical signs and symptoms and/or radiological abnormalities from baseline attributable to *Candida* infection) and a mycological response (mycological clearance (direct and/or negative cultures [when obtainable] and/or normal serological results [when appropriate]) Global failure: Global failure is defined as either stable disease and/or progressive disease

MAJOR CHANGES	
Main Affected Protocol Sections	**Change and Rationale** (Major changes shown as underlined font)
	• Stable disease is defined as minor or no clinical improvement but without deterioration and/or unchanged serological response. • Progressive disease is defined as clinical deterioration necessitating alternative antifungal therapy or resulting in death, and/or worsened serological response, and/or persistence of fungal infection on the basis of culture, microscopic evaluation, or histopathological testing. Clinical success: clinical success is defined as a complete clinical response or a partial clinical response. Mycological success: mycological success is defined as a mycological response. Added definition of recurrence for completion and a summary list of the procedures that will be performed to assess treatment outcome.
○ Study Procedures, Subject Discontinuation Criteria	Added pregnancy as a subject discontinuation criterion.
○ Dosing and Drug Accountability Procedures, Prior and Concomitant Medications & Prohibited Medications and Medications to be Administered with Caution ○ Appendix A	Clarified that subjects will record all concomitant medications used in the subject diary. Clarified that all medications used from 28 days before enrollment through the EoT visit will be recorded and that only the use of antifungal medications, antibiotics for any reason or medications to treat an AE will be recorded after EoT and through the Week 6 Follow-up visit. Clarified that no antifungal medications other than the study drug are allowed during the study treatment. Revised requirements for the timing of sirolimus and tacrolimus administration.
○ Dosing and Drug Accountability Procedures, Dietary Requirements for	Clarified that the study drug should be taken with approximately 8 oz/240 mL of water, preferably with food. For subjects on continuous feeding via an NG or PEG tube, the drug should be crushed and administered with approximately 8 oz/240 mL of water and the tube should be flushed with

MAJOR CHANGES	
Main Affected Protocol Sections	**Change and Rationale** (Major changes shown as underlined font)
Study Drug Administration o Other sections as applicable.	approximately 8 oz/240 mL of water before and after drug administration.
o Safety Assessments and Monitoring, Events of Clinical Interest	Removed reporting timeframe requirement for and revised list of events of clinical interest for clarity, as follows: • QTc > 500 ms or a > 60 ms change from Baseline, confirmed by repeat testing • ALT or AST > 8 x ULN, if new compared to Baseline, confirmed by repeat testing ALT or AST > 5 x ULN for more than 2 weeks and if new compared to Baseline, confirmed by repeat testing • ALT or AST > 3 x ULN **and** either total bilirubin >2 x ULN or INR >1.5) and if new compared to Baseline, confirmed by repeat testing • ALT or AST > 3 x ULN, confirmed by repeat testing, with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
o Safety Assessments and Monitoring, Overdose	Clarified that an overdose is any dose higher than the protocol-specified dose and that overdoses should be reported within 24 hours if associated with a serious adverse event and within 5 working days otherwise.
o Safety Assessment and Monitoring, AE Collection Timeframe o Other sections as applicable	Clarified that AEs will be collected and evaluated from the time the informed consent is signed through the EoT and that, after the EoT and up to the last observation in the study (Week 6 Follow-up), new AEs will be collected only if deemed related to the study drug, if they are SAEs, or if they are related to a fungal infection.
o Safety Assessments and Monitoring, SAE Reporting	Updated requirements and details for the reporting of serious adverse events.

MAJOR CHANGES	
Main Affected Protocol Sections	**Change and Rationale** (Major changes shown as underlined font)
○ Analytical Plan, Sample Size Determination	Updated the planned sample size to a total of 60 subjects.
○ Analytical Plan, Efficacy Analyses	Revised confidence interval details to clarify that endpoints will be presented with 95% confidence intervals.
○ Ethics and Protection of Human Subjects, Declaration of Helsinki	Revised language to include ICH GCP guidelines, US and EU regulations and other local requirements as applicable, in addition to the Declaration of Helsinki.
○ Appendix B, Enrollment Form	Updated the Enrollment Form for the study.

MINOR AND/OR GENERAL CHANGES	
○ Abbreviations	Updated list of abbreviations and abbreviations used in text.
○ Synopsis	Updated based on major and minor/general changes listed in this Revision History Included only key inclusion and exclusion criteria for clarity and convenience. Revised storage conditions for SCY-078 tablets to clarify that tablets do not need to be protected from moisture. Additional revisions made (language added or removed) for consistency with the body of the protocol amendment.
○ Schematic of Study Design	Clarified that the End of Treatment visit will occur following a maximum of 90 days of treatment with SCY-078 and that Survival visits will occur 42 and 84 days after Baseline/Treatment Day 1.
○ Background Information ○ Rationale for the Study	Updated to reflect the latest, currently available data for SCY-078.
○ Rationale for the Study ○ Study Design	Updated to reflect major and minor/general changes listed in this Revision History.

MINOR AND/OR GENERAL CHANGES	
○ Inclusion and Exclusion Criteria	Reorganized inclusion and exclusion criteria from key, protocol-specific criteria to standard, general criteria, and renumbered criteria accordingly.
○ Study Procedures ○ Study Schedule	Reorganized and updated description of study procedures for clarity and to ensure consistency with the Schedule of Visits and Procedures and vice versa. Added a ±2 day window to the every-14-day visit, the End of Treatment visit and the Week 6 Follow-up visit.
○ Ethics and Protection of Human Subjects, Financial Disclosure	Clarified timing for collection of financial disclosure forms.
○ References	Updated bibliographic cross references and citations.
Miscellaneous	Updated protocol date and version. The following changes were made for clarity and for internal consistency and consistency with other protocols in the SCY-078 development program • Changed “proportion” to “percentage” in Study Endpoints • Changed “microbiological” to “mycological” throughout • Changed “radiographic” to “radiological” • Changed “biochemistry” to “blood chemistry” for safety laboratory tests • Changed “patient(s)” to “subject(s)” • Changed “Data Review Committee (DRC)” to “Data Monitoring Committee (DMC)” • Changed “Week 6 (follow up)” to “Week 6 Follow-up” • Changed “Baseline” and “Treatment Day 1” to “Baseline/Treatment Day 1” Introduced minor typographical and grammatical edits and reworded language slightly as needed for clarity.

21.2 Appendix B: Prohibited Medications and Medications to be Administered with Caution

21.2.1 Prohibited Medications

No antifungal treatment other than the study drug is allowed during the study except in subject subgroups where combination therapy is allowed or where an exception was granted by the Sponsor on a per-subject basis.

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. Additional ibrexafungerp PK and/or therapeutic drug monitoring may be needed in these cases.

Strong CYP3A4/5 inhibitors and CYP3A4/5 inducers

CYP	Strong/Moderate Inhibitors		Inducer[a]
3A4/5	Reversible inhibitors:[b]		• avasimibe
	• boceprevir	• nefazodone	• carbamazepine
	• conivaptan	• nelfinavir	• phenytoin
	• indinavir	• telaprevir	• rifampin
	• ketoconazole[c]	• telithromycin	• St. John's wort
	• lopinavir/ritonavir	• itraconazole[c]	
	• mibefradil	• posaconazole[c]	
	• fluconazole[c]	• voriconazole[c]	
	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 14 days prior to enrollment and during study treatment.

b. The reversible CYP3A4/5 inhibitors listed in this table are not permitted during 48 hours prior to the administration of ibrexafungerp (except for the antifungal drug administered for the eligible fungal disease), and during the study.

c. No antifungal treatment other than the study drug is allowed during the study. Fluconazole, itraconazole, posaconazole and voriconazole are prohibited except in subject subgroups where combination therapy is allowed or where an exception was granted by the Sponsor on a per-subject basis.

P-glycoprotein (P-gp) substrates

P-gp Drug Substrate[a]
digoxin, colchicine, vinblastine, talinolol

a. The P-gp substrates listed in this table are not permitted during the administration of ibrexafungerp.

21.2.2 Medications to be administered with Caution and Monitored as Appropriate

CYP3A4 substrates

CYP	Substrates
3A4	*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.

Sources:

- FDA Draft Guidance for Industry. Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling. 2012.
- Drug interactions in infectious disease by Stephen C. Piscitelli, Keith Rodvold (2007).
- UCSF-FDA Transportal.

21.3 Appendix C: Sample Eligibility Form

Note: The eligibility form shown below is a sample form. This form may be modified as needed for specific fungal diseases and per local regulations.

21.4 Appendix D: Vulvovaginal Signs and Symptoms Scale

SIGNS:

To be rated by the Investigator during the vulvovaginal examination

Sign	Absent 0	Mild 1	Moderate 2	Severe 3
Edema				
Erythema				
Excoriation or fissures				

Definitions:

Absent: none

Mild: slight

Moderate: definitely noticeable

Severe: marked, intense

SYMPTOMS:

To be rated by the subject

Symptom	Absent 0	Mild 1	Moderate 2	Severe 3
Burning				
Itching				
Irritation				

Definitions:

Absent: I have no discomfort (i.e., burning, itching, irritation)

Mild: I have some discomfort (i.e., burning, itching, irritation), but it does not bother me much

Moderate: I have discomfort (i.e., burning, itching, irritation), which is annoying, but not enough to affect what I am doing

Severe: I have discomfort (i.e., burning, itching, irritation), which is annoying enough to affect what I am doing