STATISTICAL ANALYSIS PLAN

SCYNEXIS, Inc.

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 Clinical Protocol No. SCY-078-301

Date and Version: 8 April 2024 / Version 1.1

STATISTICAL ANALYSIS PLAN

SIGNATURE PAGE

SCYNEXIS, Inc.
1 Evertrust Plaza
Jersey City, NJ 07302

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 Clinical Protocol No. SCY-078-301

STATISTICAL ANALYSIS PLAN DOCUMENT HISTORY

Version Number	Author	Date	Change
Draft		21Dec2022	Initial
Final 1.0		14Apr2023	NA

Version Number	Author	Date	Change
Final 1.1		8April2024	Section 3.2 – Update definition of Per-Protocol Population to clarify major protocol violations. Section 6.2.2 – Clarified that the missed dose information is located in the Missed Dose Log when calculating compliance. Section 7 – Clarification around baseline enrollment categories and determination of the potential impact of protocol deviations on the efficacy-related outcomes. Table 5 – Clarification around definitions used for Global, Clinical, and Mycological Response. Section 7.1.1 – Clarification on TOC definition for CMC, CPA, and ABPA subjects. Addition of the Step-down baseline enrollment category determined by the PI. Section 7.2 – Clarification around how survival status information was collected and how censoring was performed. Table 7 – Addition of VVC specific endpoints to be consistent with the information in Table 5. Section 7.2.3 – Clarification around mycological response definitions and alignment with protocol versions. Section 8.2.1 – Clarification around how child-bearing potential information was collected.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABPA	allergic bronchopulmonary aspergillosis
ACM	all-cause mortality
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate transaminase
BID	twice a day
BMI	body mass index
CI	confidence interval
CMC	chronic mucocutaneous candidiasis
CPA	chronic pulmonary aspergillosis
CRF	case report form
CSR	clinical study report
DRC	data review committee
EC	esophageal candidiasis
ECG	electrocardiogram
eCRF	electronic case report forms
e-diary	electronic diary
EOT	end of treatment
ET	early termination
HR	heart rate
IPA	invasive pulmonary aspergillosis
ITT	Intent-to-Treat
IV	intravenous
LOCF	last observation carried forward
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MSG-EORTC	Mycosis study group and European organization for research and treatment of cancer consensus criteria
n	number of subjects
OPC	oropharyngeal candidiasis
PK	pharmacokinetics
PP	Per Protocol
PT	preferred term
QD	once daily
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TOC	test of cure

WHO Drug	World Health Organization Drug Dictionary
VVC	vulvovaginal candidiasis

1. Introduction

Ibrexafungerp (formerly "SCY-078") is a member of a new class of antifungal agents that 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.

Although four classes of antifungal agents are currently available to treat fungal 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 and the toxicity associated with polyenes, signals the need for new agents that are well tolerated and that retain activity against resistant strains. Ibrexafungerp has been shown to retain activity 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 genus and, as such, would represent the first 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.

Ibrexafungerp has been evaluated by numerous independent laboratories against an extensive panel of clinically relevant yeast and mold isolates. Overall, the epidemiological studies have demonstrated that ibrexafungerp has potent, broad-spectrum activity against the majority of the clinical isolates tested laying the foundation in support of the use of ibrexafungerp for the treatment of invasive fungal diseases.

This study aims to provide evidence of the efficacy and evaluate the safety and Pharmacokinetics (PK) of oral SCY-078 in the treatment of subjects with 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.

The purpose of this statistical analysis plan (SAP) is to ensure the statistical methodologies that will be used are complete and appropriate to allow valid conclusions regarding the study objectives. Results obtained from the analyses outlined in this document will be the basis of the final clinical study report (CSR) for this protocol.

2. Study Objectives

2.1 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 timepoint for the fungal disease
- To evaluate the safety of ibrexafungerp

2.2 Secondary Objectives

2.2.1 Overall Secondary Objectives

The overall secondary objectives of the study 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 (type of fungal disease)
- 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

2.2.2 Disease-Specific Secondary Objectives

- To evaluate the efficacy of ibrexafungerp as determined by other disease-specific endpoints (Table 7)

2.3 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 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 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, for a maximum of 180 days. A summary of the overall treatment and follow-up schedule for these subjects is provided in Table 1.

Table 1 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], Day 17 (TOC), 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 2.

Table 2 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 invasive pulmonary aspergillosis, 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 [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.

2.4 Study Timepoints

Detailed schedules of all study visits and procedures for all subjects (except VVC subjects) are presented in Table 3 and detailed schedules of all study visits and procedures for VVC subjects are presented in Table 4.

Table 3 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}	

|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
6-Minute Walk Test	X[e]	X[e]							X[e]		X[e]				
MRC Dyspnea Scale	X[e]	X[e]							X[e]		X [e]				
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.

|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

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.

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.

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 4 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]								

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]	

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 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 [redacted]. 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.

3. General Statistical Considerations

Continuous data will be described using descriptive statistics (i.e. number of subjects, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be described using the subject count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." Data will be displayed in all listings sorted by disease category.

All analyses for ibrexafungerp will present the results by fungal disease, disease category (Table 5), and enrollment category. Overall response for global, clinical, and mycological responses will be presented for all disease categories combined.

Unless otherwise specified, baseline will be defined as the last non-missing assessment prior to or on the date (and time if appropriate) of the first dose of study drug. Change from baseline is defined as: post-baseline value – baseline value. For parameters measured over time, observed data and changes from baseline will be described for each time point.

The study day will be calculated as follows:

If the assessment date occurs on or after the date of the first dose of study drug:

Study day = assessment date – first dose date + 1.

If the date of interest occurs before the date of the first dose of study drug:

Study day = assessment date – first dose date

There is no study day 0.

All analyses will be conducted using SAS® Version 9.4 or higher. All statistical tests will be two-sided and interpreted at a 5% significance level.

3.1 Determination of Sample Size

This is an exploratory study and no formal sample size calculations was performed. A total of 220 subjects (+10%) 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 or subjects have intolerance to or demonstrated toxicities resulting from an approved SOC antifungal treatment.

3.2 Analysis Populations

The analysis populations to be used in the analysis 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 study drug (ibrexafungerp) to enable clinical efficacy judgement as determined by the DRC, who have an EOT (TOC for VVC, CMC, CPA and ABPA as applicable) assessment and who have no major protocol violations that could impact the assessment of efficacy (Refer to Section 7).

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 pharmacokinetic (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.

3.3 General Handling of Missing Data

For incomplete dates related to concomitant medications, the dates will be imputed as follows:

If the incomplete date is a start/onset date:

(1) if the month and year are present, then the first day of the month will be used for day.
(2) if only the year is present, then the first day of January will be used for month and day.

If the incomplete date is an end date:

(1) if the month and year are present, then the last day of the month will be used for day.
(2) if only the year is present, then the last day of December will be used for month and day. If the reported year is the same as the informed consent year, then the informed consent date will be used.

Dates that are completely missing will not be imputed.

Baseline values that are missing will not be imputed. Subjects who have missing subgroup values will not be included in that particular subgroup analyses.

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

4. Subject Disposition

4.1 Disposition

A disposition of subjects will include the number of enrolled subjects and the number and percentage of subjects for the following categories: subjects in each analysis population, subjects who completed EOT/TOC visit (as applicable), subjects who completed the study, subjects who discontinued from the study, and the reasons for discontinuations will be presented by disease category and overall for all subjects.

The reason for study discontinuation may include any of the following: adverse event; death; disease relapse; progressive disease; lost to follow-up; physician decision; pregnancy; withdrawal by subject; other.

Subject disposition data will be presented in a listing.

4.2 Protocol Deviations

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study.

Major protocol deviations will be defined in the significant protocol deviations rules document. Each significant deviation will be assigned a rule number. As the study is ongoing, additional significant protocol deviations can also be spontaneously identified or defined by the sponsor and/or the project team during the regularly planned study deviation review meetings and the significant protocol deviations rules document can be updated.

All protocol deviations will be reviewed and assessed as to significance prior to the database lock. The list of protocol deviations (major or minor) that are additionally considered major clinically relevant for the purposes of analysis will also be identified and documented prior to the database lock.

All major protocol deviations will be summarized for all enrolled subjects. Major protocol deviations will also be presented in a listing.

5. Demographics and Baseline Characteristics

5.1 Demographics

Demographics such as age, sex, race, ethnicity, BMI, and reason for enrollment will be summarized descriptively for the ITT Population. The age collected in CRF will be used for analysis if it is non-missing. If the age is not collected in the CRF, the age in years is calculated using the date of the informed consent and date of birth.

$$\text{Age (years)} = [(\text{Informed Consent Date} - \text{Date of Birth} + 1) / 365.25].$$

BMI is calculated as:

$$\text{BMI} = (\text{body weight in kilograms}) / (\text{height in meters})^2.$$

Demographics for all subjects in the ITT set will be presented in a listing.

5.2 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) March 2023, version 26.0 and listed by System Organ Class (SOC), Preferred Term (PT), and verbatim term. Medical history will also be summarized by disease group using frequencies and percentages with SOCs sorted in alphabetical order and PTs within each SOC in descending order of frequency for all subjects in the ITT population.

A by-subject listing of medical history will be provided.

5.3 Inclusion and Exclusion Criteria

Prior to enrollment, the investigator will assess if the subject fulfills all of the inclusion and none of the exclusion criteria outlined in the protocol (sections 11.1 and 11.2). The specific inclusion criterion not met or exclusion criterion which was met will be recorded in the eCRF. This information and whether the sponsor granted a waiver will be presented in a listing.

6. Treatment and Medications

6.1 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.

All prior and concomitant medications will be coded using the current version of the World Health Organization Drug Dictionary Enhanced (WHO-DD) and summarized based on the ITT population. A by-subject listing of prior and concomitant medications will be provided.

6.1.1 Prior Medications

Prior medications are defined as medications taken and stopped prior to the first dose of study drug. The number and percentage of subjects who took prior medications will be presented by WHO therapeutic drug class and generic drug name.

6.1.2 Concomitant Medications

Concomitant medications are defined as medications that are ongoing at or started after the first dose of study drug and started on or before the FU visit date, regardless of whether the stop date is missing. Medications with a stop date after the first dose of study drug are also considered concomitant medications. Medications with incomplete or missing dates will be handled as detailed in Section 3.3. A summary showing the number and percentage of subjects who took concomitant medications will be presented by WHO therapeutic drug class and generic drug name.

6.2 Study Treatments

Please refer to Section 2.3 for the details of the study treatment. Data related to the study treatment will be presented in a listing.

6.2.1 Study Participation Calculation and Extent of Exposure

The duration of study participation (days) is calculated as date of Study Completion/Termination recorded on the End of Study page – Informed Consent date + 1. If the date of Study Completion/Termination on the End of Study page is missing, or if a subject is lost to follow-up, the latest available visit date will be used.

The duration of study treatment (days) is calculated as the date of the last dose date – the date of the first dose date + 1.

The cumulative doses taken across the treatment period for all fungal diseases will use the exposure and missed dose log. For all fungal diseases, excluding VVC, the dosing regimen is 2 doses on study days 1 and 2 and then 1 dose from study day 3 to EOT. The dosing regimen for VVC is [redacted]. The missed dose log will be used to subtract the total number of missed doses from these total cumulative doses.

The duration of study participation, duration of study treatment, and the cumulative doses will be summarized by summary statistics. All this exposure information will be presented in a listing.

6.2.2 Treatment Compliance

Treatment compliance is defined as the ratio of total study dose to the planned dose, in terms of percentage. Treatment compliance will be summarized descriptively.

Treatment compliance = the cumulative dose / the planned dose *100%. The planned dose for all fungal diseases, excluding VVC, is defined as 2 doses for the first 2 days and then 1 dose for up to 180 days, depending on the fungal disease. The planned dose for VVC is defined [redacted]. The cumulative dose uses information from the missed dose log to identify missed doses.

The treatment compliance will be classified as 0, 25%, 50%, 75%, and ≥100%. This categorical data will be summarized with the frequency and percentage of subjects.

7. EFFICACY

The primary efficacy and secondary efficacy endpoints will be performed on the ITT, Myco-ITT and PP populations. The ITT analyses will be considered primary and the Myco-ITT and PP analysis will be considered supportive of the primary analyses on the ITT population.

The primary efficacy endpoint of the study is the percentage of subjects who achieve 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 the DRC. The primary efficacy endpoint will also be summarized by disease category and reason for enrollment separately. Secondary efficacy endpoints include the percentage of subjects who achieve Global Response, Clinical Response and Mycological Response by pathogen, fungal disease, disease category, and reason for enrollment at several time points as assessed by the DRC and by the Investigator. The following enrollment categories, as determined by the DRC unless stated otherwise, will be utilized: Refractory, Intolerant, Resistant (includes step-down cases), Toxicities, Relapse, Step-Down (as determined by PI). Each subject's enrollment reason will be validated by the DRC. The percentage of subjects with a recurrence, ACM and time to death will also be assessed.

Efficacy outcomes will be based on definitions captured in Table 5 and Table 6. Criteria for the DRC assessment of response will be further detailed in the DRC Charter. Criteria for the Investigator is outlined in Section 7.2.

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.

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 status data was collected at Day 42 and Day 84. A subject's date of death will be used to determine their survival status at Day 30. Survival will be determined at Day 30 for IC/Candidemia and at Day 42 for all subjects. Additional disease-specific efficacy endpoints will be evaluated for selected fungal diseases at additional time points (Table 7).

A determination of the potential impact of protocol deviations on the efficacy-related outcomes was done by the sponsor for the purpose of defining the PPP:

- Unapproved co-administration of other systemic or topical (in case of mucosal infections) antifungal for =>10% of the ibrexafungerp treatment duration or for longer than 3 days (whichever is shorter) was considered a protocol deviation warranting exclusion from the PPP.
- An EOT visit that occurred > 2 weeks after last dose of ibrexafungerp for non-VVC subjects was considered a protocol deviation warranting exclusion from the PPP.

Table 5 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]	Global Response (as defined) [f]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) [f]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) [f]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); **OR** • Resolved VVC infection (VSS < 3) Mycological Response: • = mycological eradication of the baseline pathogen OR • Presumed eradication of the baseline pathogen Symptom resolution at FU (clinical cure, resolved infection, clinical success) Responder outcome (clinical cure and mycological eradication)

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) [f]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 improvement or stability in the St. George's Respiratory Questionnaire (SGRQ) score. 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) [f]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) [f]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 7.2.2 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.

[f] Clinical response will be reported as determined by both the PI and the DRC based on MSG-EORTC outcome response definitions that includes signs (including radiological signs) and symptoms

7.1 Primary Endpoint

The primary efficacy objective is to evaluate the efficacy of ibrexafungerp in the treatment of severe fungal diseases by a Data Review Committee (DRC) at the primary timepoint for the fungal disease (as defined in Table 5). The primary efficacy endpoint of the study is the percentage of subjects who achieve Global Response (as defined in Table 6) at TOC (Day 17) for VVC, 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 the DRC. The analysis criteria will be based on EORTC-MSG Consensus Criteria for all diseases except ABPA, CPA and VVC.

Table 6 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 in Amendment 3 for subjects enrolled for step-down therapy and asymptomatic at baseline. DRC adjudications followed this definition for all subjects, PI adjudication followed this definition for subjects enrolled after Amendment 3.
[b]Category added for non-evaluable subjects due to missing data

7.1.1 Primary Analysis

The primary efficacy analysis will be performed 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. For CMC, CPA, and ABPA, if Day 84 or Day 90 is the earlier visit and the Global Response is not evaluable or was not done, and the EOT visit has a Global Response, then the EOT information will be used. The number and percentage of subjects with Successful Global Response as determined by the DRC will be presented separately for each fungal disease, disease category, enrollment category, and pathogen along with a 95% confidence interval (CI) for a single binomial proportion in the ITT and PP populations. The Clopper Pearson method will be used for the confidence interval. CI will not be estimated when the subjects in a particular disease, disease category, enrollment category, or pathogen is less than 5. In addition, the overall response will be presented for all disease categories combined.

The following disease categories and fungal diseases will be used for the analysis.

- Acute invasive candidiasis (IC), including candidemia
    - Acute IC with/without candidemia
    - Candidemia only
- Chronic candidiasis
    - Chronic IC
    - Chronic mucocutaneous candidiasis (CMC)
- Mucocutaneous candidiasis
    - OPC (including oropharyngeal, laryngeal)
    - EC
    - VVC
- Disseminated /invasive dimorphic fungi
- Aspergillus syndromes
    - CPA
    - ABPA
    - IPA
- Other emerging fungi

The following pathogens will be used for the analysis.

- Invasive Candidiasis, including candidemia
    - Albicans
    - Auris
    - Glabrata
    - Krusei
    - Parapsilosis
    - Tropicalis

    - Other Candida species
- Mucocutaneous Candidiasis (CMC, OPC, EC, VVC)
    - Albicans
    - Auris
    - Glabrata
    - Krusei
    - Parapsilosis
    - Tropicalis
    - Other Candida species
- Dimorphic fungi
    - Coccidioidomycosis
    - Histoplasmosis
    - Blastomyces
    - Other Dimorphic fungi species
- Aspergillus Syndromes (CPA, ABPA, IPA)
    - Flavus
    - Fumigatus
    - Nidulens
    - Terreus
    - Other Aspergillus species

Invasive Candidiasis will be grouped according to the following sites of infection:

- Pleural/Pulmonary
- Intraabdominal / Pelvic
- Soft tissue/wound
- Endovascular/endocarditis
- Mediastinitis
- Osteomyelitis
- Native joint
- Prosthetic joint
- Urinary tract
- Other

The following enrollment categories (as determined by DRC unless otherwise stated) will be used for the analysis.

- Refractory
- Suspected or confirmed Resistance (includes step-down cases)
- Intolerant
- Toxicities

- Relapse
- Step-down (as determined by PI-assigned enrollment category)
- Other

If Global Response has not been deemed a success or failure, the outcome will be categorized as not evaluable.

7.2 Secondary Endpoints

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 percentage of subjects surviving at the defined time points will be presented for the ITT, Myco-ITT and PP populations, and will also be presented by disease category. A Kaplan Meier plot will also be produced summarizing the survival curve over time and the median time to death. Survival status information was collected at Day 42 and Day 84 of the study. A subject's date of death will be used to determine their survival status at Day 30. Any subject without a death date and without a record of being contacted on or after Day 30, Day 42, or Day 84 will have a survival status of unknown at those visits. A subject without a reported death will be censored at the point of last time the subject was known to be alive.

The probability of survival will be calculated for the following fungal diseases and timepoints:

- Acute IC with/without Candidemia Day 30
- Candidemia only Day 30
- IPA Day 42

7.2.1 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 5), 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 5), 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 5), 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 5), 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 5), 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 (IC and candidemia) and Day 42 for all diseases
- Time to death from any cause
- Describe ibrexafungerp plasma concentrations

7.2.2 Disease-Specific Secondary Endpoints

Disease-specific secondary endpoints, as assessed by the DRC and/or PI in Table 7.

Table 7 Disease-Specific Secondary Endpoints

Disease-Specific Secondary Endpoints
Acute Invasive candidiasis / Candidemia o Completion of study drug antifungal treatment (i.e. no recurrence, no use of other antifungal treatment, no discontinuation for any reason)
Chronic Severe Mucocutaneous Candidiasis (CMC) o Percentage subjects with mycological cure at Day 84 o Percentage subjects with clinical response by Day 42 and Day 84 o 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

- 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
- Time to achieve a clinically meaningful GMI absolute (<0.5) and percent (=>50%) 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

Vulvovaginal candidiasis (VVC) disease-specific endpoint

- Symptom resolution at FU (clinical cure, resolved infection, clinical success)
- Responder outcome (clinical cure and mycological eradication)

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

7.2.3 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 (initial Protocol and Amendment 1):

1. Complete response
2. Partial response
3. Stable response
4. Progression of disease
5. Death
6. Not applicable (not feasible or available)

Mycological Response (Protocol Amendments 2 and 3 aligned with MSG-EORTC outcome response definitions):

1. Eradication (eradication of the original causative organism cultured or identified by histology/cytology 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. Reporting of mycological response by PI used different definitions for subjects enrolled under final protocol and subsequent amendments. Complete and partial response were mapped as successful mycological response for subjects under final protocol: Eradication and presumed eradication were mapped as successful mycological response for subjects enrolled under subsequent amendments. The DRC adjudicated mycological responses used the same definition for all subjects as included in the latest amendment.

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.

8. Safety

The safety analyses will be performed on all subjects in the safety population. Analyses will be based on adverse events, vital signs, clinical laboratory assessments, and physical examination findings. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

Individual subject listings will be provided to support the tables.

8.1 Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs) only. A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

For the purpose of inclusion in TEAE tables, incomplete AE start and end dates will be imputed as follows:

Missing onset dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the date of first dose, assume 01-MMM-YYYY. If the month and year are the same as the month and year for the date of first dose, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the month and year are the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.
- DD-UNK-YYYY/UK-UNK-YYYY: If the year is different from the year of the date of first dose, assume 01-JAN-YYYY of the collected year. If the year is the same as the date of first dose year, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the year is the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.

Missing end dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UNK-YYYY/UK-UNK-YYYY: Assume 31-DEC-YYYY.

All adverse events will be classified by SOC and PT according to the Medical Dictionary for Regulatory Activities (MedDRA, March 2023 Version 26.0). An overview summary of the number and percentage of subjects with any TEAE, serious TEAE, treatment-related TEAE,

treatment-related serious TEAE, TEAE leading to study treatment discontinuation, TEAE leading to study discontinuation, and AE leading to death will be provided.

All AEs will be presented in a listing.

8.1.1 Treatment-Emergent Adverse Events

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided. Treatment-emergent AEs will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the safety population.

The summary of TEAEs will be presented in alphabetical order of SOC. Within each SOC, PTs will be sorted in descending order from the PT with the highest total to the PT with the lowest total frequency. If the total frequency for any two or more PTs is equal, the PTs will be presented in alphabetical order.

The summarization described above will also be repeated for the following:

- Serious Adverse Events;
- Treatment-Related Adverse Events;
- Treatment-Related Serious Adverse Events;
- Adverse Events Leading to Dose Interruption.

8.1.2 Related Adverse Event to Study Treatment

A summary of related TEAEs to study treatment will be presented in a table. The investigator will provide an assessment of the relationship of the event to the study treatment. Related AEs are those reported as “Possibly Related”, “Probably Related”, or “Related”. If a subject reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. Treatment-emergent AEs that are missing a relationship will considered “Related” and be presented in the summary table but will be presented in the data listing with a missing relationship. Percentages will be calculated based on the number of subjects in the safety population.

The TEAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 8.1.1.

Related treatment-emergent SAEs to study treatment will also be presented in a table. Treatment-emergent SAEs that are missing a relationship will be presented in the table as “Related” but will be presented in the data listing with a missing relationship.

8.1.3 Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are "Mild", "Moderate", and "Severe".

In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. Percentages will be calculated out of the number of subjects in the safety population.

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 8.1.1.

Additionally, the related TEAE data will be categorized and presented by SOC, PT, and severity. If a subject reported multiple occurrences of the same related TEAE, only the most severe will be presented. Percentages will be calculated out of the number of subjects in the safety population.

Treatment-emergent SAEs by severity will also be presented in a table.

8.1.4 Adverse Events Leading to Treatment Discontinuation

A summary of the TEAEs with an action taken with study treatment of "Drug Withdrawn" will be presented in a manner similar to that described in Section 8.1.1.

Any TEAEs leading to treatment discontinuation will be presented in a listing for all subjects.

8.1.5 Death

All subjects who have an AE with an outcome of "Death Related to Adverse Event" will be presented in a listing.

8.2 Clinical Laboratory Evaluations

Summary tables will be presented for clinical laboratory test results (hematology, blood chemistry, and urinalysis) at collection visits for subjects in the safety population. 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, 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.

All relevant clinical laboratory tests in chemistry, hematology, and urinalysis will be classified as Low, Normal, and High according to the normal ranges. This categorical data will be summarized in shift tables comparing the extreme results at each visit with those at the baseline visit. Extreme post-baseline results will also be summarized as described in Section 8.2.2. When there are multiple values within a visit for a particular laboratory variable, the worst value will be taken (worst being the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold). If a subject has a value below the threshold and above the threshold, the value furthest from the threshold will be chosen.

In data listings, laboratory values will be compared to normal ranges; out-of-range and clinically significant laboratory values will be identified.

8.2.1 Pregnancy

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. Any subjects with positive pregnancy test results at any time during the study will be presented in a listing.

8.2.2 Events of Clinical Interest

The frequency and percentage of subjects with the following elevations will be summarized at any post-baseline visit:

- ALT or AST > 8 x the upper limit of normal (ULN);
- ALT or AST > 5 x ULN if new compared to Baseline;
- ALT or AST > 3 x ULN and total bilirubin >2 x ULN if new compared to Baseline;
- ALT or AST > 3 x ULN.

If subjects meet the criterion ALT or AST > 3 x ULN, the additional summary of the frequency and percentage of subjects with ALT or AST > 3 x ULN, confirmed by repeat test, and with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) will be provided.

A listing will be provided for the above elevations, including the actual measurement of ALT, AST, and total bilirubin, and their reference high limits.

8.3 Vital Signs

Summary tables will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body temperature (°C), respiratory rate (bpm), pulse rate (bpm), height, and weight for subjects in the safety population. Observed results at the scheduled visits and changes from baseline to post-baseline visits will be presented. All vital sign data by subject will be presented in a listing.

8.4 Physical Examination

The abbreviated physical examinations will be conducted at Screening and EOT visits. A general physical exam will also be conducted at the 6-Week FU for all subjects, except VVC subjects. The abbreviated physical examination comprises a routine medical examination including general appearance, skin, eyes, heart, chest, and abdomen.

All abbreviated physical examinations will be classified as Normal, and Abnormal at baseline. Post-baseline examinations will be classified as “Changes from baseline” or “No change from baseline”. This categorical data will be summarized with the frequency and percentage of subjects by body system at each scheduled visit.

Any abnormalities noted during the physical examination and associated with adverse events, will be presented in a listing for all subjects.

8.5 Mycological Testing

For VVC subjects, samples for fungal culture will be collected at Screening, EOT, TOC, and 25-Day FU. 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. For all other fungal disease subjects excluding VVC, 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 3.

The KOH testing results will be classified as Positive (Yeast Only), Positive (Yeast and other pathogens), Negative (Yeast and other pathogens), and Positive (Other pathogens only). All other testing results will be classified as Positive or Negative. This categorical data will be summarized with the frequency and percentage of subjects at the scheduled post-baseline visits.

All by-subject mycological testing will be presented in a listing.

9. Pharmacokinetics

A detailed description of PK parameters and analysis will be presented in a separate pharmacokinetics report.

10. Interim Analysis and Supplemental Analysis

No interim analysis is planned for this study.

11. Tables, Listings, and Figures

A list of tables, listings, and figures will be maintained outside of this document and may be amended as needed.